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Acknowledgments should only be made to funding institutions and organizations and, if to persons, only to those who have made substantial contributions to the study.

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Examples of correct form of references

1- Standard journal article

List all authors when six or less. When seven or more, list only first six and addetal. Toppozada MK, Gaafar AA, Shaala SA. In - vivo inhibition of the human non pregnant uterus by prostaglan din E2. Prostaglandins, 1974; 8: 401 - 406.

2- Books:

(a) Personal author: Speroff L, Glass RH, Kase NO. clinical gynecologic endocrinology and infertility. 4th edition, Baltimore, Williams & Wilkins; 1988: 105

(b) Chapter in book; Wilhelmsson L, Norstrom A, Tjugum 1, Hamberger L. Interaction between prostaglan dins and catecholamines on cervical collagen. In: Toppozada M., Bygdeman '. M., Hafez ESE, Eds. Prostaglandins and fertility regulation. Advances in reproductive health care. Lancaster, England, MTP Press Ltd., 1985 : 75 - 80.

3- Agency publication

National Center for Health Statistics. Acute conditions: incidences and associated disability, United States July 1908 - June 1909. Rockville. MD.: National Center for Health Statistics, 1972.

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Contents :

Letter from the Editor:

Dear colleagues,

Dear colleagues, very interesting subjects are included in this edition. Combination of vaginal progesterone and aspirin didn't significantly reduce the risk of recurrent spontaneous PTB than vaginal progesterone alone but had better neonatal outcomes by decreasing perinatal morbidity and mortality that might be secondary to reducing the rate of preterm rupture of membranes. ADNEX model is more sensitive than RMI for differentiating between benign and malignant tumors and it can be used as screening test. However, the application of ADNEX model needs significant experience in ultrasound evaluation of adnexal masses before it can be an integral part in the screening pathway of ovarian malignancy in postmenopausal patients with adnexal masses.

Maternal serum copeptin levels can serve as a valuable diagnostic and predictive marker in cases of threatened preterm labor and preterm birth.

Scoring System for severity prediction of PAS is simple and feasible modality to ascertain the presence of PAS in women with placenta previa. In women undergoing abdominal hysterectomy single pedicle ligation surgical technique help in lowering surgical related blood loss and costs with no statistically significant difference compared with traditional methods.

Endometrial volume, sub-endometrial VFI, uterine RI, and uterine PI had an impact on the pregnancy outcome and clinical pregnancy rate in IVF and ICSI cycles. Adhesion scoring system could simply and noninvasively predict the degree of endometriosis adhesions. As a result, we could assess the actual condition of endometriotic adhesions with this approach both presurgically and postoperatively

Although Candida albicans was the most prevalent species causing vaginal candidiasis in pregnant and non-pregnant using contraception women, candida non albicans are also incriminated in high percentage, e.g. C.glabrata, and C. krusei. Both C. albicans and C. non albicans were highly sensitive to voriconazole and Caspofungin in contrast to other drugs tested.

Best regards.

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Comparative Study Between Vaginal Progesterone Alone or Combined with Aspirin in Prevention of Recurrent Preterm Birth

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Abstract

Background: Preterm birth (PTB) carries the greatest risk of perinatal morbidity and mortality because of its neurological and developmental consequences later in life.

Objectives: To evaluate the efficacy and safety of vaginal progesterone alone or in combination with aspirin for the prevention of recurrent spontaneous PTB.

Methods: This was a randomized, double blind, placebo controlled trial conducted on 256 pregnant females with previous history of spontaneous PTB who randomly divided into 2 groups; **Group 1:** 128 females received combined vaginal progesterone plus aspirin, and **Group 2:** 128 females received vaginal progesterone plus placebo started at 16-20 weeks' gestation. The primary outcome was the occurrence of PTB prior to 34 weeks' gestation. Secondary outcomes were maternal: (1) harm to the mother from intervention, (2) maternal infection or inflammation, (3) prelabour rupture of membranes, (4) maternal mortality, and neonatal: (1) The gestational age at birth (2) respiratory morbidity, (3) birth weight, (4) infection (neonatal sepsis), (5) gastrointestinal morbidity, (6) early neurodevelopmental morbidity (within one month of delivery), (7) harm to the neonate from intervention, (8) perinatal mortality.

Results: Both groups showed non-significant difference regarding socio-demographic data. Rates of deliveries <34 weeks were 44% and 49% in group 1 and 2, respectively (p=0.072). Subgroup analysis according to the gestational age at delivery also done to detect if the drug combination (progesterone with aspirin) can have more effect at certain gestational age than others but the results were also non-significant. When considering other secondary outcomes, the rate of preterm rupture of membranes, neonatal birth weight, GIT morbidity, and perinatal deaths all showed significant difference between both groups (p<0.05) with cases received both progesterone and aspirin had improvement of theses parameters.

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Conclusion: Combination of vaginal progesterone and aspirin didn't significantly reduce the risk of recurrent spontaneous PTB than vaginal progesterone alone but had better neonatal outcomes by decreasing perinatal morbidity and mortality that might be secondary to reducing the rate of preterm rupture of membranes.

Keywords: PTB, Progesterone, Aspirin, Neonatal outcomes.

Introduction

The highest risk of perinatal and neonatal mortality and morbidity was associated with preterm birth (PTB) (defined as delivery at gestational age < 37 weeks) due to its developmental and neurological repercussions in later life [1].

The gestational age at delivery is directly proportional to the survival rate of preterm infants. Survival rates are less than 50% before 24 weeks and reach 95% by 33 weeks [2].

The identification of cases at risk for recurrent PTB can enable successful intervention, thereby reducing the burden on the family and community. Consequently, scientists are motivated to conduct trials in order to identify not only a single drug regimen, but also to potentially use a drug combination to achieve the most effective prevention [3].

Numerous interventions have been proposed to prevent PTB, such as home uterine monitoring, psychosocial interventions, risk scoring systems, aspirin, tocolysis, progestogens, optimal birth spacing, bed rest, activity restriction, health system interventions (packages of antenatal care, specialized antenatal clinics, midwifery-led care), nutritional interventions, cervical cerclage, and cervical pessary. Regrettably, numerous of these interventions have been shown to be ineffective in reducing the risk of PTB in both singleton and twin gestation [4,5].

Nine years ago, the United States Food and Drug Administration (FDA) authorized progesterone for the prevention of PTB. The majority of studies indicate that pregnant women who are treated with progesterone experience significant reductions in perinatal mortality and major morbidity, irrespective of the method of administration [5].

At present, the ACOG advises the vaginal progesterone administration to women who have a singleton gestation, a transvaginal cervical length of less than 25 mm, and no spontaneous PTB history at 18–22 weeks of gestation. This recommendation was recently revised in 2021 [6].

Aspirin was an additional medication that was evaluated for its potential to prevent PTB. It was recommended for use in at-risk pregnancies in numerous studies, with implementation commencing at 12 weeks gestation. It has been reported that aspirin resulted in improved placental implantation, while defective placentation may be one of the theories in this regard [7].

Our study conducted to detect the vaginal progesterone safety and efficacy either alone or in combination with aspirin in the prevention of recurrent spontaneous PTB.

Methods

This was a randomized, double blinded, placebo controlled trial held in the department of Obstetrics and Gynecology at Menoufia University Hospitals where the ethical committee of the University approved the protocol in January 2022 and after that registered at Clinical Trials.gov (https://clinicaltrials.gov/) as (NCT05319834).

Inclusion criteria: Women of any age, parity and gestational age between 16 to 20 weeks who were carrying a healthy singleton pregnancy in the current pregnancy and had a previous history of one or more spontaneous PTB in a singleton pregnancy at a gestational age between 24 and 36+6 weeks. Spontaneous PTB was defined as PTB that occurred following spontaneous contractions with intact membranes or spontaneously ruptured

membranes followed by PTB.

Exclusion criteria: A history of PTB due to cervical incompetence, medical disorder complicating a previous pregnancy, current cervical cerclage, known fetal anomaly, major chronic medical disorder (For example; chronic renal disease, chronic hypertension, and pregestational diabetes mellitus, as these conditions would increase the PTB risk and potentially confound the study outcome), known allergy to aspirin or progesterone, known liver disease, established preterm labor with advanced cervical dilatation (>4 cm), ruptured fetal membranes, and a short cervix <1cm. Women who presented at the outpatient clinic, emergency room, or were referred from other hospitals were eligible for the trial. One of the authors has conducted counseling on the benefits of the trial and its impact on the family and community. All participants have the right to withdraw from the trial at any point during the treatment process. The CONSORT guidelines were adhered to and implemented.

The medical research officer at the hospital prepared sealed, numbered opaque envelopes to conceal the trial sequence, which obtained by randomly assigning the included women to two trial groups in a 1:1 ratio utilizing a computerized random number table generator (MedCalc© version 13). An assignment for a single patient was inside each envelope.

Women were randomly assigned to either vaginal progesterone in combination with aspirin (Group 1) or vaginal progesterone in combination with a placebo (Group 2). Progesterone was administered to all women in the trial in the form of 200 mg vaginal suppositories every 12 hours (Prontogest® 200mg micronized vaginal suppositories, Marcyrl Pharmaceutical Industries/ Industrial zone – West Extension – Block 20016 El Obour City – Egypt). In group 1, aspirin administered once daily in a 100-mg dose in conjunction with progesterone (Aspirin® protect Memphis Co. for pharmaceuticals / Bayer Bitterfeld GmbH – Germany), while in group 2, an oral placebo (manufactured in a standard manner to resemble an aspirin tablet in size and shape) was administered. Administration initiated at 16 to 20 weeks' gestation and continued until 36 weeks or delivery, whichever occurred first. All cases advised to have additional bed rest periods and also instructed on the PTB symptoms. Antenatal care managed at 2-week intervals until delivery.

For all participants: A comprehensive history is obtained, with a particular emphasis on high-risk factors for PTB including past medical, surgical, and obstetric history, including full details of previous pregnancies (mode of conception, gestational age at delivery, cause and course of PTB, onset and mode of delivery, neonatal outcome, and any associated maternal or fetal complications). An account on the current pregnancy (mode of conception, estimated gestational age from the LMP, or an early pregnancy ultrasound) also obtained.

Physical examination: General examination, including maternal BMI, pulse, temperature, and blood pressure. For local examination, speculum was done to assess cervical dilation for cases presented with pelvic heaviness and ultrasound done for cervical measures and to exclude fetal anomalies.

Routine antenatal laboratory investigations, such as random blood sugar, urine analysis, full blood count, blood group and Rh typing.

Gestational age at delivery, mode of delivery, neonatal outcomes (Apgar score, birth weight, NICU admission, postpartum complications, and neonatal morbidity or mortality), drug side effects and maternal complications during delivery (if present) were all documented.

US Examination:

All patients underwent US using convex transducer with frequency of 2.5-10 MHz (Mindray 2200 digital Ultrasonic imaging system, China) with transabdominal probe

3.5 MHz and transvaginal probe 8 MHz before being enrolled in the trial to confirm their eligibility and cervical assessment also performed to exclude cervical insufficiency as being a cause of previous PTB. Further assessments were carried as per antenatal care.

Outcome:

The primary outcome was the occurrence of PTB prior to 34 weeks of gestation. As per ACOG practice bulletin no. 127 (2012), a 60-minute observation period was utilized to define preterm labor as the persistence of at least two symptomatic uterine contractions within a 10-minute period, as well as cervical changes (cervical dilation between 0 and 3 cm for nulliparous and from 1 to 3 cm for multiparous, with cervical effacement <50%) [8]. Secondary outcomes were either maternal that included: (1) harm to the mother from intervention, (2) maternal infection or inflammation, (3) prelabour rupture of membranes, and (4) maternal mortality, or neonatal that included: (1) The gestational age at birth which is classified according to standard subcategories, which include extremely preterm (gestation from <28+0 weeks), very preterm (gestation from 28+0 weeks to <32+0 weeks), and moderate to late preterm (gestation from 32+0 to <37+0 weeks), (2) respiratory morbidity, (3) birth weight, (4) infection (neonatal sepsis), (5) gastrointestinal morbidity, (6) early neurodevelopmental morbidity (within one month of delivery), (7) harm to the neonate from intervention, and (8) perinatal mortality. Other related outcomes were: admission to the NICU, and any adverse drug effects.

Statistical analysis:

We assumed an anticipated increase of 15% in the rate of reduction of PTB with the addition of both drugs, increasing the rate of prevention of PTB to 30-35%; accordingly, at a study power of 95% and two-tailed alpha of 0.05, a minimum total sample size of 256 women is required, considering a possible dropout rate of 10% of cases. The Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc. Released 2018) was employed to collect, tabulate, and conduct statistical analyses of the data.

In order to determine whether the quantitative data were normally distributed, the Kolmogorov-Smirnov test was implemented. The Student's t-test was employed to compare the data if they were normally distributed, and the results were expressed as the mean SD. The Mann-Whitney U-test was employed to compare the data if they were not normally distributed, and they were expressed as the median (range). In order to assess qualitative data discrepancies, Fisher's exact test or chi-square test was implemented. Significant differences were defined as P-values <0.05, while highly significant differences were defined as P <0.001.

Results

Two hundred and fifty-six women were randomized: 128 received progesterone with aspirin, and 128 received progesterone with placebo. There were 11 (8.6%) cases in group 1 and 16 (12.5%) cases in group 2 excluded from final analysis due to discontinuation of treatment. The treatment, randomization, and follow-up of the cases are illustrated in **Figure 1.**

Table 1 Illustrates the baseline characteristics of the study participants. The parameters assessed did not exhibit any significant differences among both groups.

As regard the gestational age at delivery, rate of deliveries <34 weeks were 44% and 49% in group 1 and 2, respectively with insignificant difference (p=0.072). Also the difference among both groups regarding deliveries ≥ 34 weeks was insignificant (56% in group 1 versus 51% in group 2, p=0.0.87). Furthermore, no significant difference among both groups regarding deliveries more than 37 weeks as illustrated in **Table 2**.

Maternal outcomes were shown in **Table 3**;

there were non significant differences in maternal need for admission, tocolytic therapy or complications among both groups.

The neonatal outcomes demonstrated in **Table 4**. Progesterone with aspirin group had significantly better neonatal outcomes regarding the neonatal birth weight with lower gastrointestinal morbidity and perinatal death, but with no significant differences between both groups regarding other parameters including NICU admission.

Discussion

The large contributor to the perinatal morbidity and mortality worldwide was recurrent spontaneous PTB, which always motivated the need for additional preventive methods **[1]**.

Survival in preterm is directly related to gestational age at delivery; with less than 50% survival before 24 weeks and increased up to 95% by 33 weeks' gestation **[9]**.

Progesterone for prevention of PTB was approved by the United States Food and Drug Administration (FDA) nine years ago. Most studies suggest a significant risk reduction of perinatal mortality, and major morbidity among pregnant women treated with progesterone regardless of its route of administration **[10]**.

In the past, it was suggested that the action of progesterone was through nuclear receptors; however, it is now clear that some of the actions of progesterone are mediated through membrane receptors as well. Several studies have demonstrated a number of actions that could contribute to prevention of PTB. These actions may be seen at the following four different levels: (i) reducing cervical stromal degradation, altering the barrier to ascending infection, inhibiting cervical ripening and improving cervical length in patients with a short cervix; (ii) decreasing the concentration of myometrial oxytocin receptors, reducing contraction frequency and possibly acting as a tocolytic agent; (iii) attenuating the response to hemorrhage and inflammation in the decidua; and (iv) suppressing prostaglandin synthesis in fetal membranes and in the placenta, reducing apoptosis and altering estrogen synthesis. Additionally, progesterone alters endocrine-mediated effects in the fetus **[11]**.

Given that prophylactic intervention to prevent PTB entails a long duration of progesterone administration, less invasive forms of administration are preferred. Vaginal administration is characterized by very high endometrial concentrations because it avoids the first-pass metabolism prior to reaching the genital tract; so we prefer its use for our patients **[11]**. Data regarding the optimal route, dose or duration of progesterone are still lacking, and it remains unknown whether there is a dose–response relation between progesterone and its action to reduce PTB.

Despite the use of progestagens, at least one third of the women will have a recurrent spontaneous PTB, suggesting that multiple underlying mechanisms contribute to its pathogenesis **[12]**.

It was suggested that utero-placental ischemia plays a major role in the pathogenesis of spontaneous PTB. Placental vascular pathology and placental bed pathology are common findings in women with a spontaneous PTB **[13]**. Also, abnormal angiogenic/anti-angiogenic profile in maternal plasma is seen in a subset of patients with spontaneous PTB, and increased resistance at mid-trimester Doppler measurement of uterine artery flow provides an increased risk of spontaneous PTB **[14]**. These findings suggest an overlap of PTB with other ischemic placental diseases as pre-eclampsia.

Placental ischemia, as being one of the causes of spontaneous PTB, makes suggestions that any intervention to improve the placental blood flow might be effective in reducing the number of cases of recurrent PTB **[7]**.

One of these drugs is aspirin which considered safe in pregnancy and was already widely tested in pregnant women in other indica-

tions. Therefore, if the current study could prove aspirin to be effective in reducing recurrent spontaneous PTB, then it would be possible to implement in women with positive history of one or more spontaneous PTB.

Our study conducted to assess the difference in efficacy between vaginal progesterone when combined with aspirin vs vaginal progesterone when used alone in reducing the rate of recurrent spontaneous PTB. As the primary outcome was the occurrence of PTB prior to 34 weeks of gestation, we failed to find any favor for adding aspirin to progesterone when compared with using progesterone alone with percentage of deliveries 44 and 49% in group 1 and 2, respectively, (p=0.072; the primary outcome). Also, the difference among both groups regarding overall rates of delivery ≥ 34 weeks wasn't statistically significant (56% in group 1 versus 51% in group 2, p=0.087). We also did subgroup analysis according to the gestational age at delivery with the aim to find if the drug combination (progesterone with aspirin) can have more effect at certain gestational age than others but unfortunately, we couldn't prove any significant differences among both groups regarding deliveries at <28 weeks , 28-32 weeks, 32-34 weeks, 34-37 weeks and >37 weeks gestation (p>0.05; secondary outcome). These findings were in agreement with **Jessel et al., [15]** who found no reduction in the rate of PTB in any subgroup treated with aspirin as stratified by gestational age at delivery, type of PTB, or risk-group, with the exception of PPROM <35 weeks, a finding of doubtful significance given multiple comparisons. As attributable risk of PTB was high and aspirin started relatively late, possibly limiting the generalizability of their findings.

In agreement with **Jessel et al., [15]** our study showed significant difference in preterm rupture of membranes among both groups with 6 cases (4.7%) in (progesterone and aspirin) group vs 15 cases (11.7%) in (progesterone and placebo) group (p=0.044). These findings also reported by **Allshouse et al., [16]** who observed an effect size for aspirin for both low- and high-risk women as a PTB prevention strategy, although not reaching significance. Another study also reported that preterm rupture of membranes is linked to an increased risk of PTB **[17]**.

These findings were inconsistent with **Andrikopoulou and his colleagues [18]** who included 2543 women, 1262 (49.6%) received low-dose aspirin and 1281 (50.4%) received placebo. Baseline characteristics were similar between groups, except for marital status. The rate of spontaneous BTB <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo group, respectively (odds ratio, 0.43, 95% confidence interval, 0.26-0.84). Additionally, the rate of spontaneous preterm birth <37 weeks was 6.58% (n=83) in the low-dose aspirin group and 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71-1.33), and the rate of overall preterm birth <37 weeks was 7.84% (n = 99) in the low-dose aspirin group and 8.2% (n = 105) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.72-1.31). After adjustment for variables that were clinically relevant or statistically significant, including body mass index, race, tobacco use, marital status, and education level, there was a significant reduction in spontaneous preterm birth <34 weeks in the low-dose aspirin group (adjusted odds ratio, 0.46, 95% confidence interval, 0.23-0.89). The rates of overall preterm birth <34 and <37 weeks and spontaneous preterm birth <37 weeks were similar in women who received low-dose aspirin compared with placebo. So they concluded that aspirin was associated with a substantial decrease in spontaneous PTB <34 weeks in healthy nulliparous women without co-morbidities.

The study of **Hoffman et al., [19]** also found rate of PTB occurred in 5787 women who received aspirin and 5771 women who received placebo to be 11.6% in women randomized

to aspirin and 13.1% for those randomized to placebo (Relative Risk [RR], 0.89; 95% CI, 0.81 to 0.98; Risk Difference, −0.02; 95% CI, −0.03, −0.01) which is not statistically significant.

Our study also found significant difference between both groups regarding fetal weight at delivery with mean fetal weight of 2772.66 and 2379.3 gm in (progesterone and aspirin) and (progesterone and placebo), respectively ($p < 0.001$). These results were different from that reported by **Silver et al., [20]** who did not find significant impact of using aspirin on birth weight with mean values at delivery of 2437 ± 808 vs 2570 ± 554 gm in the aspirin and placebo groups, respectively.

Regarding NICU admission, 17 neonates (14.5%) vs 19 neonates (16.9%) were in need for admission in (progesterone and aspirin) and (progesterone and placebo), respectively ($p=0.095$). Similar non significant NICU admission were reported in 2015 by Martinez de **Tejada et al. [21]** with 29.8% and 25.4% of the neonates in the progesterone and placebo groups needed NICU admission.

Our study showed also significant difference between both groups regarding gastrointestinal morbidity, 6 (5.1%) cases vs 9 (8%) cases in (progesterone and aspirin) and (progesterone and placebo), respectively ($p=0.046$). Low-dose aspirin (started at < 16 weeks gestation) was linked to a higher reduction in perinatal death and other adverse perinatal outcomes, according to the meta-analysis by **Roberge et al. [22]**.

Perinatal deaths reported in 3 (2.5%) cases in (progesterone and aspirin) and 8 (7.1%) cases in (progesterone and placebo) groups ($p=0.045$). This significant difference in both groups can be attributed to less neonatal morbidity (GIT) shown in (progesterone and aspirin) group.

Taking the medical disorders that could arise during pregnancy into consideration, our study detected non significant difference between both groups regarding pre-eclampsia. Similar results were also detected by **Hoffman et al., [19]** with hypertensive pregnancy disorders noted in 6.1% and 5.6% of patients in the aspirin and placebo groups, respectively.

One of the exclusion criteria considered among our patients was history of PTB due to cervical incompetence. Accordingly, non of our patients having cervical length <2.5 cm. **O'Hara et al., [23]** reported that one of the most potent markers of PTB in women carrying singletons and twins is a shorter cervix. The probability of spontaneous PTB increases with decreased cervical length. Moreover, **Romero et al., [11]** came to the conclusion that the probability of spontaneous PTB increased with decreased cervical length.

In the present study, patients with cervical cerclage were excluded in order to measure the solely effect of progesterone either alone or with aspirin. Controversy about the interaction between cerclage and progesterone remains. **Rebarber et al., [24]** reported a benefit from 17α-hydroxyprogesterone in women with cerclage. On the contrary, **Berghella et al., [25]** showed no additional benefit of 17α-hydroxyprogesterone caproate for the prevention of PTB in women who had ultrasound-indicated cerclage if their cervical length was <25 mm, but if these women did not have cerclage the drug reduced previable and perinatal mortality. The additive effect of progesterone and cerclage for the prevention of PTB depends on different factors, including prior obstetric history, risk factors for PTB and the degree of cervical shortening; therefore, while a cerclage suture may be better for women with a shorter cervix, progesterone may be more beneficial for women with lesser degrees of cervical shortening [11]. More research regarding the mechanisms of progesterone and cerclage in PTB may help clinicians to understand how these two interventions can be used together.

The strengths of our study were: (1) : it is a randomized trial with well-designed method of randomization (computer based) and ad-

equate power calculations; (2) both patients and physician were blind regarding group assignment; (3) aspirin was tested at the usual doses used in previous studies to clinically confirm the hypothesis; (4) participants' outcomes were tracked until delivery to ensure the effect of implementation; (5) cervical status was taken at baseline; and (6) the outcomes were subdivided into primary and secondary for comparison and combination in any meta-analysis.

On the other hand, negative aspects could still be detected as: (1) the aetiology of premature uterine contractions (infection/inflammation?) was not considered before randomization; (2) aspirin was only used in combination with progesterone, so testing the effect of aspirin alone on spontaneous PTB was not done; (3) only one dose regimen of aspirin was used, although comparing the effect of different regimens may give different results; (4) one-center study (Menoufia University), future studies on multi-center bases may confirm and strengthen our results; (5) lack of funding with no cost-effectiveness analysis; (6) we were unable to determine the efficacy of this new combination for twins or preterm premature rupture of membranes due to their exclusion.

In conclusion, our data showed that although the combination of vaginal progesterone with aspirin failed to reduce the rate of recurrent spontaneous PTB, it was associated with significant reduction in the rate of preterm rupture of membranes as well as improvement of some neonatal outcomes (neonatal birth weight, GIT morbidity, and perinatal deaths). More data from different populations are needed to support our results.

References

1. Manuck TA, Rice MM, Bailit JL, et al. Pretermneonatal morbidity and mortality by gestationalage: a contemporary cohort. American journal ofobstetrics and gynecology. 2016; 215(1):103..
2. Berghella V, Palacio M, Ness A, Alfirevic Z, Nicolaides KH, Saccone G. Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol. 2017 Mar;49(3):322-329.
3. Green NS, Damus K, Simpson JL, Iams J, Reece EA, Hobel CJ, Merkatz IR, Greene MF, Schwarz RH. March Of Dimes Scientific Advisory Committee On Prematurity. Research agenda for preterm birth: recommendations from the March of Dimes. American journal of obstetrics and gynecology. 2005 Sep 1;193(3):626-35.
4. Campbell F, Salam S, Sutton A, Jayasooriya SM, Mitchell C, Amabebe E, et al. Interventions for the prevention of spontaneous preterm birth: a scoping review of systematic reviews. BMJ Open. 2022;12:e052576.
5. Currell R, Harlow F, Callow L, et al. Homeuterine monitoring for detecting preterm labour.The Cochrane Database of Systematic Reviews.2017; (2)
6. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics Prediction and prevention of spontaneous preterm birth: ACOG practice bulletin, number 234. Obstet Gynecol. 2021;138:e65–90
7. Magee LA, Rey E, Asztalos E, et al. Management of non-severe pregnancy hypertension–A summary of the CHIPS Trial (Control of Hypertension in Pregnancy Study) research publications. Pregnancy hypertension. 2019 Oct 1;18:156-62
8. American College of Obstetricians and Gynecologists; Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 127: Management of preterm labor. Obstet Gynecol. 2012 Jun;119(6):1308-17..
9. Armanian AM, Barekatain B, Sohrabi F,

Salehimehr N, Mansourian M. The prevalence of complications of prematurity among 1000 newborns in Isfahan, Iran. Adv Biomed Res 2019;8:12.

10. Alsulmi ES, Alfaraj M, Faden Y, Al Qahtani N. The use of progesterone during pregnancy to prevent preterm birth. Saudi Med J. 2020 Apr;41(4):333-340.
11. Romero R, Nicolaides K, Conde-Agudelo A et al. : Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. American Journal of Obstetrics and Gynecology, 2012;206(2):124.
12. Arias F, Rodriquez L, Rayne SC, Kraus FT. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. Am J Obstet Gynecol. 1993;168(2):585–91.
13. Kelly R, Holzman C, Senagore P, Wang J, Tian Y, Rahbar MH, et al. Placental vascular pathology findings and pathways to preterm delivery. Am J Epidemiol. 2009;170(2):148–58.
14. Misra VK, Hobel CJ, Sing CF. Placental blood flow and the risk of preterm delivery. Placenta. 2009;30(7):619–24.
15. 15. Jessel R, Allshouse A and Heyborne K: Does Low dose Aspirin prevent preterm birth published in American Journal of Obstetrics and Gynecology,2015; 212 (1): S342.
16. Allshouse, A., Jessel, R. & Heyborne, K. The impact of low-dose aspirin on preterm birth: secondary analysis of a randomized controlled trial. J Perinatol, 2016;36, 427–431
17. Medina T, Hill D (2006): Preterm premature rupture of membranes: diagnosis and management. American Family Physician, 73(4):659-64.
18. Andrikopoulou M, Purisch SE, Handal-Orefice R, Gyamfi-Bannerman C. Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women. American journal of obstetrics and gynecology. 2018 Oct 1;219(4):399-e1.
19. Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jan 25;395(10220):285-293.
20. Silver RM, Ahrens K, Wong LF, Perkins NJ, Galai N, Lesher LL, et al. Low-dose aspirin and preterm birth: a randomized controlled trial. Obstet Gynecol. 2015;125(4):876–84.
21. Martinez de Tejada B, Karolinski A, Ocampo M et al. : Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. BJOG., 2015;122(1):80-91.
22. Roberge S, Nicolaides K, Demers S et al. : Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. Ultrasound in Obstetrics & Gynecology, 2013;41(5):491-9.
23. O'Hara S, Zelesco M, Sun Z : Cervical length for predicting preterm birth and a comparison of ultrasonic measurement techniques. Australasian Journal of Ultrasound in Medicine,2013; 16(3):124-34.
24. Rebarber A, Cleary-Goldman J, Istman NB. The use of 17 alpha-hydroxyprogesterone caproate (17p) in women with cervical cerclage. Am J Perinatol. 2008;25(5): 271–5.
25. Berghella V, Figueroa D, Szychowski JM, Owen J, Hankins GD, Iams JD, et al. 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length. Am J Obstet Gynecol. 2010;202(4):351.e1–6.

Figure legend

Figure (1): Flow chart of the study group.

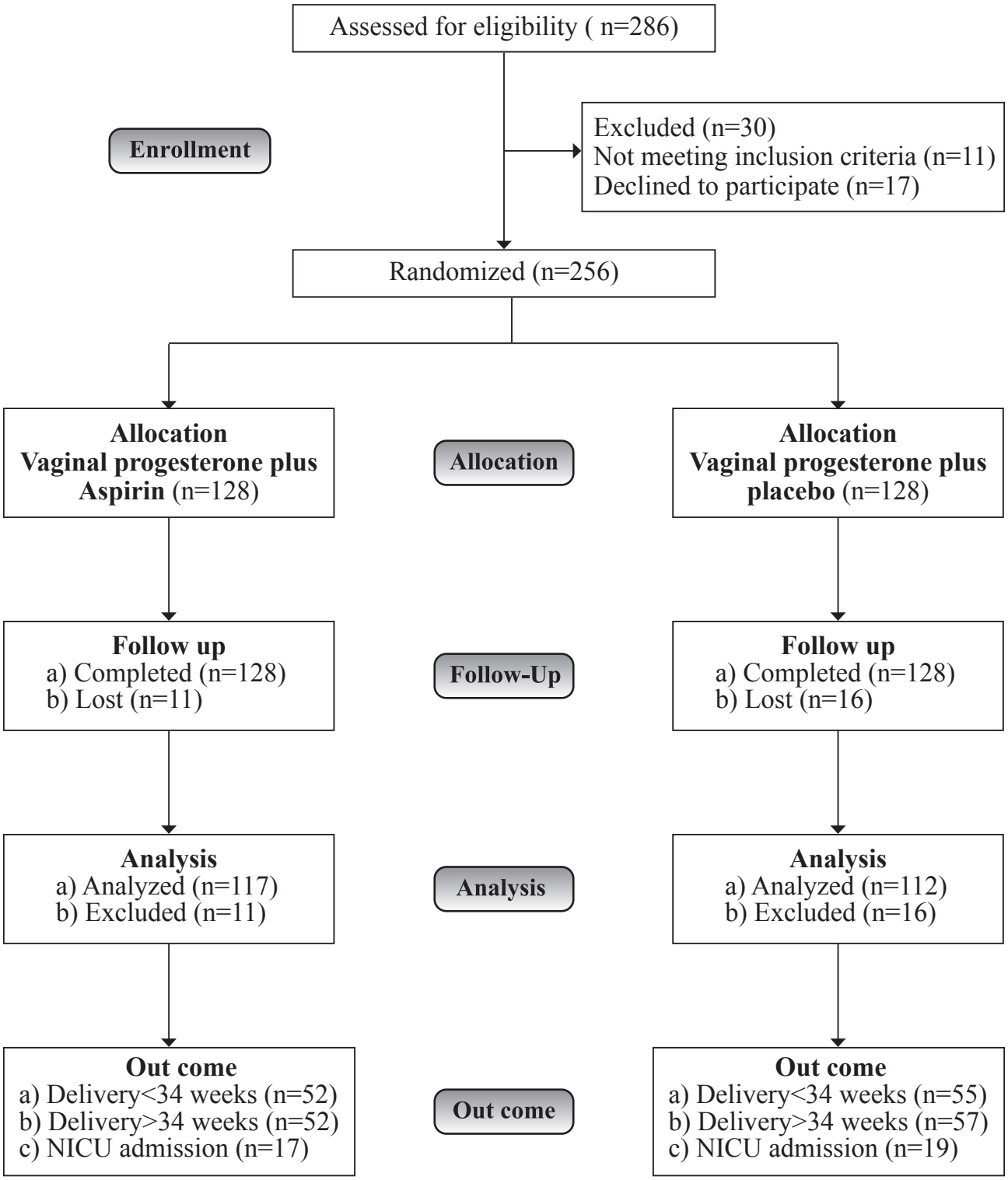

Table (1): Socio-demographic and clinical data of studied groups:

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n =128)	P-value
Maternal age, years (Mean ±SD) Range	29.9±3.88 22-41	28.91±4.11 22-41	0.05
Parity (No., %) a) 2 times b) 3 times c) 4 times	62 (48.4) 57 (44.5) 9 (7.0)	68 (53.1) 48 (37.5) 12 (9.4)	0.478
BMI, kg/m^2 (Mean± SD) Range	28.05±1.981 24-38	28.07±2.392 25-35	0.955
History of PTB (No., %) a) Once b) Twice c) 3 or more	5 (3.9) 118 (92.2) 5 (3.9)	7 (5.5) 117 (91.4) 4 (3.1)	0.449
Mode of conception (No., %) a) Spontaneous b) Induction ovulation c) IVF	56 (43.8) 36 (28.1) 36 (28.1)	60 (46.9) 36 (28.1) 32 (25.0)	0.830
GA at randomization, days (Mean ±SD) Range	126.1±7 112-140	124.5±11 112-140	0.168
Cervical length in cm (No., %) a) 2.5-4b) b) >4	86 (67.2) 42 (32.8)	91 (71.1) 37 (28.9)	0.499
Medical disorders complicating pregnancy a) None b) Mild preeclampsia c) Sever preeclampsia d) Gestational DM	89 (69.5) 12 (9.4) 7 (5.5) 20 (15.6)	90 (70.3) 17 (13.3) 5 (3.9) 16 (12.5)	0.649

Table (2): Comparison between studied groups according to gestational age at delivery

GA at delivery (wks)	Progesterone with aspirin group (n =117)	Progesterone with placebo group (n =112)	P-value
All Deliveries < 34 w (No., %)	**52 (44)**	**55 (49)**	**0.072**
All Deliveries ≥ 34 w (No., %)	**65 (56)**	**57 (51)**	**0.087**
Delivery < 28 w	1 (0.8)	2 (1.7)	0.561
Delivery from 28 to <32 w	12 (10.24)	13 (11.6)	0.833
Delivery from 32 to <34 w	39 (33.3)	40 (35.7)	0.62
Delivery from 34 to <37w	39 (33.3)	34 (30.3)	0.065
Delivery ≥ 37 w	26 (20.3)	23 (20.5)	0.074

Table (3): Secondary Maternal outcomes according to treatment

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n = 128)	P-value	Odds ratio (95% CI)
Admission for threatened PTB	47 (35.2%)	60 (46.9%)	0.057	0.614 (0.372-1.015)
Tocolytic therapy	47 (36.7%)	60 (46.9%)	0.099	0.658 (0.399 – 1.084)
Preterm rupture of membranes	6 (4.7%)	15 (11.7%)	0.044*	0.670 (0.139– 0.988)
Mode of delivery SVD CS	 71 (55.5%) 57 (44.5%)	 68 (53.1%) 60 (46.9%)	0.707	1.099 (0.672 -1.798)
Patients compliant to treatment	117 (91.4%)	112 (87.5%)	0.309	1.519 (0.676 – 3.416)
Patients discontinue treatment	11 (8.6%)	16 (12.5%)	0.309	0.658 (0.293 – 1.480)
Patients develop drug side effects	34 (26.6%)	36 (28.1)	0.779	0.924 (0.533 – 1.602)
Harm to mothers from intervention	0 (0)	0 (0)	---	---
Maternal infection	0 (0)	0 (0)	---	---
Maternal mortality	0 (0)	0 (0)	---	---

*Significant statistically

Table (4):Secondary fetal outcomes according to treatment

Variables	Progesterone with aspirin group (n =128)	Progesterone with placebo group (n = 128)	P-value	Odds ratio (95% CI)
Neonatal weight (gm) Mean ±SD Range	 2772.66±519 1100-3500	 2379.3±512.7 800-3500	<0.001*	0.988 (0.988 – 0.999)
Admission to NICU	17 (14.5%)	19 (16.9%)	0.095	0.435 (0.160-1.183)
Respiratory morbidity	5 (4.2%)	9 (7%)	0.05	0.255 (0.069 -0.938)
Gastrointestinal morbidity	6 (5.1%)	9 (8%)	0.046*	0.255 (0.069 -0.938)
Neonatal sepsis	7 (5.9%)	8 (7.1%)	0.08	0.283 (0.076 – 1.054)
Perinatal death	3 (2.5%)	8 (7.1%)	0.045*	0.255 (0.069-0.038
Harm to offspring from intervention	0 (0)	0 (0)	---	---

*statistically significant

Preconception Helicobacter pylori infection might adversely affect pregnancy outcome

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Impact statement

What is already known on this subject?
HP infections is significantly higher in diabetic patients than controls with high prevalence rate of symptoms among T2DM patients who were HP+ than those were HP-. However, there is no significant association between HP infection and glycemic control status in these patients.

What do the results of this study add?
HP+ infection was significantly (p=0.026) higher among diabetic women. Risk of GDM with significantly (p=0.033) higher incidence among HP+ with poor glycemic control. Diabetic HP+ women showed significantly higher HbA1c levels in comparison to diabetic HP- women both at booking time and at the 24th GW. There was significantly higher frequency of PE among DM than No DM women and among HP+ than HP- women. There was higher incidence of PTB among HP+ and diabetic women.

What are the implications of these findings for clinical practice and/or further research?
HP infection with or without DM increased the incidence of PE and PTB. HP infection also increased the incidence of GDM in non-diabetics and aggravates DM in diabetic women. Statistical analysis defined high at booking FBG, preconception HP infection and BMI as the significant predictors for pregnancy complications.

Abstract

Objectives: Evaluation of the effect of preconception H pylori (HP) infection on the incidence of preeclampsia (PE), gestational diabetes mellitus (GDM) and preterm birth (PTB) in diabetic and non-diabetic women.

Patients & Methods: 305 pregnant women were evaluated for body mass index (BMI), presence of diabetes mellitus (DM), and HP infection and estimation of at booking fasting (FBG) and postprandial blood glucose and glycated hemoglobin A1c (HbA1c) and blood pressure measures. Women were categorized in two groups: DM and No DM groups, and were subcategorized according to presence of positive blood for HP IgG as HP+ and

HP- subgroups and were followed for development of complications.

Results: 117 women had preconception DM and 188 women had no DM; and 132 women were HP+ and 173 were HP- with significantly (p=0.026) higher incidence of HP infection among diabetic women. Forty-two women of No DM group developed GDM with significantly (p=0.033) higher incidence among HP+. Thirty-seven diabetic women developed poor glycemic control and glucosuria with significantly (p=0.0165) higher incidence among HP+ women. Diabetic HP+ women showed significantly higher HbA1c levels in comparison to diabetic HP- women both at booking time and at the 24th GW. Thirty-six women developed PE with significantly higher frequency of PE among DM than No DM women and among HP+ than HP- women. Twenty women got PTB with significantly higher incidence among HP+ and diabetic women. Statistical analysis defined high at booking FBG, preconception HP infection and BMI as the significant predictors for pregnancy complications.

Conclusion: HP infection with or without DM increased the incidence of PE and PTB. HP infection also increased the incidence of GDM in non-diabetics and aggravates DM in diabetic women.

Key words: Pregnancy complications, Diabetes mellitus, H pylori infection, Preeclampsia, preterm birth.

Introduction

The spiral-shaped, numerous unipolar flagellated, urease-producing, gram-negative Helicobacter pylori (HP) bacterium causes chronic inflammatory response of the gastric mucosa brought on by gastric HP colonization modifies the physiology of the stomach and alters DNA methylation in the stomach mucosae, a process linked to gastric cancer [1],[2]. Furthermore, the synthesis of the enzymes glycosulfatase and phospholipases A2 and C damages the stomach mucosa and ultimately raises the pH of the stomach [3]. Tragically, 44.3% of people worldwide suffer from stomach infections caused by HP bacteria, which is one of the most prevalent gastric carcinogens [4].

Because of their compromised immune systems, changed physiologies, and increased susceptibility to infections, pregnant women represent a specific demographic that is particularly vulnerable to infections [5],[6]. Obesity before conception is linked to a number of unfavorable consequences for mother health, including an elevated risk of infection, which may indicate a disruption of the "immune clock" throughout pregnancy [7]. Preeclampsia and premature birth are two pregnancy-related problems that obesity and its related immunological disturbance can cause [8]. In addition, women whose pregnancies were complicated by preeclampsia and premature delivery are more likely to develop chronic renal disease and end-stage kidney disease in the future [9].

Consequently, there was a substantial correlation found between maternal difficulties, low birth weight and short gestational age fetuses, and gestational hypertension and preeclampsia [10]. Gestational diabetes mellitus (GDM) is a condition that is rapidly spreading throughout the world. It is thought to have serious both short- and long-term adverse impacts on both the mother and the fetus [11]. Deviation of maternal immune clock towards inflammatory direction with concomitant release of pro-inflammatory cytokines could be considered the crosslink between pregnancy-associated complication, obesity and maternal infection [12].

Hypothesis

This study suggests that preconception HP infection causes higher incidence of pregnancy-induced complications and this effect is magnified in pregnant diabetic women.

Objectives

Evaluation of the impact of preconception HP infection on maternal outcome concerning the incidence of preeclampsia, gestational diabetes mellitus and preterm labor in diabetic and non-diabetic women.

Design

Prospective comparative observational study.

Setting

Department of Obstetrics & Gynecology, Faculty of Medicine, Tanta university.

Patients & Methods

The current study intended to include women attending the antenatal care unit to assure of being pregnant through the period from Jan 2019. All women with chemically approved pregnancy underwent clinical evaluation and US determination of the pregnancy sac. Clinical evaluation included collection of demographic data including age, body weight and height for calculation of body mass index (BMI) according to the equation: BMI (kg/m2) =weight (kg)/height (m2). Full history concerning family history or current diabetes mellitus (DM), hypertension (HTN), renal or cardiac diseases, gastrointestinal disorders was taken. Obstetric history included number of gravidities, parity, offspring, and incidence of previous pregnancy-induced complications especially GDM, PE, preterm birth (PTB), having newborn with small-for-gestational age or macrosomia, premature rupture of membrane and modes of delivery for the previous pregnancies. History taking concerning previous HP infection, how it was diagnosed and what the outcome of received treatment, if any.

Clinical evaluation

1. Diagnosis of DM/GDM

- Glycemic state diagnosis: To diagnose glucose intolerance or frank diabetes, all women were required to fast for at least six hours before attending the clinic for the 75-gram oral glucose tolerance test (OGTT). This test involves measuring the 2-hour postprandial blood glucose (PPBG), estimating the fasting blood glucose (FBG), and giving a 75-gram oral glucose snack. To identify the women who had GDM, the test was re-tested at the 24-week mark in pregnancy (GW). The findings of the OGTT were used to diagnose DM/GDM. The results were analyzed in accordance with the guidelines provided by the international association of diabetes and pregnancy study groups, which were as follows: 2-h PPBG ≥153 mg/dl and FBG ≥92 mg/dl [(13)].

- Glycemic control state: To ensure blood glucose control, the amount of glycated hemoglobin (HbA1c) was measured at baseline and at the 24th GW. It was analyzed as per Charuruks et al.: A HbA1c of 4-6% suggests no diabetes, a range of 6–6.5% shows pre-diabetes or a goal of control, a range of 6.5–8% implies adequate diabetic control, and a value of >8% suggests an urgent requirement for intervention to bring the condition under control [(14)].

2. Diagnosis of PE

- The American Society of Hypertension [(15)] defines preeclampsia (PE) as the onset of prenatal hypertension in a pregnant woman who had been not hypertensive (NT), and it is linked to proteinuria measured as 1+ on a dipstick. According to the American College of Obstetricians and Gynecologists' guidelines, PE was classified as mild or severe based on blood pressure measurements taken during follow-up visits. Mild PE (MPE) was diagnosed when systemic symptoms were absent and SBP and DBP were less than 160 and 110 mmHg, respectively, along with proteinuria of less than 2+. If a voided random urine sample showed proteinuria >2+ and SBP of ≥160 mmHg and DBP of ≥110 mmHg, or if elevated blood pressure measurements were linked to systemic symptoms, then severe PE (SPE) was confirmed [(16)]. PE was classified as

having an early onset (EPE) if it was discovered before the 34th gestational week (GW) and a late onset (LPE) if it was discovered after the 34th gestational week [17, 18].

3. Diagnosis of HP

- The identification of anti-Helicobacter pylori IgG in a blood sample taken at the date of booking led to the diagnosis of HP. The serum samples were obtained in a clean Eppindorff tube and stored at -20oC for ELISA estimation of human anti-Helicobacter pylori IgG using an ELISA kit (catalogue no. ab108736, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique. The blood sample was placed in a plain tube, left to clot, and centrifuged at 1500×g for 15 minutes [19]. **This laboratory investigation was done by the authors after patient consent. Patients did not bear any expenses.**

Patients' categorization

Enrolled women were categorized according to presence DM, which is diagnosed at booking time, as DM and No DM groups. Then each group was re-categorized according to positivity of blood samples for anti-HP IgG as HP+ and HP-.

Study outcomes

1. The primary outcome is the incidence of pregnancy-induced complication; GDM for women of No DM group, aggravation of or loss of control of glycemic state in women of DM group, development of PE, or PTB.

2. The secondary outcome is the relation between the incidence of these complications and serum positivity for anti-HP IgG.

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers and percentages. Non-parametric data were analyzed using Chi-square test, parametric data of the same group were analyzed using paired t-test and between groups using One-way Anova test with Tukey HDS. Correlations between studied variables were performed using Pearson's correlation of parametric data. Regression analysis, Stepwise method, was used to determine the predictors for pregnancy complications. Statistical analysis was performed using SPSS software package, 2015. P value of <0.05 was considered significant.

Results

There were 327 women eligible for evaluation; 22 were excluded for not fulfilling the inclusion criteria and 305 women were enrolled in the study. The OGTT defined 117 women had preconception DM (DM group) and 188 women had no preconception DM (No DM group), (Fig.1). Diabetic women had significantly BMI than non-diabetic women, while other at enrolment data showed non-significant (p>0.05) differences between patients of both groups (Table 1). The anti-HP IgG testing defined 132 HP+ women (43.3%) and 173 HP- women (56.7%) with significantly (p=0.026) higher incidence of HP infection among diabetic (48.7% vs. 38.3%) than non-diabetic pregnant women (Fig. 1).

Table (1): Enrolment data of studied patients

Data		Group No DM (n=188)	Group DM (n=117)	P
Age (years)		28.2±2.8	27.6±3.3	0.102
BMI data	Weight (kg)	84.5±7.1	96.5±5.5	0.009
	Height (cm)	169.4±3	168.7±3.3	0.066
	BMI (kg/m^2)	29.5±2.5	30.4±2.5	0.001

Obstetric| history	Gravidity	Primigravida	69 (36.7%)	55 (47%)	0.075
		Multigravida	119 (63.3%)	62 (53%)	
	Number of previous labors	One	78 (65.5%)	43 (69.4%)	0.606
		Two	41 (34.5%)	19 (30.6%)	
	Number of living offspring	One	81 (68.1%)	47 (75.8%)	0.278
		Two	38 (31.9%)	15 (24.2%)	

Data are presented as mean, standard deviation, numbers, percentages; DM: Diabetes mellitus; BMI: Body mass index; P value indicates significance of variance between groups; $p>0.05$ indicates non-significant difference; $p<0.05$ indicates significant difference

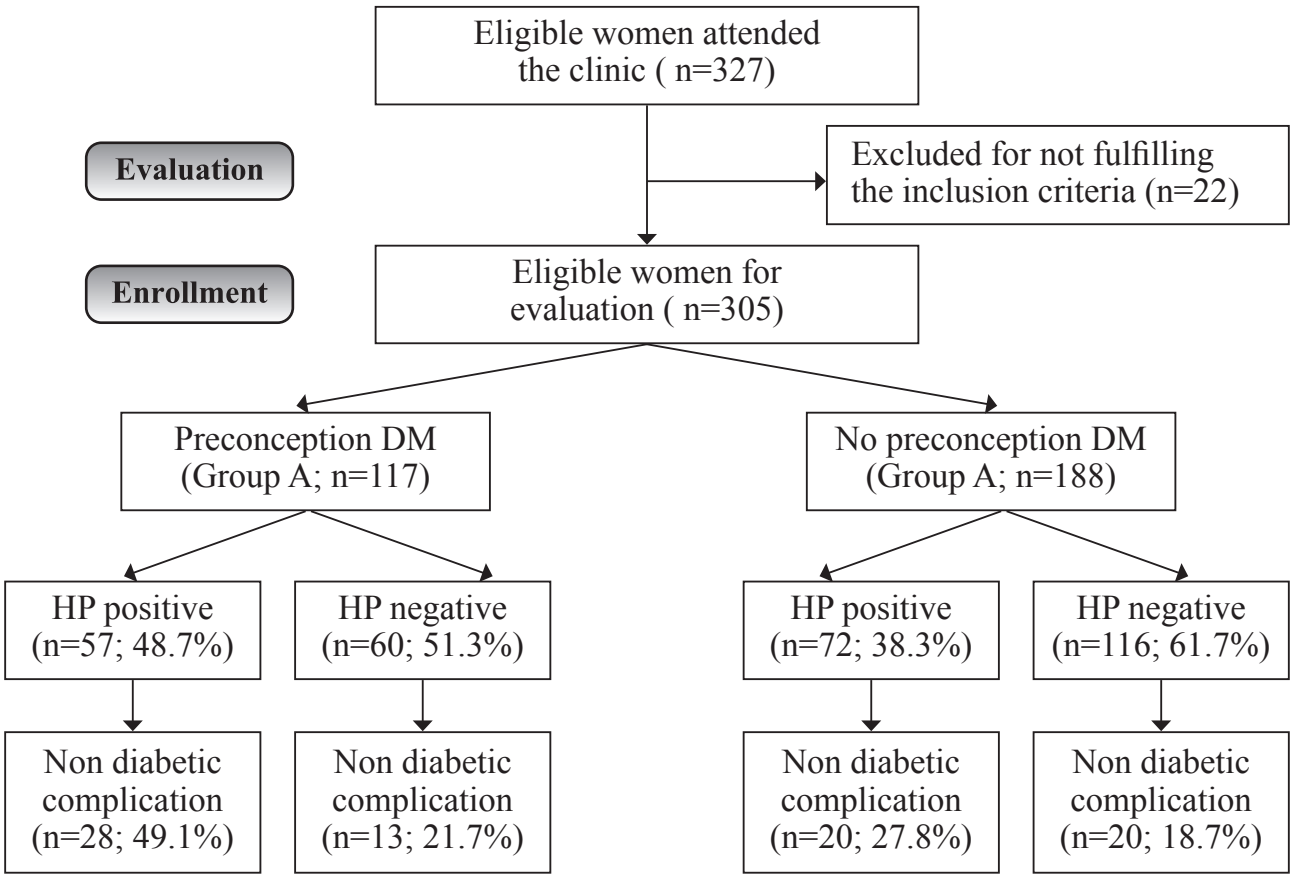

Fig. (1): Study Flow Chart

All women showed significantly higher glucose concentrations at the 24th GW in comparison to the concentrations measured at booking time with significantly higher HbA1c concentrations. The OGTT defined 42 women developed GDM among non-diabetic women at booking time, for an incidence of 22.3%. The incidence of GDM was significantly (p=0.033) higher among HP+ women (n=22; 30.6%) than in HP- women (n=20; 17.2).

Among DM women, 37 women developed aggravation of DM with poor glycemic control and glucosuria with significantly (p=0.0165) higher incidence among HP+ (n=25; 41.7%) than HP- women (n=12; 21.1%). Moreover, diabetic HP+ women had poorly controlled glycemic state with significantly higher HbA1c level in comparison to diabetic HP- women both at booking time (p=0.019) and at the 24th GW (p=0.0054). On contrary, in non-diabetic women concen-

tration of HbA1c was non-significantly higher (p=0.334) at booking time, but was significantly higher at the 24th GW (p=0.017) in HP+ than in HP- women (Table 2).

Table (2): Glycemic data of studied patients

Group Variable Time		Group No DM (n=188)			Group DM (n=117)		
		HP- (n=116)	HP+ (n=72)	P1	HP- (n=57)	HP+ (n=60)	P3
FBG (mg/dl)	Booking time	83.8±5.7	84±6.6	0.888	102±8.3	103.8±6.6	0.196
	24th GW	88±7.1	89.4±7.8	0.194	107.7±6.8	110.7±9.5	0.055
	P2	<0.0001	0.0001		0.0001	<0.0001	
2-hr PPBG	Booking time	97.2±7.5	102±12.7	0.0013	159.4±12.8	162±11.9	0.251
	24th GW	123.5±14.6	128.2±14.9	0.0337	170.7±6.8	175.1±15.7	0.105
	P2	<0.0001	<0.0001		<0.0001	<0.0001	
HbA1c	Booking time	4.36±0.33	4.3±0.39	0.334	6.3±0.6	6.5±0.3	0.019
	24th GW	5.63±1.16	6.05±1.2	0.017	7.15±0.91	7.65±1	0.0054
	P2	<0.0001	<0.0001		<0.0001	<0.0001	

Data are presented as mean, standard deviation; DM: Diabetes mellitus, HP: H pylori; FBG: Fasting blood glucose; PPBG: Postprandial blood glucose; GW: Gestational week; P1 value indicates significance of variance between HP+ and HP- women of either group; P2: indicates the significance of difference between concentrations estimated at booking time and the 24th GW; p>0.05 indicates non-significant difference; p<0.05 indicates significant difference

Pregnancy per se is a hypertensive condition as evidenced by the significantly higher mean SBP and DBP estimated during follow-up visits in comparison to measures obtained at booking time in all women with non-significantly (p>0.05) higher measures in HP+ women in comparison to HP- women. Moreover, during pregnancy course, 36 women developed PE for an incidence of 11.8%; 14 non-diabetic women (7.4%) and 22 diabetic women (18.8%) with significantly (p=0.0028) higher frequency of PE among diabetic patients. The incidence of PE was significantly (p=0.0007) higher among HP+ (n=25; 18.94%) than HP- (n=11; 6.35%). Among women of No DM group, the incidence of PE among HP+ women (n=9; 12.5%) was significantly (p=0.0376) higher in comparison to HP- women (n=5; 4.3%). Similarly, among women of DM group, the incidence of PE was significantly (p=0.0255) higher in HP+ women (n=16; 26.7%) than in HP- women (n=6; 10.5%). DM increased the risk of early PE by 1.5 folds and of severe PE by 4-fold, while HP infection increased the risk of early PE by 2.33 folds and of severe PE by 4-fold risk (Table 3).

Table (3): Blood pressure data of studied patients

Group Variable Time			Group No DM (n=188)			Group DM (n=117)		
			HP- (n=116)	HP+ (n=72)	P1	HP- (n=57)	HP+ (n=60)	P3
Incidence of PE	NT		111 (95.7%	63 (87.5%)	0.0376	51 (89.5%)	38 (73.3%)	0.0255
Time of diagnosis	PE	Total	5 (4.3%)	9 (12.5%)		6 (10.5%)	16 (26.7%)	
		Early	1 (20%)	3 (33.3%)		2 (33.3%)	4 (25%)	
		Late	4 (80%)	6 (66.7%)		4 (66.7%)	12 (75%)	
PE severity		Mild	5 (100%)	8 (88.9%)		5 (83.3%)	13 (81.2%)	
		severe	0	1 (11.1%)		1 (16.7%)	3 (18.8%)	
SBP (mmHg)	Booking time		112.6±5.3	113±4.8	0.631	114±5.9	115.8±7	0.137
	PE diagnosis		122.4±7.5	125.9±10.9	0.0113	125.6±12.7	131.8±16.6	0.024
	P2		<0.0001	<0.0001		<0.0001	<0.0001	
DBP (mmHg)	Booking time		74.5±5.5	75.6±4.9	0.165	76.5±6.5	76.8±5.3	0.789
	PE diagnosis		84±6.4	85.7±7.3	0.327	86.2±7	88.1±6.7	0.131
	P2		<0.0001	<0.0001		<0.0001	<0.0001	

Data are presented as numbers, percentages, mean, standard deviation; DM: Diabetes mellitus, HP: H pylori; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PE: Preeclampsia; P1 value indicates significance of variance between HP+ and HP- women of either group; P2: indicates the significance of difference between measures estimated at booking time and time of PE diagnosis; $p>0.05$ indicates non-significant difference; $p<0.05$ indicates significant difference.

Twenty women go preterm labor for an incidence of 6.55%, the incidence of preterm labor was significantly (p=0.0126) higher among HP+ (n=14; 10.6%) than HP- women (n=6; 3.5%), irrespective of their glycemic state and was significantly (p=0.0395) higher in diabetic (n=12; 10.25%) in comparison to non-diabetic women (n=8; 4.25%), irrespective of HP status.

The percentage of HbA1c as a measure for glycemic control showed positive significant correlations with preconception DM, HP infection and high BMI with positive significant correlation with at booking FBG. SBP measures at time of PE diagnosis showed positive significant correlation with preconception DM and at booking time FBG, irrespective of presence of DM. PTB showed positive significant correlations with at booking FBG and BMI (Table 4). Regression analysis "Stepwise method" to define at booking predictors of pregnancy-related complications showed that high at booking time FBG was a significant predictor for 24th GW HbA1c ($\beta=0.626$, $p<0.001$), SBP at time of PE diagnosis ($\beta=0.174$, $p=0.002$) and PTB ($\beta=0.128$, $p=0.025$). Preconception HP infection is a significant predictor for high 24th GW HbA1c ($\beta=0.107$, $p=0.017$) and at booking time high BMI is a significant predictor for PTB ($\beta=0.148$, $p=0.010$).

Table (4): Pearson's correlation regression analysis for at booking data and pregnancy outcomes

	24th GW HbA1c		SBP at time of PE diagnosis		PTB	
	"r"	p	"r"	P	"r"	p
DM	0.623	<0.001	0.205	<0.001	0.052	0.368
HP	0.138	0.016	0.040	0.487	0.108	0.060
BMI	0.177	0.002	0.015	0.789	0.168	0.003
Booking FBG	0.174	0.002	0.632	<0.001	0.151	0.008

Discussion

The prevalence of H pylori infection among the studied sample of pregnant women was found to be high and accounts for 43.3% of studied women, a figure that was coincided with that previously reported in literature [20-22]. H pylori infection was more prevalent among diabetic pregnant than non-diabetic women and incidence of GDM was higher among HP+ than HP- women with no history of preconception DM. on the other hand, HP+ diabetic pregnant women showed higher incidence of getting glucosuria with significantly higher concentration of HbA1c, a finding indicated progress of diabetes and lost glycemic.

According to Bener et al. [23], who also found a high prevalence rate of manifestations among patients with T2DM who were HP+ compared to HP-, HP infections were substantially more common in diabetic patients than in controls. Nevertheless, Dooki et al. [24] discovered no conclusive link between HP infection and T1DM, and infection had no bearing on the patients' state of glycemic control. Furthermore, a cross-sectional study by Mabeku et al. [25] found that the development of diabetes mellitus is favoured by high BMI and HP infection, whether they are present simultaneously or not. Subsequently, Haj et al. [26] found a correlation between HP infection and poorer glycemic control as well as elevated levels of total and LDL cholesterol. Li et al. [27] also reported that HP infection is highly prevalent in pregnant women with diabetes.

The obtained results and the previous literature pointed to an association between HP infection and T2DM which is mostly due to insulin resistance (IR). Multiple previous studies tried to explore the underlying mechanisms for this relation; Cani et al., [28] attributed this relation to the lipopolysaccharide which is derived from the outer membrane of gut Gram-negative bacteria and released into the circulation causing metabolic endotoxemia characterized by low-grade inflammation and IR with subsequent glucose intolerance and development of DM. Yet, Patro-Malysza et al. [29] found that inflammation brought on by HP infections and the release of inflammatory cytokines could interfere with the phosphorylation of the serine moiety of the insulin receptor, which is a physiological response that is time-controlled in insulin signaling. Wang and colleagues [30] also observed elevated hepatic TNF-α mRNA and protein levels in conjunction with serine residue phosphorylation of insulin receptor-1 (IRS-1), which was followed by a decrease in basal and insulin-stimulated tyrosine phosphorylation of IRS-1 and AKT proteins, as well as the formation of IR under stress.

The detected relation between HP infection and development of GDM in non-diabetics and the poor control of blood glucose and progression to glucosuria could be attributed to multiple variables especially obesity that was considered as the cornerstone of this dilemma, obesity induces altered signaling pathways that regulate gut permeability and

bacterial translocation to the host to promote the metabolic endotoxemia[31], which is hallmark of obesity, IR and DM, and other obesity-associated complications [32]. The present research found a positive considerable link between BMI measured at booking time and HP infection and blood glucose levels calculated during OGTT at the 24th GW, as well as considerably higher BMIs of diabetic women, supporting this theory. Obesity is more prevalent in diabetic patients[31]which stands with our findings, however age difference between groups (which was statistically non-significant)is essentially related to the sample of population enrolled in the study which is totally an incidental finding.

The current study detected significantly higher frequencies of pregnancy-induced complications in HP+ women especially those who had preconception DM. Similarly, Zhou & Wang [33] found HP infection is related with pregnancy-related diseases; PE, GDM hyperemesis gravidarium; pregnancy outcomes as premature delivery, abortion, and the health status of offspring. In addition, Tang et al. [34] found that pregnant women with positive HP infection had a significantly greater rate of PE, GDM, and fetal growth restriction than pregnant women without HP infection. They also decided that HP infection had a separate link with a number of unfavorable pregnancy outcomes. Furthermore, Li et al. [27] found that HP infection raises the risk of pregnancy-related illnesses, such as GDM and PE, as well as impaired fetal development among women with diabetes. According to Xia et al. [35] pregnancy-related HP infection is a significant risk factor for metabolic syndrome and influences the likelihood of a number of unfavorable pregnancy outcomes.

Regarding PE, the incidences of PE especially early-onset and severe PE are more frequent among HP+ women especially the diabetic ones. Similarly, Li et al. (27), Su et al., (36) and Ahmed et al. (37) found HP infection significantly increased the incidence of pregnancy-induced hypertension and PE. This relation between preconception HP infection and development of PE could be attributed to the effect of the released inflammatory cytokines secondary to HP on the placenta leading to PE development. In support of this attribution, experimental studies found HP membrane protein-1 to be a member of TNF-α-inducing protein gene family [38] and in HP-infected animal model, significantly higher levels of pro-inflammatory mediators, NF-κB expression and apoptotic cells are detected [39] and reduction of the production of virulence factors by sodium butyrate treatment inhibited the IκBα/NF-κB pathway and reduced the production of TNF-α and IL-6 [40].

Interestingly, the current study detected significantly higher incidence of preterm labor among HP+ women in comparison to HP- women. This result is consistent with that of Hollander et al. [20] and Huang et al. [40], who found a link between the likelihood of preterm birth and the level of antibodies against H. pylori in mother's blood. As a result, they identified HP colonization as a risk indicator for preterm birth and small-for-gestational age. Thereafter, Lee & Ahn [41] and Lee et al. [42] considered maternal HP infection as one of major determinants of preterm birth. The reported incidence of PTL could be the net outcome of the detected risk factors for PTL; namely DM, obesity, HP infection and preeclampsia and each of these variables has a relation with PTL if it was present separately, so the effect was amplified by this collection of risk factors. These data supported that previously reported concerning the relation and higher incidence of PTL with HP infection, obesity, PE and DM [43-45]. According to previous researches done in this area of knowledge , H. pylori infection is associated with increased IL-6 and TNF-α levels [46].As such , The H. Pylori-positive group had significantly higher odds, and risks of hyperemesis gravidarum, iron deficiency anemia, preeclampsia, gestational diabetes mellitus, and preterm deliveries compared to H. Pylori-negative controls [47] , which all are risk factors for pterterm labor.

In recent years, studies of H. pylori have become increasingly extensive, and the relationships between H. pylori and various extragastric diseases have gradually been reported, including pregnancy-related diseases, such as HG, PE, fetal growth restriction (FGR), premature delivery, abortion, and fetal malformation [48].

Conclusion

HP infection is prevalent among pregnant women especially women had preconception DM. HP infection with or without DM increased the incidence of preeclampsia and preterm labor. HP infection also increased the incidence of GDM in non-diabetics and aggravation of DM in diabetics. Screening of women seeking for pregnancy for HP infection and trial to eradicate the infection if present is mandatory to reduce pregnancy-associated complications especially in those with preconception diabetes.

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References

1. Weyermann M, Rothenbacher D, Brenner H. Acquisition of Helicobacter pylori infection in early childhood: independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol., 2009; 104(1):182-9.
2. Yoshida T, Kato J, Maekita T, Yamashita S, Enomoto S, Ando T, et al. Altered mucosal DNA methylation in parallel with highly active Helicobacter pylori-related gastritis. Gastric Cancer, 2013;16(4):488-97.
3. Slomiany B, Slomiany A. Helicobacter pylori-elicited induction in gastric mucosal matrix metalloproteinase-9 (MMP-9) release involves ERK-dependent cPLA2 activation and its recruitment to the membrane-localized Rac1/p38 complex. Inflammopharmacology,2016;24(2-3):87-95.
4. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther., 2018; 47(7):868-876.
5. Degu A, Nibret G, Gebrehana H, Getie A, Getnet B. Knowledge and Attitude Towards the Current Pandemic Corona Virus Disease and Associated Factors Among Pregnant Women Attending Antenatal Care in Debre Tabor General Hospital Northwest Ethiopia: An Institutional-Based Cross-Sectional Study. Int J Womens Health.,2021;13:61-71.
6. Sells C, Maes A, Fleddermann R, Otero-Bell E, Hartley R. Impact of the COVID-19 pandemic on rural obstetrics practices in New Mexico. J Family Med Prim Care , 2021;10(3):1336-1340.
7. Sureshchandra S, Marshall N, Mendoza N, Jankeel A, Zulu M, Messaoudi I et al. Functional and genomic adaptations of blood monocytes to pregravid obesity during pregnancy. iScience,2021 ;24(6):102690.
8. Beauchesne A, Cara K, Chen J, Yao Q, Penkert L, Yang W, Chung M: Effectiveness of multimodal nutrition interventions during pregnancy to achieve 2009 Institute of Medicine gestational weight gain guidelines: a systematic review and meta-analysis. Ann Med., 2021;53(1):1179-1197.

9. Goetz M, Müller M, Gutsfeld R, Dijkstra T, Hassdenteufel K, Brucker S, et al. An observational claims data analysis on the risk of maternal chronic kidney disease after preterm delivery and preeclampsia. Sci Rep., 2021;11(1):12596.
10. Jiang W, Mo M, Si S, Wu J, Pu L, Huang M, et al. Association of hypertensive disorders of pregnancy with infant growth in the first 36 months of life. Eur J Pediatr., 2021;14(3):12798 .
11. Byakwaga E, Sekikubo M, Nakimuli A. Level of and factors associated with awareness of gestational diabetes mellitus among pregnant women attending antenatal care at Kawempe National Referral Hospital: a cross sectional study. BMC Pregnancy Childbirth, 2021;21(1):467.
12. Romanowska-Próchnicka K, Felis-Giemza A, Olesińska M, Wojdasiewicz P, Paradowska-Gorycka A, Szukiewicz D et al. The Role of TNF-α and Anti-TNF-α Agents during Preconception, Pregnancy, and Breastfeeding. Int J Mol Sci., 2021;22(6):2922.
13. International association of diabetes and pregnancy study groups (IADPSG): recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33:676–682.
14. Charuruks N, Milintagas A, Watanaboonyoungcharoen P, Ariyaboonsiri C. Determination of reference intervals of HbA1C (DCCT/NGSP) and HbA1C (IFCC) in adults. J Med Assoc Thai., 2005;88(6):810-6
15. Lindheimer MD, Taler SJ, Cunningham FG; American Society of Hypertension: ASH position paper: hypertension in pregnancy. J Clin Hypertens (Greenwich). 2009; 11(4):214-25.
16. Bernhard KA, Siddiqui DS, Leonard KM, Chauhan SP. American college of obstetricians and gynecologists practice bulletins: ascertaining their citation, influence, and utilization. Am J Perinatol., 2014; 31(5):373-82.
17. Von Dadelszen P, Magee LA, Roberts JM. Sub classification of preeclampsia. Hypertens Pregnancy.,2003; 22:143–148.
18. Xu Z, Jin X, Cai W, Zhou M, Shao P, Yang Z, et al. Proteomics Analysis Reveals Abnormal Electron Transport and Excessive Oxidative Stress Cause Mitochondrial Dysfunction in Placental Tissues of Early-Onset Preeclampsia. Proteomics Clin Appl., 2018; 12(5):e1700165.
19. Koçak I, Akcan Y, Ustün C, Demirel C, Cengiz L, Yanik F et al. Helicobacter pylori seropositivity in patients with hyperemesis gravidarum. Int J Gynaecol Obstet., 1999;66(3):251-4.
20. Hollander W, Schalekamp-Timmermans S, Holster I, Jaddoe V, Hofman A, Moll H, Perez-Perez G, et al. Helicobacter pylori colonization and pregnancies complicated by preeclampsia, spontaneous prematurity, and small for gestational age birth. Helicobacter. 2017;22(2):10.1111/hel.12364.
21. Mustafa A, Bilal N, Abass A, Elhassan E, Adam I. The association between Helicobacter pylori seropositivity and low birthweight in a Sudanese maternity hospital. Int J Gynaecol Obstet., 2018;143(2):191-194.
22. Merino J, Araneda L, Lincoñir-Campos P, Parra C, Sáez K, García A et al. Dynamics of Helicobacter pylori infection in infants during the first six months of life. Enferm Infecc Microbiol Clin (Engl Ed)., 2019;37(2):109-111.
23. Bener A, Ağan A, Al-Hamaq A, Barisik C, Öztürk M, Ömer A et al. Prevalence of Helicobacter pylori Infection among Type 2 Diabetes Mellitus. Adv Biomed Res., 2020;9:27.
24. Dooki M, Aghamaleki M, Noushiravani N, Hosseini S, Moslemi L, Hajiahmadi M, et al. Helicobacter pylori infection

and type 1 diabetes mellitus in children. J Diabetes Metab Disord. 2020;19(1):243-247.

25. Mabeku L, Ngamga M, Leundji H. Helicobacter pylori infection, a risk factor for Type 2 diabetes mellitus: a hospital-based cross-sectional study among dyspeptic patients in Douala-Cameroon. Sci Rep. 2020;10(1):12141.
26. Haj S, Chodick G, Goren S, Na'amnih W, Shalev V, Muhsen K et al. Differences in glycated hemoglobin levels and cholesterol levels in individuals with diabetes according to Helicobacter pylori infection. Sci Rep. 2021;11(1):8416.
27. Li J, Fan M, Ma F, Zhang S, Li Q. The effects of Helicobacter pylori infection on pregnancy-related diseases and fetal development in diabetes in pregnancy. Ann Transl Med., 2021;9(8):686.
28. Cani P, Osto M, Geurts L, Everard A. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes.,2012;3(4):279-88.
29. Patro-Malysza J, Kimber-Trojnar Z, Skorzynska-Dziduszko K, Marciniak B, Darmochwal-Kolarz D, Bartosiewicz J, et al. The impact of substance P on the pathogenesis of insulin resistance leading to gestational diabetes. Curr Pharm Biotechnol., 2014;15(1):32-7.
30. Wang Y, Lin S, Chuang Y, Sheu W, Tung K, Chen C et al. Activation of hepatic inflammatory pathways by catecholamines is associated with hepatic insulin resistance in male ischemic stroke rats. Endocrinology, 2014;155(4):1235-46.
31. Shen J, Obin M, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Aspects Med., 2013;34(1):39-58.
32. Miele L, Giorgio V, Alberelli M, De Candia E, Gasbarrini A, Grieco A et al. Impact of Gut Microbiota on Obesity, Diabetes, and Cardiovascular Disease Risk. Curr Cardiol Rep., 2015;17(12):120.
33. Zhou B, Wang F. Research progress in relation of Helicobacter pylori infection with pregnancy-related diseases and adverse pregnancy outcomes. Zhong Nan Da Xue Xue Bao Yi Xue Ban., 2020;45(3):338-344.
34. Tang Y, Yang Y, Lv Z. Adverse pregnancy outcomes and Helicobacter pylori infection: A meta-analysis. Int J Clin Pract., 2021;e14588.
35. Xia B, Wang W, Lu Y, Chen C. Helicobacter pylori infection increases the risk of metabolic syndrome in pregnancy: a cohort study. Ann Transl Med., 2020;8(14):875.
36. Su Y, Xie X, Zhou Y, Lin H, Li Y, Feng N, et al. Association of induced abortion with hypertensive disorders of pregnancy risk among nulliparous women in China. A prospective cohort study. Sci Rep. 2020; 10(1):5128.
37. Ahmed M, Hassan M, Omer M, Rostami A, Rayis D, Adam I et al. Helicobacter pylori and Chlamydia trachomatis in Sudanese women with preeclampsia. J Matern Fetal Neonatal Med., 2020; 33(12):2023-2026.
38. Suganuma M, Watanabe T, Sueoka E, Lim I, Fujiki H. Role of TNF-α-Inducing Protein Secreted by Helicobacter pylori as a Tumor Promoter in Gastric Cancer and Emerging Preventive Strategies. Toxins (Basel), 2021;13(3):181.
39. Siriviriyakul P, Werawatganon D, Phetnoo N, Somanawat K, Chatsuwan T, Klaikeaw N, et al. Genistein attenuated gastric inflammation and apoptosis in Helicobacter pylori-induced gastropathy in rats. BMC Gastroenterol. 2020; 20(1):410.
40. Huang Y, Ding Y, Xu H, Shen C, Chen X, Li C et al. Effects of sodium butyrate supplementation on inflammation, gut microbiota, and short-chain fatty acids in

Helicobacter pylori-infected mice. Helicobacter. 2021;26(2):e12785.

41. Lee K, Ahn K. Application of Artificial Intelligence in Early Diagnosis of Spontaneous Preterm Labor and Birth. Diagnostics (Basel)., 2020;10(9):733.
42. Lee K, Song I, Kim E, Ahn K. Determinants of Spontaneous Preterm Labor and Birth Including Gastroesophageal Reflux Disease and Periodontitis. J Korean Med Sci. 2020;35(14):e105.
43. Kalafat E, Abiola A, Thilaganathan B, Bhide A, Khalil A et al. The Association Between Hypertension in Pregnancy and Preterm Birth with Fetal Growth Restriction in Singleton and Twin Pregnancy: Use of Twin Versus Singleton Charts. J Clin Med., 2020;9(8):2518.
44. Tang J, Chen R, Yu Y, Bao W, Tiemeier H, Rodney A et al. Associations of pre-pregnancy impaired fasting glucose and body mass index among pregnant women without pre-existing diabetes with offspring being large for gestational age and preterm birth: a cohort study in China. BMJ Open Diabetes Res Care.,2021;9(1):e001641.
45. Ghosh C, Wojtowycz M. Effect of gestational disorders on preterm birth, low birthweight, and NICU admission. Arch Gynecol Obstet., 2021;303(2):419-426.
46. Yu B, Xiang L, Peppelenbosch MP, Fuhler GM. Overlapping cytokines in H. pylori infection and gastric cancer: A tandem meta-analysis. Front Immunol. 2023;14:1125658. doi: 10.3389/fimmu.2023.1125658. PMID: 37006300; PMCID: PMC10050690.
47. Hagras, A , Abdelazim I, Abdou A. , Hussien, N , Samaha I , Elhamamy N et al. Preconception Helicobacter pylori infection might adversely affect pregnancy outcome.2023; 10.21203/rs.3.rs-2578935/v1.
48. Li J, Fan M, Ma F, Zhang S, Li Q. The effects of Helicobacter pylori infection on pregnancy-related diseases and fetal development in diabetes in pregnancy. Ann Transl Med. 2021;9(8):686. doi: 10.21037/atm-21-1209. PMID: 33987384; PMCID: PMC8106047.

Trans-cerebellar diameter/Abdominal Circumference (TCD/AC) ratio and femur length/mid-thigh circumference (FL/MTC) ratio in both normal and growth restricted fetuses

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Synopsis

Maternal DM is not associated with significant Doppler abnormalities. UA and MCA had low sensitivity in the prediction of adverse neonatal outcome.

Impact statement

What is already known on this subject?
Cerebellar diameter is the least affected parameter by intrauterine growth restriction; therefore TCD measurement is used in prediction of gestational age especially those with unknown last menstrual period. IUGR fetuses have decreased hepatic glycogen and subcutaneous fat stores which result in decreased AC, so AC is a sensitive parameter for prediction and diagnosis of fetal IUGR .

What do the results of this study add?
A significant correlation between TCD/AC ratio and EFW was found. Also, the correlation between the EFW with either MTC or FL/MTC ratio. However, the FL/MTC ratio was not significant.

What are the implications of these findings for clinical practice and/or further research?
TCD/AC and FL/MTC ratios are good, easy to perform and reliable predictors of IUGR.

Abstract

IUGR defined as fetal weight below the 10th percentile for gestational age. In Egypt it affects about 12.1% of cases with singleton pregnancy. Sonographic assessment of fetal growth for estimation of fetal weight (EFW) and diagnosis of intrauterine growth restriction (IUGR) is a common practice in obstetrics, providing valuable information for timing and planning the mode of delivery and management of labor.

Objectives: to compare TCD/AC ratio and FL/MTC in both normal and growth restricted fetuses in third trimesters.

Patient and methods : This prospective case-control study including 60 pregnant female are included in the

study (30 normal control group and 30 patients with IUGR fetus) all are subjected to US assessment.

Results: Significant difference in TCD/AC and FL/MTC between the 2 studied groups.

Conclusion: TCD/AC and FL/MTC ratios are good, easy to perform and reliable predictors of IUGR.

Keywords: IUGR, mid-thigh circumference, trans-cerebellar diameter.

Introduction

The time-dependent alterations to the fetal body measures that take place during pregnancy are referred to as fetal growth [(1)]. Fetal weight that is less than the 10th percentile for gestational age is the most widely used criterion for growth restriction. In Egypt, 12.1% of cases of singleton gestation are impacted by IUGR [(2),(3)]. A proportionately tiny fetus with symmetrical IUGR is typically the result of early damages like chromosomal anomalies, early teratogenic exposure that led to cellular hypotrophy/hypoplasia, or a decrease in overall number of cells [(4)].

Abdominal circumference decreases more than head circumference in asymmetric IUGR. This is believed to be caused by the redirection of blood from non-vital organs (liver, abdominal viscera) to critical organs (heart, brain) as a result of decreasing placental blood supply [(5)]. Because IUGR has a wide range of core explanations, a thorough history, physical, ultrasound fetal examination, and placental examination are necessary to determine the proper diagnosis, initiate appropriate treatment, and recognize fetuses susceptible for unfavorable outcomes [(6)].

In obstetrics, sonographic measurement of fetal development is routinely used to estimate fetal weight (EFW) and diagnose intrauterine growth restriction (IUGR). This method yields important data for managing labor and scheduling the mode of delivery. The majority of fetal weight calculation formulas were first developed in the first half of the 1980s, and they made use of various combinations of specified fetal biometric characteristics, including femur length (FL), head circumference (HC), abdominal circumference (AC), and biparietal diameter (BPD). Regrettably, considerable intra- and inter-observer variability compromises the reliability of EFW, and many of the current formulas can be inaccurate, particularly when fetal weight is at an extreme [(7)].

Since cerebellar diameter is the factor that is least impacted by intrauterine growth restriction, TCD estimation is used to forecast gestational age, particularly in cases where the last menstrual period is unreported. Fetal IUGR is diagnosed and predicted by AC, a sensitive parameter due to reduced hepatic glycogen and subcutaneous fat storage in IUGR fetuses [(8)].

The suggested technique in the current study for the determination of fetal soft tissue mass was a linear estimation of the tissue above the outer surface of the fetal femur, which serves as an intuitive and straightforward way to assess the volume of fat and muscular mass of the fetal thigh. This strategy was motivated by the fact that body weight can be calculated using using both of height as well as lean and fat mass [(9)].

The current research investigation compares the TCD/AC ratio and FL/MTC ratio in the third trimester of growth-restricted and normal fetuses to see if there is any relationship between them and estimated fetal weight (EFW). Assess the potential application of FL/MTC ratio and TCD/AC ratio in IUGR screening and diagnosis.

Patients and Methods

This is prospective case-control clinical study. It was approved by Tanta University hospital ethical committee. This study conducted on pregnant women admitted to Tanta University Hospital in period of May 2023

till December 2023.

Groups of the patients:

Sixty singleton pregnant females in 3rd trimester were enrolled in the study and divided to 2 groups:

Group I (control group) included 30 pregnant females with normally growing fetuses.

Group II: included 30 pregnant females with growth restricted fetuses. This growth restricted fetus is diagnosed by fetal weight below the 10th percentile for gestational age.

Any unexpected risk during the study will be cleared to the participants and the ethical committee.

Study Design:

All demographic data of enrolled patients were collected, including age, gestational age, gravidity, parity. Fetal wellbeing, and estimated fetal body weight EFBW are also assessed.

All the patients are subjected to US assessment of fetal parameter:
1- Biparietal diameter (BPD)
2- Head circumference (HC)
3- Abdominal circumference (AC)
4- Femur length (FL)
5-The transverse cerebellar diameter (TCD)
6- Mid-thigh circumference (MTC) (calipers are placed on the outer margin of the skin and the outer margin of the femur shaft)

Also the three ratio (HC) / (AC), TCD/AC and FL/MTC were calculated and compared in both groups.

The privacy of patients and confidentiality of data collected are guaranteed.

Statistical methods

The data were analyzed using SPSS version 26, USA. The tests used were mean, standard deviation and P value. P value less than 0.05 was considered significant.

Results

A total of 60 patients were recruited in this study. In the group 1

Only 30 pregnant female with normal fetal weight are included. In group 2 the pregnant female with diagnosed IUGR fetus are recruited.

The enrolled patients in both group were similar regarding baseline demographic characteristics including age, parity and gestational age at time of examination (Table 1). There is no difference in age gravidity and parity in both groups and P value were (0.099, 0.378, 0.365 respectively). The mean duration of pregnancy was the same whatever the method of calculation either by LMP or by US. But There was significant difference between both groups (P= 0.004) as regard to EFW.

Table (1): Demographic and clinical data:

	Group I		Group II		T	P
	range	Mean ± SD	range	Mean ± SD		
Age (in years	19-36	28.35± 4.524	22-33	27.17 ± 3.142	2.769	0.099 NS
Gravidity	1-3	1.70 ± 0.72	1-3	1.82 ± 0.75	0.782	0.378 NS
Parity	0-2	0.70 ± 0.70	0-2	0.82 ± 0.75	0.788	0.365 NS
Gest. age by LMP	26-40	31.9 ± 4.05	26-38	31.8 ± 4.27	0.082	0.998 NS
Gest. age by US	25-38.2	31.77 ± 3.7	21-38	30.01 ± 4.99	0.088	0.130 NS
EFBW (gram)	824-3740	1992.7±801.30	340-2457	1510.03±990.11	8.616	0.004*

LMP: last menstrual period US: ultrasound NS: non-significant EFBW: estimated fetal body weight

When the fetal parameters were compared between two groups as shown in Table 2 all the parameters of the fetuses in group 2 were less than that of group. There was significant difference between both groups as regard to BPD (P= 0.001), HC (P=0.002), AC (P=0.002) and MTC(P=0.001) with non-significant FL=(p=0.052),and TCD(P=0.061).

Table (2): ultrasonic measurements:

Measurements (in cm)	Group (I)			Group (I)			Significance
	Range	Mean	S.D.	Range	Mean	S.D.	
Biparietal diameter (BPD)	6.50-9.67	8.05	0.93	4.94-9.48	7.34	1.38	**T = 10.824 P =0.001***
Head circumference (HC)	23.88-33.5	29.11	3.18	18.03-32.95	26.67	5.21	**T = 9.556 P =0.002***
Abdominal circumference(AC)	21.52-35.95	27.72	4.03	13.37-35.03	24.77	6.32	**T = 10.540 P = 0.002***
Femur length (FL)	4.44-7.50	6.06	0.91	3.60-7.44	5.92	1.23	**T = 10.512 P =0.052**
Transcerebellar diameter (TCD)	3.08-5.26	4.01	0.72	1.87-4.90	3.966	0.883	**T = 13.540 P = 0.061**
Mid-thigh circumference (MTC)	**8.49-16.52**	**11.96**	**2.26**	**5.11-13.02**	**9.13**	**2.45**	**T = 43.164 P < 0.001***

Table 3 shows that when the ration were estimated and compared in both groups all the three ratios show the same significant difference between both groups. The mean HC/AC was 1.048 in group 1and 1.099 in group 2(P=0.004). **As for TCD/AC the mean was 0.142, 0.151 respectively with P =0.023* (statistically significant). As such, Femur length to mid-thigh circumference ratio(FL/MTC) shows mean 0.515± 0.074 in group 1 0.632 ±0.224in group 2 with P < 0.001*(statistically significant).**

Table (3): HC/AC, TCD/AC, FL/MTC ratios:

Measurements	Group (I)			Group (I)			Significance
	Range	Mean	S.D.	Range	Mean	S.D.	
HC/AC	0.93-1.13	1.048	0.059	0.84-1.43	1.099	0.117	**T = 8.812 P = 0.004***
TCD/AC	0.12-0.16	0.142	0.012	0.14-0.18	0.151	0.001	**T = 3.570 P =0.023***
Femur length to mid-thigh circumference ratio (FL/MTC)	**0.40-0.70**	**0.515**	**0.074**	**0.32-1.40**	**0.632**	**0.224**	**T = 14.747 P < 0.001***

On studying table 4, the correlation between TCD/AC ratio and EFW was found. Also, the correlation between the EFW with either MTC or FL/MTC ratio. The MTC showed significant correlation but the ratio was not significant.

Table (4): correlation study:

Correlation between EFW with:	Group (I)	Group (II)
TCD/AC ratio	**R= 0.746** **P= 0.001***	R= 0.785 P= 0,001*
Thigh circumference	**R= 0.732** **P= 0.001***	R= 0.751 P= 0.001*
FL/MTC ratio	**R= 0.144** **P= 0.079^{NS}**	R= 0.239 P= 0.088^{NS}

Discussion

Intrauterine growth restriction (IUGR) has been a prevalent and intricate obstetric concern. It is believed that between 10% and 15% of pregnant women have IUGR. As opposed to 8.4 for screened/detected SGA (10), the perinatal rate for unscreened/undetected SGA is 21.3 per 1,000 live births. To reduce neonatal mortality, it is thus imperative to recognize these fetuses, initiate early antenatal surveillance, and promptly deploy obstetric procedures. It has been shown that IUGR babies are more likely to experience negative short- and long-term impacts than SGA children.(11)

Asphyxia or a reduction in the flow of utero-placental blood are common causes of IUGR. The heart, brain, and adrenal glands in the center get the majority of blood flow (7). A study found that the redistribution of cardiac output during acute hypoxia maintained steady cerebral blood flow. Since IUGR has less of an impact on cerebellar growth in human beings, TCD measurement is mostly useful in estimating gestational age. Reduced AC is the result of decreased hepatic glycogen and subcutaneous fat reserves in IUGR fetuses. So far, the AC has shown sensitivity in predicting IUGR in fetuses. As far as biometric parameters go, the TCD/AC ratio has shown to be the least impacted and could be a sensitive technique to identify asymmetric IUGR at any gestational age (12).

The principal of this study is that trans-cerebellar diameter (TCD) is the factor that is least impacted by intrauterine growth restriction . In case if the pregnant patient is unsure of her LMP , we can use TCD to calculate the gestational age regardless of the fetal weight for age . In our study , there was no significant difference between appropriate for GA and SGA regarding TCD . We concluded that only TCD and FL was not different with EFW affection , thus more accurate for their specific gestational age. Conversely , AC is the most affected parameter in cases of FGR , A TCD/AC ratio will be affected (increased TCD/AC ratio) in all cases of FGR. This ratio may be used to confirm a diagnosis of FGR. And also there is a strong significant difference between MTC in normal fetuses compared to IUGR fetuses. The standard morphometric biometry of the fetus (HC, AC, FL, etc.) was also evaluated in relation to fetal growth.

As for TCD/AC the mean was 0.142, 0.151 respectively with P =0.023 (statistically significant). As such, Femur length to mid-thigh circumference ratio (FL/MTC) shows mean 0.515± 0.074 in group 1 0.632 ±0.224in group 2 with $P < 0.001$ which was also statistically significant.

In coincidence with our study, and according to Lees et al., the sensitivity of the TCD/AC ratio in predicting IUGR was only 71% in symmetrical IUGR but as high as 98% in asymmetrical IUGR. The theory that human cerebellar growth is comparatively refractory to prolonged low oxygen levels as a consequence of the brain sparing effect is supported by the fact that TCD is only slightly reduced in prenatal growth restriction. The optimal TCD/AC ratio threshold value for IUGR prediction was 13.75%, resulting in

100%, 63.33%, 73.17%, and 100% for sensitivity, specificity, positive predictive value, and negative predictive value, respectively (13).

The TCD/AC ratio and EFW showed a positive association in our investigation. According to Chawan et al., the mean TCD/AC ratio was substantially higher in the IUGR newborns than in the control group, and the TCD/AC ratio was aberrant in 16 out of 20 (80%) of the IUGR infants (10).

Our research demonstrates a statistically significant difference in MTC between IUGR and normal fetuses. The basis for this assessment stems from the need to obtain an accurate estimation of the fetal thigh's lean and fat mass in order to develop a unique formula for EFW. Furthermore The current study's objective was to assess the relationship between birth weight in normal and IUGR cases and this sonographic ratio (FL/MTC) metric.

Our opinion was supported by the findings of Scioscia et al., who demonstrated the potential of the linear measurement of MTC as a useful parameter for the sonographic evaluation of fetal growth and EFW. There were 388 singleton pregnancies in this study. They evaluated the accuracy of the mid-thigh soft-tissue density measurement (11). Additionally, as has been demonstrated by a number of studies, including those conducted by Brown et al., the use of subcutaneous fat tissue indicators (including MTC) in the future may offer a chance to identify and gauge the effects of various innovative therapies, such as the use of maternal amino acid infusions on the growth-restricted fetus (12,13).

This study had limitations. Despite we adopted the standard definition of SGA, the wide gestational age range (26-40 weeks) and the subsequent age-specific EFW the mean EFW in the normal group looked smaller (1992.7±801.30) but the range was (842-3740). We should have standardized a narrower gestational age range for proper comparison and analysis. However, multiple comparisons were done to confirm our results and to exclude other measures that may have the same impact on results as TCD & FL.

Conclusion

According to our research, MTC is a useful new metric for estimating birth weight and assessing fetal growth sonographically. This measurement is highly reproducible and simple to perform. Additionally, the TCD/AC and FL/MTC ratios are accurate, simple to use, and dependable indicators of IUGR.

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Conflicts of interest: Authors declared no conflicts of interest.

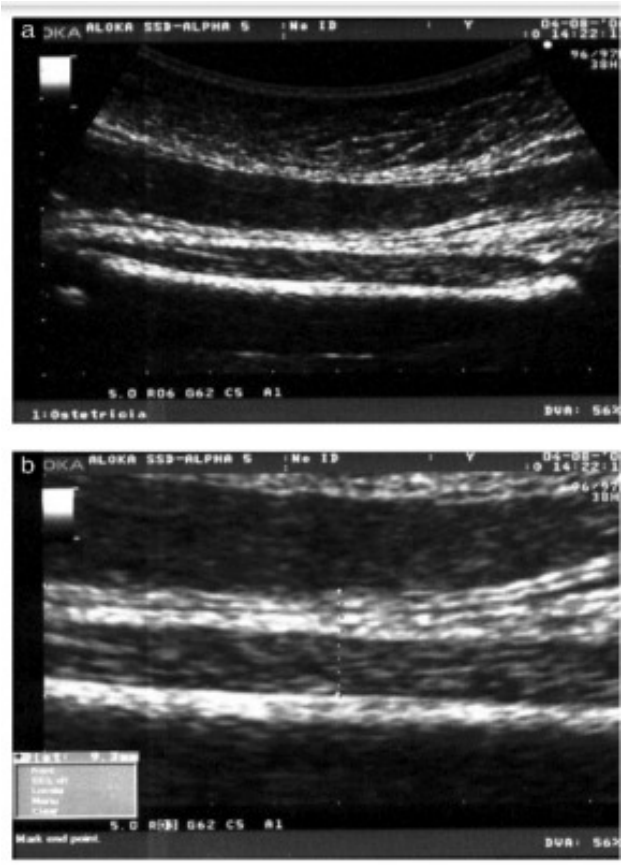
References

1. S. J. Gordijn, I. M. Beune, B. Thilaganathan et al., "Consensus definition of fetal growth restriction: a Delphi procedure," Ultrasound in Obstetrics & Gynecology, vol. 48, no. 3, 2016: 333–339.
2. Groom KM, Poppe KK, North RA, McCowan LM. Small-for-gestational-age infants classified by customized or population birthweight centiles: impact of gestational age at delivery. Am J Obstet Gynecol., 2017; 197(3):239. 1-5.
3. Grivell RM, Wong L, Bhatia V. Regimens of fetal surveillance for impaired fetal growth. Cochrane Database Syst Rev. , 2009;113.
4. Thakkar D, Aladangady N. Appropriately grown baby with multiple congenital abnormalities: A Case Report. Medscape J Med., 2008; 10(9):210.
5. American College of Obstetricians and Gynecologists ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol., 2013;121:1122–1133.
6. DeCherney AH, Nathan L. Current Obstetrics and Gynecologic diagnosis and

treatment. Pregnancy at risk. 9th edition, by Mc Graw Hill, USA. 2003; 461-8.

7. Kurmanavicius J, Burkhardt T, Wisser J, Huch R. Ultrasonographic fetal weight estimation: accuracy of formulas and accuracy of examiners by birth weight from 500 to 5000 g. J Perinat Med., 2004;32:155-61.
8. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol., 2007; 109:253–61.
9. Lees SC, Moldenhauer J, Hassan SS, Wolfe HM, Berry SM. Relationship between the sonographic pattern of intrauterine growth restriction and acid-base status at the time of cordocentesis. Arch Gynecol Obstet., 2001; 264:191-93.
10. Chauhan SP, West DJ, Scardo JA, Boyd JM, Joiner J, Hendrix NW et al. Antepartum detection of macrosomic fetus: clinical versus sonographic, including soft-tissue measurements. Obstet Gynecol., 2000;95:639-42.
11. Scioscia M, Scioscia F, Vimercati A, Caradonna F, Nardelli C, Pinto LR, et al. Estimation of fetal weight by measurement of fetal thigh soft-tissue thickness in the late third trimester. Ultrasound Obstet Gynecol., 2008;31:314-20.
12. Brown LD, Green AS, Limesand SW, Rozance PJ. Maternal amino acid supplementation for intrauterine growth restriction. Front Biosci., 2011;3:428-44.
13. Brown LD, Rozance PJ, Thorn SR, Friedman JE, Hay WW. Acute supplementation of amino acids increases net protein accretion in IUGR fetal sheep. J Physiol Endocrinol Metab., 2012;303:352-64.

comparisons were done to confirm our results STT was measured linearlyin the standard longitudinal section used for FLmeasurement5,6(Figure 1): after the appropriate sectionwas obtained, the image was frozen on the screen and thenmagnified. STT was then measured from the outer marginof the skin to the outer margin of the femur shaft, with thefemur lying parallel to the transducer. The measurementwas taken in the middle third of the fetal thigh, providingthat the greater and the lesser trochanters were turnedupwards. This section ensured the correct view of thelateral side of the femur (vastus lateralis, which is thelargest part of the quadriceps femoris). In each case, threesatisfactory images from different frozen images weremeasured (in mm to one decimal place) and the meanvalue was recorded.



Assessment of Different Neoplasias in the Adnexa Model Versus Risk of Malignancy Index as a Tool for Predicting Ovarian Malignancy in Postmenopausal Ovarian Cysts.

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Abstract

Background: Ovarian cancer is the most lethal gynecologic malignancy and every attempt should be made to develop screening programs to detect it at its early stages in order to improve survival rate. Using the ADNEX model in screening for ovarian cancer will help in triaging patients with adnexal masses before undergoing surgery which will help in optimizing outcomes particularly for those with ovarian malignancy.

Patients & methods: This was a prospective study which included fifty postmenopausal patients with adnexal mass. All the included patients underwent ultrasound assessment of the adnexal mass and measurement of CA 125 level. Then, the data were collected to calculate the RMI, and integrated to IOTA ADNEX calculator. The primary outcome was determining the predictive accuracy of both RMI and ADNEX model for differentiating between benign and malignant ovarian tumors by setting both against the gold standard histopathology.

Results: Out of the included 50 patients, 56% had benign ovarian lesions, 12% had borderline ovarian tumors, and 24% had malignant ovarian tumors. The Area under the receiver operating characteristic curve (AUC) for the RMI was 0.799 and with cutoff value of 115, the sensitivity was 81.8%, the specificity was 60.7% while the AUC was 0.864 for the ADNEX model and at 10% cutoff, the sensitivity was 91.1% and the specificity was 65%. Performance of the ADNEX for the five tumor types was highest when benign histopathology was compared as stage □ - □ malignant cases with AUC of 0.823.

Conclusion: ADNEX model is more sensitive than RMI for differentiating between benign and malignant tumors and it can be used as screening test. However, the application of ADNEX model needs significant experience in ultrasound evaluation of adnexal masses before it can be an integral part in the screening pathway of ovarian malignancy in postmenopausal patients with adnexal masses.

Clinicaltrials.gov ID: NCT05755841 – Data of registration: 3/30/2024 "retrospectively registered".

Keywords: ADNEX model – Risk of malignancy index - Ovarian cancer – Postmenopausal ovarian cysts.

Introduction

Ovarian cancer (OC) is the third most common gynecological malignancy worldwide and is associated with the highest mortality rate. OC has an incidence of 11.7 - 12.1 per 100,000 in the USA and Europe, with slightly lower rates of disease in Asia and the Middle East. About 60% of patients are diagnosed at an advanced stage which contributes to the high mortality rate (1). Stage of ovarian cancer is the most important element influencing prognosis and searching for a tool to detect the disease at an early stage is of paramount importance. At the time being, there is no effective screening strategy for ovarian malignancy (2). In 1990, Jacobs et al. developed a scoring system known as the risk of malignancy index 1 (RMI □) to stratify ovarian masses into benign and malignant before intervention (3). RMI is a combined parameter that is simple, specific, and highly sensitive for the evaluation of adnexal masses. It is a product of ultrasound findings (U), the menopausal status (M), and serum CA-125 levels (RMI = U X M XCA-125). Tingulstad et al., modified the RMI □ to the RMI □ (4) and again to RMI □ (5) with the last modification named RMI □ made by Yamamoto et al., by adding the size of the tumor to the equation (6). A systematic review of diagnostic studies concluded that the RMI I was the most effective for women with suspected ovarian malignancy (7).

Management of ovarian malignancies and borderline ovarian tumors in specialized oncology centers by experienced gyne-oncologists has a favorable impact on prognosis. Different diagnostic models have been developed to help in triaging ovarian masses and predicting the probability of malignancy and based on this prediction, a treatment plan can be implemented (8). The Assessment of Different NEoplasias in the adenXa (ADNEX) model is a model which has been developed by the International Ovarian Tumor Analysis Group (IOTA) that includes a detailed description of the adnexal mass. The model includes six ultrasound parameters and three clinical variables and distinguishes the mass into five subtypes; benign, borderline, stage □ OC, stage □ - □ OC, and metastatic deposits in the ovary (9).

This study aims to determine the diagnostic performance of the ADNEX model in differentiating between benign and malignant ovarian tumors by testing its accuracy against the gold-standard histopathology.

Patients and Methods

This was a prospective diagnostic test accuracy study that was carried out during the period from January 2022 to January 2023 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University. Before the initiation of the study, approval of the Ethical Committee of the Faculty of Medicine, Ain Shams University was obtained (MS 585 /2020, FWA 000017585). The sample size was calculated using the PASS program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study showed that the sensitivity of ADNEX was 96% (2). Data from the RCOG guide showed that the sensitivity of RMI was 78% (10). Calculation according to these values produced a minimal sample size of 50 cases. The study participants were 50 postmenopausal patients who presented to the general gynecology or gynecological oncology outpatient clinic with adnexal mass.

All the included patients were postmenopausal; postmenopausal status was defined as having ≥ 1 year of amenorrhea without using any contraceptive method in women ≥ 45 years while for women < 45 years, two consecutive FSH samples 1 month apart with levels ≥ 30 IU/L were required to confirm menopause. Patients with the accidental discovery of ovarian mass during surgery for other reasons

and patients with known ovarian cancer who were scheduled for interval debulking after neoadjuvant chemotherapy were excluded from the study. Moreover, asymptomatic patients with ovarian cysts with the following criteria; simple, less than 5cm, unilocular, unilateral, and clear were also excluded from the study.

Informed consent was taken from study participants before enrollment and after a thorough explanation of the purpose of the study. After history taking and physical examination to confirm that the patient meets the inclusion / exclusion criteria, both RMI and ADNEX model were evaluated.

The **RMI** is measured as follows; **Menopausal status** (score is 3 as all patients were postmenopausal **X Ultrasound score** which is based on assessment of 5 features and with the presence of one feature, the score is 1 while if more than one feature is present, the score is 3; the five ultrasound features are the presence of solid components, multilocularity, bilaterality, ascites, and metastases **X CA – 125 level**. The **ADNEX** model includes nine parameters; Age, CA-125 level, Oncology center (yes/no), and 6 ultrasound features which are the maximal diameter of the lesion, maximal diameter of the largest solid part, more than 10 locules (yes/no), number of papillary projections (0/1/2/3/more than 3), acoustic shadow, and ascites. All data were entered and calculation of the risk of malignancy was done through the ADNEX model calculator available at the website: **iotagroup.org**. All ultrasound evaluations were performed by the same specialist who had more than 10 years of experience in ultrasound evaluation of adnexal masses.

The primary outcome of the study was to assess the predictive accuracy of both the RMI and ADNEX model for differentiating between benign and malignant ovarian tumors by setting both against the gold standard which is histopathology.

Regarding the statistical analysis, Data were analyzed using the Statistical Package for Social Sciences (SPSS version 25). Descriptive analyses were performed to obtain the means, median, standard errors (SE) or SD, IQR, and frequencies. Bivariate analyses were performed using an independent samples t-test and ANOVA test. ROC curves were constructed and the Area under the receiver operator characteristic curves (AUC) with binomial exact 95% confidence intervals were calculated between benign ovarian tumors and malignant ones. The diagnostic performance of the models was also expressed as AUCs. Regarding the comparison between the ADNEX and RMI diagnostic performance AUC, sensitivity, specificity, and positive and negative likelihood ratios were calculated, and MedCalc Software Ltd. Comparison of AUC of independent ROC curves was used to calculate the difference between two AUCs.

Results

A total of 76 patients were recruited. Twenty-six patients were excluded due to the following: 18 patients didn't meet our inclusion criteria; 6 patients had missing data; and 2 patients underwent the operation in another hospital. Fifty patients had their data analyzed.

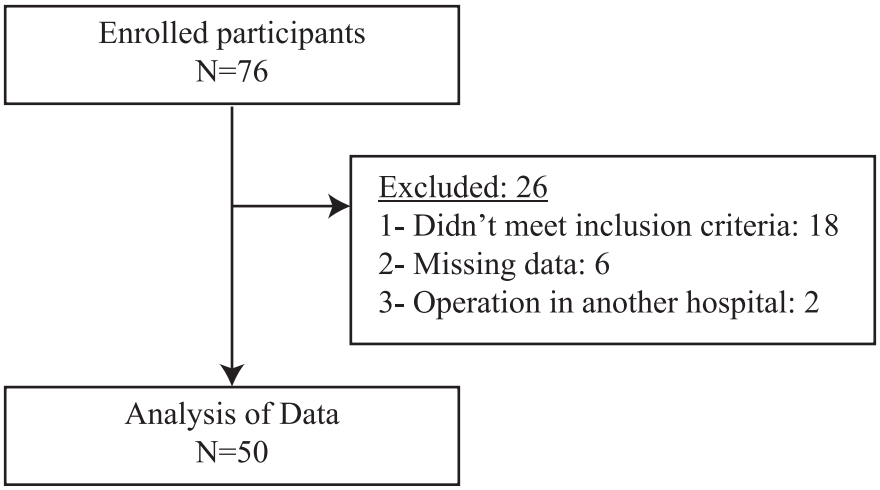

Figure 1: Flow chart of study participants

The sociodemographic data and the relevant data from history are shown in table 1. The presence of each component of the RMI in the study participants is shown in table 2 while table 3 represents the prevalence of each component of the ADNEX model in the study population.

Table 4 describes the different pathologic findings among the study cohort; Among the studied patients; 28 patients (56%) had benign pathology, 16 patients (32%) had malignant pathology, and the histopathologic examination of the specimens of the remaining 12% revealed borderline ovarian tumors. Among the patients with malignant ovarian neoplasms, 11 patients (68.75%) were stage □ - □, 4 patients (25%) had metastatic ovarian deposits while only 1 patient (6.25%) had stage □ ovarian cancer. Among the patients with benign lesions, the two predominant pathologies were serous and mucinous cystadenomas with both representing about 42.8% (21.4% each) while high grade papillary serous carcinoma was the predominant histopathology in patients with malignant OC (63.3%).

Table 5 compares the RMI values among the five histopathologic results with the values being significantly higher in patients with stage □ - □ OC. **Table 6** correlates between the sociodemographic data and the histopathologic subtypes with no significant association between any sociodemographic data and a particular subtype. **Table 7** showed that both ascites and CA-125 level are significantly higher among patients with stage □ - □ OC while the presence of 0-10 locules is significantly associated with benign pathology, there was no significant difference between the histopathologic subtypes regarding the other components of the ADNEX model.

Table 8 shows the AUC set to distinguish adnexal mass as benign or malignant for both ADNEX model and RMI (0.864 and 0.799 respectively). Sensitivity, specificity, positive likehood ratio, and negative likehood ratio for both screening models are shown in the same table; the best cutoff value obtained by this study was 10% for the ADNEX model and 115 for the RMI.

Table 9 shows the AUC when the ADNEX model is used for discrimination the type of the tumor among the five histopathologic subtypes. The highest AUC is 0.864 when the model was used to discriminate between benign and malignant cases and the lowest AUC is 0.722 when the model was used to discriminate between benign and borderline ovarian tumors.

Table 1: Sociodemographic data for the studied group (N=50)

Variable		
Age	Mean (SD)	59(6)
	Median (IQR)	59(56-61)
Parity	Mean (SD)	4 (2)
	Median (IQR)	3(2-5)
N (%)		
Education	Illiterate	3 (6)
	Primary	3(6)
	Secondary	5(10)
	Post -secondary	39(78)
PH of cancer	No	49(98)
	Yes	1(2)
FH of cancer	No	42(84)
	Yes	8(16)
	Breast	1(12.5)
	Endometrium	3(37.5)
	Ovary	1(12.5)
	Others	3(37.5)
Degree of relativity	First	6(75)
	Second	2(25)
HRT	No	50(100)
Infertility	No	42 (84)
	Yes	8 (16)
	Primary	5(10)
	Secondary	3(6)
Duration	Mean (SD)	8(2)
	Median (IQR)	9 (6-10)
Treatment	No treatment	3(37.5)
	Induction of ovulation	4(50)
	IVF	3(37.5)

Table 2: Ultrasound components of the RMI among the studied group:

		N (%)
Solid areas	No	25 (50)
	yes	25(50)
Bilaterality	No	38(76)
	yes	12(24)
Multilocularity	No	26(52)
	yes	24(48)
Ascitis	No	41(82)
	yes	9(18)
Metastasis	No	48(96)
	yes	2(4)
RMI value **Mean(SD)** **Min-Max**	**1557.6 (2988.6)** **149 (62- 1431)**	

Table 3: Components of the ADNEX model among the studied group

Age	Mean (SD)	59 (6)
	Median (IQR)	59(56-61)
Max. diameter of lesion(mm)	Mean (SD)	138(67)
	Median (IQR)	130(83-180)
Max. diameter of largest solid part (mm)	Mean (SD)	29(40)
	Median (IQR)	0 (0-39)
CA125	Mean (SD)	216.48(390.1)
	Median (IQR)	44.70 (17.9- 217.5)
	N (%)	
Oncology Center	Yes	50 (100)
Locules	No	1 (2)
	0-10	38 (76)
	>10	11 (22)
No. of papillary projections	0	33 (66)
	1	5(10)
	2	5(10)
	3	4(8)
	>3	3(6)
Acoustic shadow	No	36(72)
	Yes	14(28)
Ascites	No	36 (72)
	Yes	14(28)

Table 4: Pathological findings among the studied group

		N (%)
Pathology (n=50)	**Benign**	**28 (56)**
	Serous cystadenoma	6 (21.4)
	Mucinous cystadenoma	6 (21.4)
	Mature cystic teratoma	3 (10.7)
	Serous cystadenofibroma	3 (10.7)
	Fibroma	5 (17.8)
	Thecoma	1 (3.5)
	Paraovarian simple cyst	2 (7.1)
	Tubo-ovarian abscess	1 (3.5)
	Endometriotic cyst	1 (3.5)
	Borderline	**6 (12)**
	Mucinous	4 (66.7)
	Clear	1 (16.7)
	Serous	1 (16.7)
	Malignant stage I (Mucinous cystadenocarcinoma)	**1(2)**
	Malignant Stages II- IV	**11 (22)**
	HGSC	7 (63.6)
	Low grade serous carcinoma	1 (9.09)
	Endometrioid adenocarcinoma	3 (27.2)
	Metastatic	**4 (8)**
	Breast	1 (25)
	Appendix	1 (25)
	GIT	1 (25)
	Uterus	1 (25)

HGSC: High grade papillary serous carcinoma

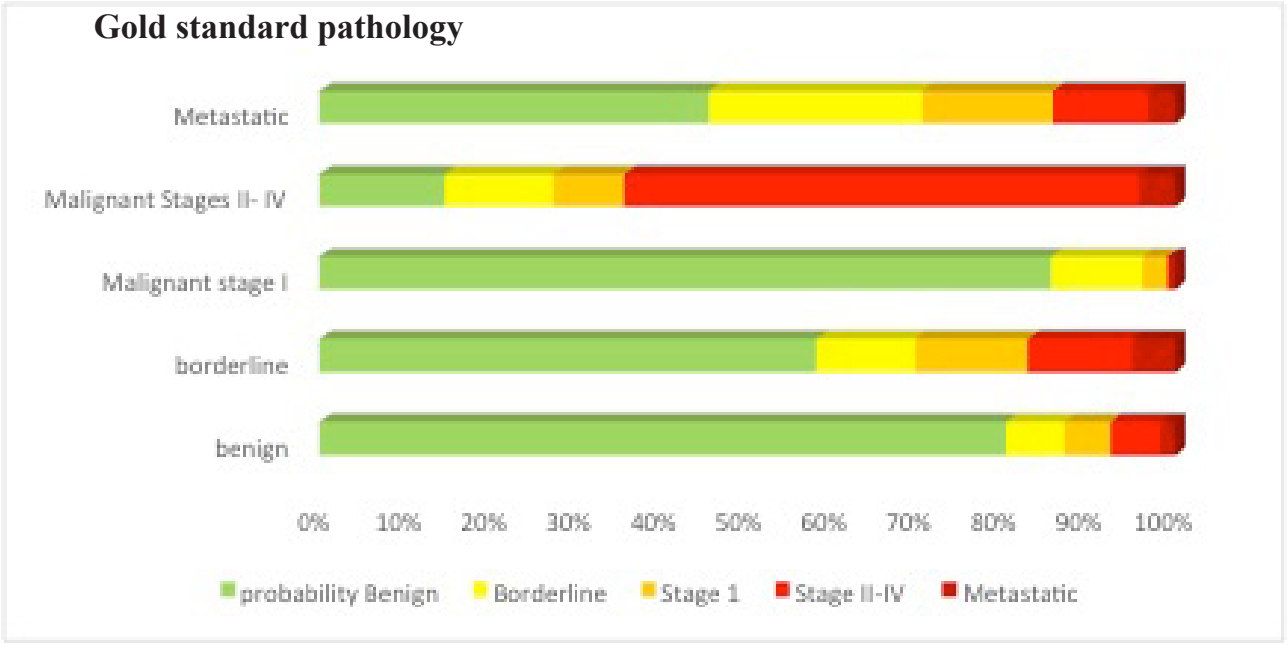

Figure 2: Average predicted risk by ADEX for different pathology results among the studied group

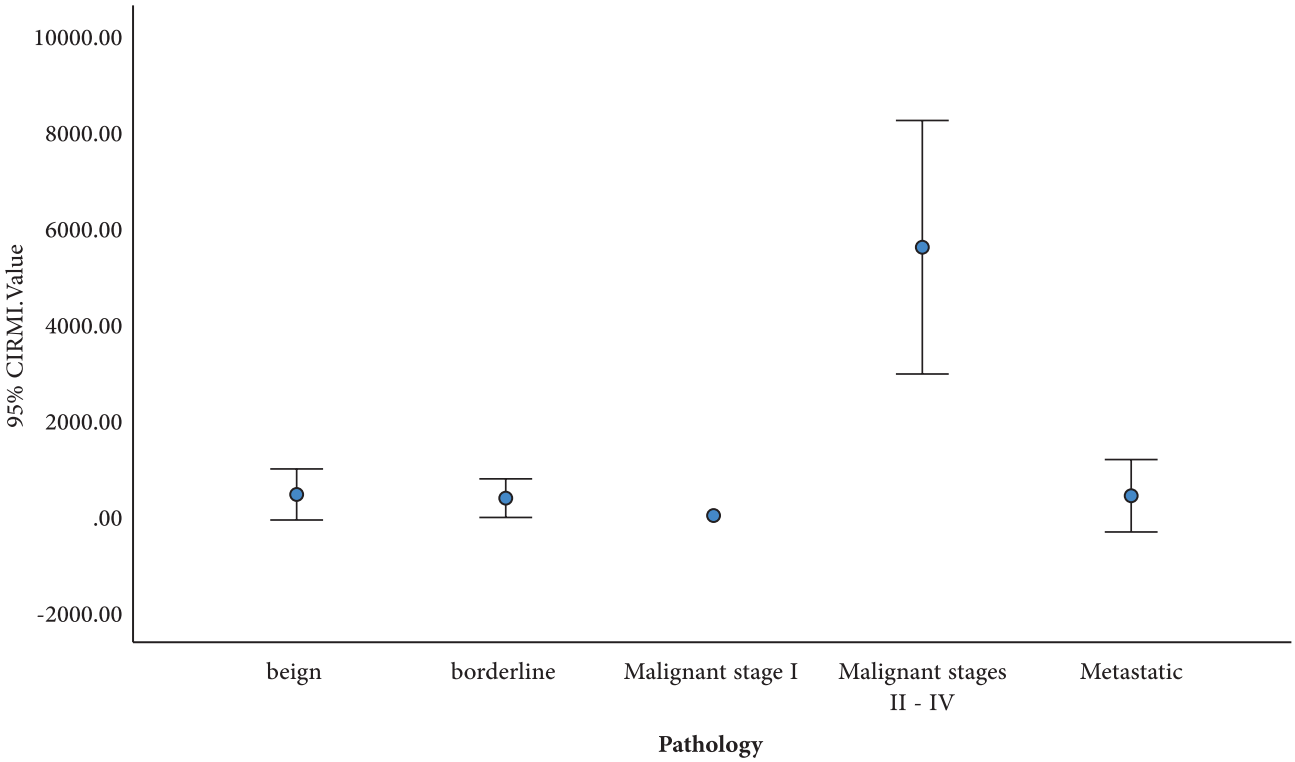

Figure 3: Error bar shows the mean and 95% CI of RMI va lues among different pathology

Table 5: Comparison of different pathology results and RMI value among the studied group (n=50)

			RMI. Value	Test of sig
Pathology	benign	Mean (SD)	439.38 (1348.2)	ANOVA F= 12.68 P value = <0.001*
		Median (IQR)	81.30 (50.3-165.6)	
	borderline	Mean	372.69 (372.69)	
		Standard Deviation	373.52	
		Median	174.58(117-762)	
	Malignant stage I	Mean	6.00 (0)	
		Median	6.00	
	Malignant Stages II- IV	Mean	5611.55 (3941)	
		Median	4599 (2394- 7110)	
	Metastatic	Mean	402.52 (458.2)	
		Median	261.0 (60- 744.3)	

* P value < 0.05: significant

Table 6: Comparison between sociodemographic data and pathology results among the studied group

		Pathology						
		Total (N=50)	Benign (N=28)	Borderline (N=6)	Malignant Stages I (N=1)	Malignant Stages II- IV (N=11)	Metastatic (N=4)	Chi-square p-value
Age cat	<59	30 (60)	18(64.3)	2(33.3)	1(100)	7 (63.6)	2(50)	0.577
	> 59	20(40)	10(35.7)	4(66.7)	0	4(36.4)	2 (50)	
Parity cat	<3	26(52)	13(46.4)	2(33.3)	1(100)	8(72.7)	2(50)	0.408
	> 3	24(48)	15(53.6)	4	0	3(27.3)	2(50)	
Education	literate	3(6)	1(3.6)	0	0	2(18.2)	0(0)	0.604
	primary	3(6)	1(3.6)	0	0	2(18.2)	0(0)	
	Secondary	5(10)	3(10.7)	1	0	0(0)	1(25)	
	University	39(78)	23(82.1)	5	1(100)	7(63.6)	3(75)	
PH of cancer	No	49(98)	28(100)	6	1(100)	11(100)	3(75)	0.019*
	Yes	1(2)	0(0)	0	0	0(0)	1(25)	
FH of cancer	No	42(84)	25(89.3)	4	1(100)	8(72.7)	4(100)	0.418
	Yes	8(16)	3(10.7)	2	0	3(27.3)	0(0)	

* P value < 0.05: significant

Table 7: Components of the ADNEX models in different histopathologic subtypes

		Benign (N=28)	Borderline (N=6)	Malignant Stages I (N=1)	Malignant Stages II-IV (N=11)	Metastatic (N=4)	p-value
ADNEX. age	Mean(SD)	58.75(7)	61 (3)	46	60 (5)	63(9)	0.199
Max. diameter of lesion(mm)	Mean(SD)	135.4 (75)	162(37)	180	123(59)	148 (85)	0.790
Max. diameter of the largest solid part (mm)	Mean(SD)	19.5(40)	29(35)	0	50(38)	41(47)	0.262
CA125	Mean(SD)	82.04(174)	57.16(34)	2.30	726.3(543)	47.9(48)	<0.001*
Locules N(%)	No	0 (0)	0(0)	0(0)	1 (9.1)	0(0)	0.031*
	0-10	26(92.9)	5(83.3)	0(0)	5(45.5)	2(50)	
	>10	2 (7.1)	1(16.7)	1 (100)	5(45.5)	2(50)	
No. of papillary projections N(%)	0	22(78.6)	5(83.3)	1 (100)	4(36.4)	1(25)	0.106
	1	2(7.1)	1(16.7)	0(0)	1(9.1)	1(25)	
	2	4(14.3)	0(0)	0(0)	1(9.1)	0(0)	
	3	0 (0)	0(0)	0(0)	3(27.3)	1(25)	
	>3	0(0)	0(0)	0(0)	2(18.2)	1(25)	
Acoustic shadow N(%)	No	22(78.2)	6(100)	1 (100)	5(45.5)	2(50)	0.087
	Yes	6(21.4)	0(0)	0(0)	6(54.5)	2(50)	
Ascites N(%)	No	26(92.9)	5(83.3)	1 (100)	2(18.2)	2(50)	<0.001*
	Yes	2(7.1)	1(16.7)	0(0)	9(81.8)	2(50)	

* P value < 0.05: significant

Table 8: Comparison between RMI value and ADNEX Performance for differentiating benign from malignant tumors

Variable(s)	AUC	Sensitivity	Specificity	LR +	LR -	SE	P value	95% CI	
								Lower	Upper
ADNEX	0.864	91.1%	65%	2.66	0.257	0.057	<0.001*	0.752	0.976
RMI	0.799	81.8%	60.7%	2.06	0.299	0.067	<0.001*	.667	.930
P value	0.460	Difference =0.065		SE of difference=0.088		Z test =0.73			

Cutoff for ADNEX = 10%, and for RMI=115
LR +: positive likehood ratio / LR - : negative likehood ratio

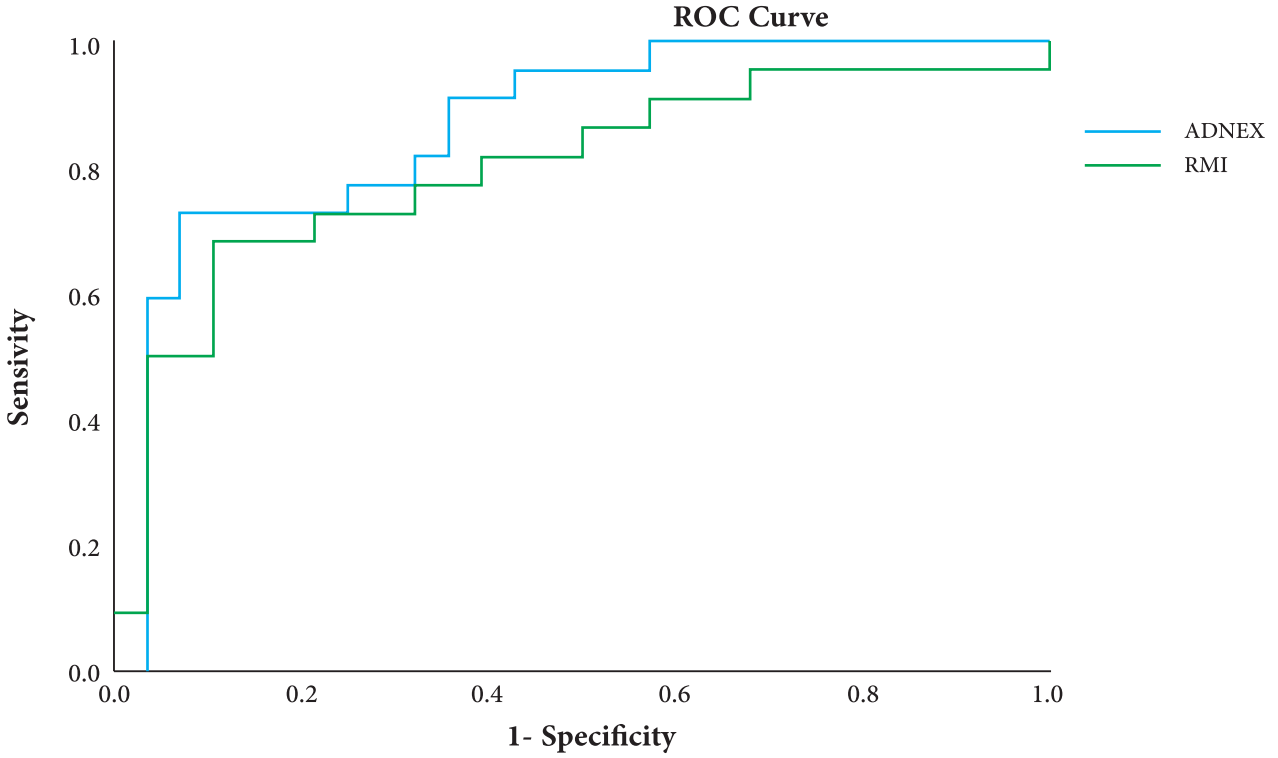

Figure 4: ROC curve for both RMI and ADNEX model

Table 9: Performance of Assessment of Different NEoplasias in the adneXa (ADNEX) model for five tumor types, expressed as area under the receiver–operating characteristics curve (AUC)

Types of tumors	AUC	P value	95% CI	
			Lower	Upper
Benign vs malignant	0.864	<0.001*	0.752	0.976
Benign vs Borderline	0.722	0.007*	0.575	0.870
Benign vs Stage 1	0.724	0.007*	0.579	0.869
Benign vs Stage II-IV	0.823	<0.001*	0.694	0.953
Benign vs Metastatic	0.791	<0.001*	0.663	0.918

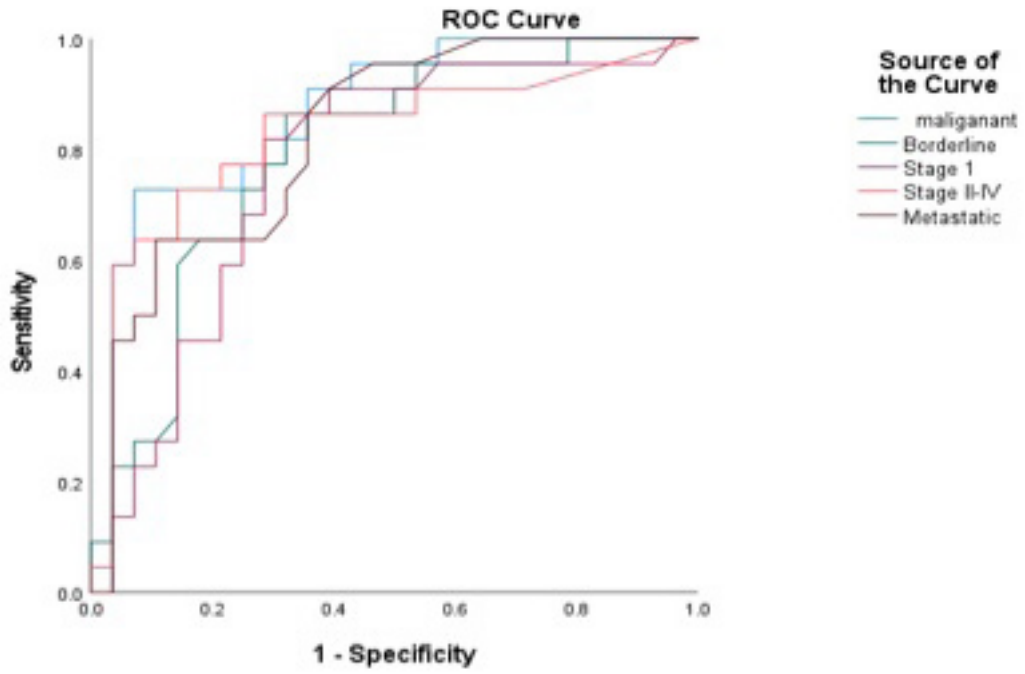

Figure 5: ROC curve shows AUCs for different pathology results

Discussion

Ovarian cancer is predominantly a cancer of postmenopausal women, and it is rare in women below the age of 40 years. Thus, it is classically described as a disease of older women. The median age for women with ovarian cancer ranges from 60 to 65 years in most developed countries. As life expectancy has increased in most countries worldwide, and because the incidence rate of ovarian cancer increases with age, more and more postmenopausal women will have ovarian cancer (11).

Regarding the **sociodemographic data** of the study participants, the overall median age of the study participants was 59 years. All of the included participants were postmenopausal and so, age didn't affect the RMI value as all patients got a score of 3. However, age is a component of the ADNEX model and with increasing age, the probability of malignancy increase. Our study showed no significant difference between those who were older than 59 years and those who were 59 years or younger regarding histopathology results as no certain pathologic entity was significantly higher in either group. Our results were consistent with Huwidi et al., who assessed the diagnostic value of RMI among patients with adnexal mass; there was no significant difference between different age groups regarding either benign or malignant pathology however, the study included different age groups and was not restricted to postmenopausal women (12). Zhang et al., showed no significant age difference between those with benign pathology and those with borderline ovarian tumors in their retrospective study which tested the predictive ability of the RMI among the study patients (13). The performance of ADNEX model for prediction of ovarian cancer was assessed and there was no significant age difference between different pathology groups in the study conducted by Yang et al., however, the study conducted by Lam Huong et al., showed significantly higher median age among patients who were diagnosed with cancer which can be attributed to the much smaller number of patients with cancer (65 VS 396) (14,15). As for parity, the median **parity** in our study was 3 and

there was no remarkable difference at any histopathologic group between patients who were para 3 or less and those who were more than para 3.

The **level of education** of the study participants was assessed in our study. More than 75% of the study cohort reached university level. Alberg et al., evaluated the socioeconomic status of African-American women and their relation to the risk of ovarian cancer, the study revealed an inverse relationship between educational level and ovarian cancer risk after adjustment for ovarian cancer risk factors (16). Such relationship could be explained the cross sectional study which was conducted by Elshami et al., and showed higher level of awareness about risk factors and protective factors of ovarian cancer among those with post-secondary education (17).

Regarding **past history of cancer** among the study participants, only one patient in the study cohort had past history of cancer which was cancer breast and the histopathology revealed that the ovarian mass was already a metastatic deposit. Studies with much larger sample size which targets the relation between past history of gynecological or GIT cancer and present ovarian cancer as its primary outcome and the associated syndromes as BRCA1 or 2 mutation and Lynch syndrome can be of value for better assessment of the relationship between certain malignancy and ovarian cancer

Family history of ovarian or ovarian cancer is well known risk factor for development of OC. At our study, 16% of the study participants had family history of malignancy; only one case had past history of breast cancer but ultimately she had benign pathology and one case with borderline ovarian tumor had family history of ovarian cancer.

Studies that have thoroughly adjusted for the effects of factors like duration of oral contraceptive use and number of full-term pregnancies, have not noted a strong association between difficulty in conceiving and the risk of ovarian cancer among parous women. However, an increased risk among infertile women who remain childless despite long periods of unprotected intercourse has been reported in two large, pooled analyses. It remains to be understood whether such women are at risk due to the primary basis for their infertility, some correlate of infertility such as exposure to ovulation-inducing drugs, a shared genetic susceptibility to ovarian cancer and infertility, or some other reason (18). Previous studies have debated whether OI could increase the risk of invasive ovarian cancer (IOC) and borderline ovarian tumors (BOT). Although most studies have concluded that OI does not contribute to the risk of IOC and BOT, some scholars still proposed that OI may be associated with them (19). Infertility, its duration and the management which was adopted to deal with it was assessed in our study; 8 patients representing 16% of the study participants had history of infertility and out of those 8 patients, 3 received induction of ovulation for treatment of their fertility problems with only one patient developing ovarian cancer. Retrospective cohort studies with much larger sample size is more suitable for evaluating the relationship between infertility and ovarian cancer.

The RMI was evaluated in different histopathologic subtypes and it was shown to be significantly higher among those with malignant pathology stages □ - □ and in those with metastatic ovarian cancer. Our results were similar to those obtained by Lycke et al., who showed significantly higher mean RMI among patients with FIGO stage □, □ ovarian cancer compared with those with benign or borderline ovarian tumors whether the patients were premenopausal or postmenopausal (20). Similar results were also achieved by Dora et al., who showed significantly higher RMI among patients with malignant ovarian masses (21). Only one patient among our study cohort was diagnosed with stage □ ovarian cancer and so a comparison with

benign cases regarding the RMI value needs further studies with more cases ultimately diagnosed with stage □ ovarian cancer.

The components of the ADNEX model were evaluated in the five histopathological categories; the three components which were significantly different between the were the CA-125 level, the presence of ascites, and the number of locules. The first 2 were associated with malignant cases while from 1-10 locules were predominant in the benign cases. Lam Huong et al., showed that ascites was more prevalent in the cancer group however, there was significant difference regarding all other components; this difference can be attributed to the fact that the study wasn't limited to postmenopausal women. Moreover, the histopathological results were either benign or malignant i.e the analysis was not based on the five histopathological groups which can be predicted by the ADNEX model (15). The results obtained by Yang et al., showed significant difference between benign and malignant cases regarding all ultrasound components of the ADNEX model however, the authors included the patients with borderline ovarian tumors into the malignant category despite being completely different entity and this could affect the reliability of the findings (14). In daily practice, the two most prevalent histological subtypes are the benign and the stage □ - □ OC and so, for prospective assessment, comparison between these two subtypes in particular would be more reliable in identifying which ultrasound feature correlate better with a given subtype. The other 3 histological subtypes are relatively rare and so, multicentric and retrospective studies would be more suitable for evaluation of the ultrasound features of these 3 subtypes.

The **diagnostic performance** of both RMI and ADNEX model for differentiating benign from malignant ovarian tumors was assessed; the ROC curve showed a bigger area under the curve (AUC) for the ADNEX model. Regarding the RMI, a cutoff of 115 was associated with 81.8% sensitivity, 60.7% specificity, positive likehood ratio of 2.06 and negative likehood ratio of 0.299 while the ADNEX model at a cutoff level of 10 was associated with 91.1% sensitivity, 65% specificity, 2.66 positive likehood ratio and 0.257 negative likehood ratio. By using the ADNEX model, Yoeli-Bik et al., achieved a sensitivity of 91%, specificity of 86%, LR+ of 6.7, and LR- of 0.7 and these results were obtained at 10% cutoff; such higher specificity could be attributed to the fact that 33% of the study cohort didn't undergo surgical intervention and were included in the study if they had adequate clinical or imaging follow-up which can point to a tendency towards operating on cases with high probability of malignancy which shall decrease the incidence of false positive results (22). Another muticenter cohort study by Van Calster et al., which included 4905 patients from 36 oncology centers assessed the predictive ability of the ADNEX model and the RMI for detecting ovarian cancer; regarding the ADNEX model, the overall sensitivity was 91% and the overall specificity was 85% and this was achieved with 10% risk threshold and 0.94 AUC. The higher AUC compared to our study can be attributed to the much larger sample size and the fact that 2151 patients (44%) of the study cohort were postmenopausal women which would increase the probability of ovarian malignancy in the cohort. Regarding the RMI, at a cutoff of 200, the overall sensitivity was 60% and the specificity was 95%, such lower sensitivity and higher specificity compared to our study is attributed to the lower cutoff value which was set (115 vs 200) (23). Another study by Pelayo et al., which assessed the predictive accuracy of the ADNEX model yielded 94% sensitivity and 82% specificity with 0.92 AUC; the lower false positive cases compared to our study can be attributed to the fact that 39% of the study participants suffer from digestive symptoms which should increase the probability of malignancy in contrast to our study participants who were asymptomatic besides the fact that 16 % of the

study participants underwent sonography by non-expert sonographers and 8 % came from the emergency room; such diversity could affect the reliability the interpretation of the ultrasound findings (24). Results obtained by Poonyakanok et al., showed 98% sensitivity and 87% specificity when using 10% threshold of malignancy probability; the higher sensitivity and specificity compared to our study can be attributed to the fact that the authors excluded 13 patients from those who were recruited as they were ultimately diagnosed with uterine or abscess lesions which would indirectly raise the accuracy of the ultrasound which is integral part of the ADNEX model (25). Results were also similar to those obtained by Peng et al., who achieved with the same cutoff value a 94% sensitivity, 74% specificity, 3.06 LR+ and 0.08 LR-; both studies were conducted at a tertiary oncology centers and the incidence of benign and malignant pathology were also similar (26). Yang et al., achieved 93% sensitivity, 73% specificity, 3.39 LR+ and 0.1 LR- using 10% malignant probability; the authors excluded masses which didn't originate from the ovary on the histopathology specimen; this exclusion will raise the predictive ability of the ultrasound and will decrease the false positive results (14).

The ADNEX model discriminates ovarian tumors into five subtypes; benign, borderline, malignant stage □, malignant stage □-□, and metastatic ovarian deposits. At our study, the model performed best at discriminating between benign and malignant ovarian tumors with AUC of 0.864 while the least performance was observed with differentiating between benign and borderline and stage I OC with AUC of 0.722 and 0.724 respectively. Results achieved by Sayasneh et al., showed the highest performance when discriminating between benign and stage □- □ OC with AUC of 0.99; the higher AUC compared to our study in particular when the model discriminated between benign and stage □ OC is attributed to the much higher sample size in the that multicenter study which led to higher percentage of patients with stage □ OC compared to our study (8% vs 2%) and the fact that the percentage of cases diagnosed with stage □ - □ OC in our study was the double (22% vs 11%) had led to the lesser AUC in our study when ADNEX model was used to discriminate between benign and malignant cases (0.864 vs 0.99) (27). Meys et al., assessed the performance of the ADNEX model for the five tumor subtypes and the highest AUC was obtained when the model was used to discriminate between benign and stage □ - □ OC (0.97) which is higher compared to our study (0.823) which could be related to the fact that the percentage of benign cases was lower in our study (56 % vs 64%) (28). These results are in agreement with the results obtained by Van Calster et al., which also showed in their multicentric study that the highest AUC obtained when benign lesions are compared against stage □ - □ OC; the comparison of power of discrimination between benign and all other four histological subtypes showed excellent performance by ADNEX model with all AUCs higher than 0.9; the high percentage of benign lesions among the studied cohort (67%) in comparison with other histological subtypes can contribute to this performance (29).

The ADNEX model can change the future management of ovarian cancer by prediction of the staging of ovarian cancer which is particularly important as it largely improves the prognosis when the cancer is detected at stage □. It has better sensitivity and specificity for differentiating between benign and malignant tumors when compared with RMI; however, it needs more experience in the ultrasound evaluation of adnexal masses so it can be implemented in screening programs on a large scale. Moreover, the discrimination between the five histopathologic subtypes is of a great value as it can lead to proper triaging of the patients; when the model predicts that the mass is benign, the patient can be managed by in a general gynecology hospital while if

it predicts a malignant nature of the mass, the patient must be referred to a gynecological oncology for multidisciplinary team (MDT) consultation as this will largely influence the management and prognosis. Such MDT consultation will guide the management to achieve the best possible results; when the model predicts borderline or stage □ OC, the patient should have optimum surgical staging by an experienced gyne-oncologist while patients with high probability of stage □ - □ can have further imaging as Computed Tomography (CT) scan abdomen and pelvis for better detection of advanced disease and then receive neoadjuvant chemotherapy first followed by interval debulking. Finally, if the model predicts that the mass is metastatic, other investigations can be ordered to find out the primary origin such as mammogram, upper and lower GIT endoscopy or even Positron Emission Tomography (PET)-Scan and the patient can avoid surgery and its potential complications.

The major drawback of the ADNEX model is the fact that it needs significant experience in the field of ultrasound so as to be fruitful and of value. Training programs must be adopted in order to upgrade the skills needed for precise evaluation of adnexal masses by ultrasound which is extremely important before using the ADNEX model for screening purposes.

Our study was not without limitations; data were collected from single tertiary center and this can negatively impact the representation of different regions of the country in this study. Further studies from different centers are needed so as to produce a larger sample size which will be a better representative of the predictive ability of the ADNEX model particularly for rare findings such as borderline and stage □ OC

Conclusion

ADNEX model is more sensitive than RMI for differentiating between benign and malignant tumors and it can be used as screening test. However, the application of ADNEX model needs significant experience in ultrasound evaluation of adnexal masses before it can be an integral part in the screening pathway of ovarian malignancy in postmenopausal patients with adnexal masses.

Declarations of interest

a) Ethical approval and informed consent:

Informed consent was obtained from study participants. The study was registered in Clinicaltrials.gov, ID: NCT05755841 , and was approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University (MS 585 /2020, FWA 000017585). All methods were carried according to the relevant guidelines and regulations in the Declaration of Helsinki

b) Authors' contribution:

Elmaraghy AM: Protocol development Manuscript writing - Data analysis

El-shalakany AH: Protocol development Manuscript editing - Data analysis

Dwedar AMM: Data collection

Ahmed ME: Data analysis

Morsi H: Data collection

Labib K: Protocol development

c) Publication statements:

The authors declare that this work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities.

d) Funding:

The study was based on investigators' self-funding

e) Conflicts of interest:

The authors declare that there are neither fi-

nancial nor non-financial conflicts of interest concerned with the manuscript of the study

f) Consent to participate:

Informed consent was obtained from all individual participants included in the study.

g) Consent to publish:

Study participants consented to publish their data prior to submitting this paper to the journal.

h) Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

i) Acknowledgments:

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References

1. Nash Z, Menon U. Ovarian cancer screening: Current status and future directions. Best Pract Res Clin Obstet Gynaecol. (2020);65:32-45.
2. Nohuz E, De Simone L, Chêne G. Reliability of IOTA score and ADNEX model in the screening of ovarian malignancy in postmenopausal women. J Gynecol Obstet Hum Reprod.(2019); 48(2):103-107.
3. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 97.(1990);(10):922-9.
4. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T et al. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Br J Obstet Gynaecol.(1996); 103(8):826-31.
5. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol.(1999); 93(3):448-52.
6. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J Obstet Gynecol Reprod Biol. (2009);144(2):163-7.
7. Ali MN, Habib D, Hassanien AI, Abbas AM. Comparison of the four malignancy risk indices in the discrimination of malignant ovarian masses: A cross-sectional study. J Gynecol Obstet Hum Reprod. (2021);50(5):101986.
8. Barreñada L, Ledger A, Dhiman P, Collins G, Wynants L, Verbakel JY et al. ADNEX risk prediction model for diagnosis of ovarian cancer: systematic review and meta-analysis of external validation studies. BMJ Med.(2024);17;3(1): e000817.
9. Wang R, Yang Z. Evaluating the risk of malignancy in adnexal masses: validation of O-RADS and comparison with ADNEX model, SA, and RMI. Ginekol Pol. (2023);94(10):799-806. h
10. Green-top Guideline. The Management of Ovarian Cysts in Postmenopausal Women No. 34 (2016).
11. Ali AT, Al-Ani O, Al-Ani F. Epidemiology and risk factors for ovarian cancer. Prz Menopauzalny.(2023); 22(2):93-104.
12. Huwidi A, Abobrege A, Assidi M, Buhmeida A, Ermiah E. Diagnostic value of risk of malignancy index in the clinical evaluation of ovarian mass. Mol Clin Oncol. (2022);30;17(1):118.

13. Zhang, S., Yu, S., Hou, W. et al. Diagnostic extended usefulness of RMI: comparison of four risk of malignancy index in preoperative differentiation of borderline ovarian tumors and benign ovarian tumors. J Ovarian Res (2019);16:12(1):87.

14. Yang S, Tang J, Rong Y, Wang M, Long J, Chen C et al. Performance of the IOTA ADNEX model combined with HE4 for identifying early-stage ovarian cancer. Front Oncol. (2022);16(12):949766.

15. Lam Huong L, Thi Phuong Dung N, Hoang Lam V, Tran Thao Nguyen N, Minh Tam L, Vu Quoc Huy N. The Optimal Cut-Off Point of the ADNEX Model for the Prediction of the Ovarian Cancer Risk. Asian Pac J Cancer Prev. (2022)1;23(8):2713-2718.

16. Alberg AJ, Moorman PG, Crankshaw S, Wang F, Bandera EV, Barnholtz-Sloan JS et al. Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study. Am J Epidemiol.(2016)15;184(4):274-83.

17. Elshami M, Tuffaha A, Yaseen A, Alser M, Al-Slaibi I, Jabr H et al. Awareness of ovarian cancer risk and protective factors: A national cross-sectional study from Palestine. PLoS One. (2022); 21;17(3): e0265452.

18. Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. Am J Epidemiol.(2004)1;160(11):1070-8.

19. Yu, L., Sun, J., Wang, Q. et al. Ovulation induction drug and ovarian cancer: an updated systematic review and meta-analysis. J Ovarian Res.(2023)24;16(1):22.

20. Lycke M, Kristjansdottir B, Sundfeldt K. A multicenter clinical trial validating the performance of HE4, CA125, risk of ovarian malignancy algorithm and risk of malignancy index. Gynecol Oncol. (2018);151(1):159-165.

21. Dora SK., Dandapat AB., Pande B, Hota JP. A prospective study to evaluate the risk malignancy index and its diagnostic implication in patients with suspected ovarian mass. J Ovarian Res. (2017)14;10(1):55.

22. Yoeli-Bik R, Longman RE, Wroblewski K, Weigert M, Abramowicz JS, Lengyel E. Diagnostic Performance of Ultrasonography-Based Risk Models in Differentiating Between Benign and Malignant Ovarian Tumors in a US Cohort. JAMA Netw Open.(2023);6(7): e2323289.

23. Van Calster B, Valentin L, Froyman W, Landolfo C, Ceusters J, Testa AC et al. Validation of models to diagnose ovarian cancer in patients managed surgically or conservatively: multicentre cohort study. BMJ.(2023)30;370:m2614.

24. Pelayo M, Sancho-Sauco J, Sanchez-Zurdo J, Abarca-Martinez L, Borrero-Gonzalez C, Sainz-Bueno JA et al. Ultrasound Features and Ultrasound Scores in the Differentiation between Benign and Malignant Adnexal Masses. Diagnostics (Basel) (2023)23;13(13):2152.

25. Poonyakanok V, Tanmahasamut P, Jaishuen A, Wongwananuruk T, Asumpinwong C, Panichyawat N et al. Preoperative Evaluation of the ADNEX Model for the Prediction of the Ovarian Cancer Risk of Adnexal Masses at Siriraj Hospital. Gynecol Obstet Invest.(2021);86(1-2):132-138.

26. Peng XS, Ma Y, Wang LL, Li HX, Zheng XL, Liu Y. Evaluation of the Diagnostic Value of the Ultrasound ADNEX Model for Benign and Malignant Ovarian Tumors. Int J Gen Med.(2021) 16;14:5665-5673.

27. Sayasneh A, Ferrara L, De Cock B, Saso S, Al-Memar M, Johnson S et al. Evaluating the risk of ovarian cancer before

surgery using the ADNEX model: a multicentre external validation study. Br J Cancer.(2016)23;115(5):542-8.

28. Meys EMJ, Jeelof LS, Achten NMJ, Slangen BFM, Lambrechts S, Kruitwagen RFPM et al. Estimating risk of malignancy in adnexal masses: external validation of the ADNEX model and comparison with other frequently used ultrasound methods. Ultrasound Obstet Gynecol. (2017) 49(6):784-792.

29. Van Calster B, Van Hoorde K, Valentin L, Testa AC, Fischerova D, Van Holsbeke C et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ. (2014)15;349:g5920.

Serum Copeptin Level as A Diagnostic and Prognostic Marker in Threatened Preterm Labor

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Abstract

Background: Copeptin is a stable by-product of the synthesis of arginine-vasopressin (AVP); it can be accurately and quantitatively measured in plasma and mimics the release of AVP.

Aim of work: to assess the importance of maternal serum copeptin levels in diagnosis of threatened preterm labor and prediction of preterm birth.

Subjects & methods: This study was carried out as a prospective case control on 88 pregnant women at Obstetrics and Gynecology Department, Faculty of Medicine, Menoufia University. They were divided into two groups: Group I (Case group n=58): including 58 pregnant ladies who admitted for threatened preterm labor. Group II (Control group n=30): including 30 healthy pregnant ladies of matched age, parity, and gestational age.

Results: Serum copeptin was significantly higher in cases with preterm labor than term controls (641.29±167.87 pg/ml vs 192.67±71.16 pg/ml) respectively. Regarding the outcome serum copeptin was significantly higher in cases with preterm birth than cases with term birth (751.57±169.923 pg/ml vs 642±163pg/dl) respectively. The serum copeptin cutoff value is ≥ 380 pg/ml, the area under the curve is equal to 1.00, according to our ROC data. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

Conclusion: Maternal serum copeptin levels can serve as a valuable diagnostic and predictive marker in cases of threatened preterm labor and preterm birth.

Keywords: Serum Copeptin, Diagnostic and Prognostic Marker, Threatened Preterm Labor.

Introduction

Globally, preterm birth is the leading cause of perinatal mortality and morbidity. There is some chance of treating and preventing premature birth. To prevent needless expenses and adverse effects, a precise diagnosis and efficient treatment are crucial. Ensuring effective therapy may also help to lower perinatal morbidity or mortality (1).

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Merely 10% of the women diagnosed with premature labor give birth before their due date. Interventions aimed at improving neonatal outcomes are less successful when preterm delivery is identified in later stages of pregnancy and when it is difficult to distinguish between true and false labor. Predictive biomarkers that are precise and timely are therefore required (2).

Preterm labor is predicted using cervical length measurement. Only a small fraction of patients who are predisposed to premature labor may be distinguished using this method. Depending on the sample population's risk of preterm labor, cervical length measurement can predict preterm delivery with a sensitivity of 35–70% (3).

Copeptin is a dependable measure of arginine vasopressin (AVP) and an endogenous stress marker. Copeptin is actually a useful biomarker that is raised in a variety of stressful situations and is utilized to help distinguish between various cases of acute myocardial infarction (4).

During pregnancy, copeptin levels rise; in preeclamptic pregnancies, this rise is more pronounced than in normal pregnancies. Copeptin levels during the first trimester may also be a predictor of gestational diabetes and preeclampsia in the future (5; 6).

The purpose of this study was to assess the predictive value of maternal serum copeptin levels for preterm birth and the identification of impending preterm labor.

Patients and Methods

A case control study conducted on 88 pregnant women at obstetrics and gynecology department, Faculty of medicine, Menoufia University during the period from November 2022 to April 2023.

Sample size estimation:

Sample size was calculated using PASS 11.0 and according to the power analysis results, with a 95% confidence interval and 80% test power, a one-way analysis of variance analysis should include a minimum of 88 pregnant women (58 of whom have threatening preterm labor and 30 of whom are healthy).

Ethical consideration:

After clarifying the purpose of the study, all of the women who were part of it gave their written informed consent. The Menoufia Faculty of Medicine's Ethical Scientific Committee approved the study protocol (IRB: 11-2022OBSG20).

Eligibility criteria:

Study included all pregnant in the second and third trimester at 24-34 weeks of gestation. Pregnant women having any of these issues were not include from our study:

1. Hypertension and diabetes either pregestational or gestational, Premature rupture of membranes, cardiac disease, kidney illness, and multiple pregnancies.
2. Those for whom continuing the pregnancy to term posed a serious risk to the fetus or mother.
3. Mothers suffering serious illnesses like sepsis, infections, and myocardial infarction.

Patients grouping:

Study included 88 pregnant women classified into:

- **Group I (Case group)**: consisted of 58 pregnant ladies who were admitted for threatened preterm labor. We depended on painful uterine contractions and the existence of changes in the cervix for the diagnosis of preterm labor. Group I was further subdivided into: **Preterm birth** including cases who gave birth prematurely before 37 weeks gestation & **Term birth** including cases who delivered at or after 37 weeks gestation.
- **Group II (Control group)**: consisted of 30 healthy pregnant ladies matching cases in age, parity and gestational age.

Study progress and evaluation:

All pregnant women included in the study had a full history taken including personal history, past history, present history and obstetric history with emphasis on age, special habits of medical importance, medical illness, gravidity, parity, miscarriage and last menstrual period. This was along with detailed clinical examination including general examination e.g. vital signs and BMI and abdominal & local examination e.g. fundal height, fundal grip, lateral or umbilical grip, 1st &2nd pelvic grip, auscultation of fetal heart sound, assessment of the membrane, determining of the presenting part, sterile speculum examination and fetal biometric measurements. Obstetric ultrasound was done for all included pregnant women to asses cervical length, cervical dilatation, status of membranes, fetal biometric measures, CTG and doppler study. Also, they were subjected to routine laboratory investigations where cases were subjected to CBC, CRP, Urea, Creatinine, AST, ALT, coagulation profile and blood grouping while controls were subjected to CBC and blood grouping.

Blood samples for the specific marker:

The laboratory work was done at Menoufia University's Faculty of Medicine, at the Clinical Pathology Department. We used meticulous aseptic precautions and obtained 5 mL peripheral blood samples in sterile tubes from each of the study's participating women. The Human Copeptin ELISA Kit (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China) was used to measure the level of copeptin in the serum.

Statistical analysis

Data was gathered throughout history, clinical examination and laboratory investigations, and SPSS (statistical program for social science) version 25 (Armonk, NY: IBM Corp.) was used to code, input, and analyze outcome measures. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, the data was examined for normality. Two types of statistics were done:

Descriptive statistics: Depending on the type of data, mean ± SD was used to describe quantitative data while numbers and percentages were used to represent **qualitative data**.

Analytic statistics: When comparing two groups with quantitative variables that had a normal distribution, the **student t-test** was employed (for parametric data). When comparing two groups with quantitative variables that don't have normal distribution, **Mann-Whitney U Test** was employed (for non-parametric data). To examine the relationship and comparison between two qualitative variables, the **chi-square test ($\chi 2$)** was employed. **Spearman's Correlation** was used for studying correlation. Receiver operating characteristic (ROC) curves were created to evaluate the parameters' clinical performance. For two-tailed tests, a **P-value** of less than 0.05 was considered significant statistically, while less than 0.001 indicated a very significant outcome.

Results

Table (1): Comparison between study group and control group regarding cervical length and dilatation:

	Cases group (n=58)	Control group (n=30)	t	P-value
Cervical length(mm) (Min. – Max.) Mean ± SD.	11.00 - 50.00 32.47 ± 8.19	30.00 - 52.00 42.77 ± 5.88	9.757	0.001**

Cervical dilatation(cm) (Min. – Max.) Mean ± SD.	1.00 - 6.00 2.26 ± 1.26	0.00 - 0.00 0.00 ± 0.00	-6.682	0.001**

t: Independent Samples t Test
p: p value for comparing between the studied groups
**: Highly significant, *: significant

This table shows us that the cervical length mean in cases group was 32.47±9.04 mm and ranged from 11 to 50 mm, and in controls it was 42.77±5.88 mm ranging from 30 to 52 mm which was significantly higher in controls than cases. In the other hand, cervical dilatation mean in cases was 2.26±1.26 cm, and the range was from 1 to 6 cm, and in controls it was zero, cervical dilatation was significantly higher in cases than controls.

Table (2): Comparison between study group and control group regarding Serum Copeptin:

	Cases group (n=58)	**Control group (n=30)**	**U**	**P-value**
Serum Copeptin(pg/ml) (Min. – Max.) Mean ± SD.	350.00 - 950.00 641.29 ± 167.87	110.00 - 350.00 192.67 ± 71.16	0.500	0.001**

U: Mann-Whitney U test, p: p value for comparing between the studied groups
**: Highly significant, *: significant

Serum Copeptin mean was 641.29±167.87 pg/ml, and the range was from 350 to 950 pg/ml in cases, and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml, serum copeptin was significantly higher in cases than controls.

Table (3): Comparison between study group outcome and control group outcome regarding Serum Copeptin:

	Cases group (n=58)		Control group (n=30)	**F**	**P-value**
	Term birth (n=51)	**Preterm birth (n=7)**			
Serum Copeptin(pg/ml) (Min. – Max.) Mean ± SD.	350 - 950 642 ± 163	400 - 900 751 ± 170	110 - 350 192.67 ± 71.16	104	0.001**
Post hoc test	P1=0.028* P2<0.001** P3<0.001**				

P1: Term birth vs Preterm, P2: Term birth vs Control, P3: Preterm birth vs Control
F: ANOVA test, p: p value for comparing between the studied groups **: Highly significant

Serum Copeptin mean was 642±163 pg/ml, and the range was from 350 to 950 pg/ml in cases with term birth, was 750±170 pg/ml, and the range was from 400 to 900 pg/ml in cases with preterm birth and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml, serum copeptin was significantly higher in cases with preterm birth than term birth and controls.

Table (4): Correlation between serum copeptin and the other parameters

	Serum Copeptin	
	r	**P**
Demographic data		
Age	-0.384	0.000**
BMI	-0.363	0.001*
Obstetric data		
Gravidity	-0.373	0.000**
Parity	-0.397	0.000**
GA	0.058	0.592
Cervical Length	-0.586	0.000**
Cervical dilatation	0.784	0.000**
Vital signs data		
MBP	0.084	0.435
Pulse	-0.148	0.168
RR	0.251	0.018*
Temp.	-0.117	0.278
Laboratory data		
HB	-0.071	0.508
WBCs	-0.333	0.002*
PLT	-0.301	0.004*
Urea	0.610	0.000**
Creatinine	0.705	0.000**
ALT	0.711	0.000**
AST	0.806	0.000**
INR	0.501	0.000**
RBG	0.394	0.002*

r: Spearman's correlation coefficient p: p value for comparing between the studied groups
**: Highly significant, *: significant

Serum copeptin was positively correlated with Cervical dilatation respiratory rate, Urea, Creatinine, ALT, AST, INR, and RBG. Serum copeptin was negatively correlated with age, BMI, gravidity, parity, cervical Length, WBCs, and PLT. Serum copeptin was not correlated with GA, MBP, pulse, temperature, and hemoglobin.

Table (5): Receiver operating characteristic (ROC) Curve and diagnostic indices of Copeptin for prediction of TPL

	AUC	P-value	95% Confidence Interval		Cut off Value	Sensitivity	Specificity	PPV	NPV
			Lower Bound	Upper Bound					
Copeptin	1.000	0.000**	0.999	1.000	≥ 380	98.3%	100%	100%	96.8%

AUC: Area Under a Curve p-value: Probability value
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$ **: Statistically highly significant at $p \leq 0.001$

ROC curve was used to determine the best cut off value of serum copeptin in predicting the threatened preterm labor. Our ROC results revealed that the serum copeptin cutoff value is ≥ 380 pg/ml and the area under the curve is equal to 1.00 which indicates that it is an excellent predictor. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

Discussion

Globally, preterm birth is the leading cause of perinatal mortality and morbidity. There is some chance of treating and preventing premature birth. To prevent needless expenses and adverse effects, a precise diagnosis and efficient treatment are crucial. Ensuring effective therapy may also help to lower perinatal morbidity or mortality (1).

Copeptin is a dependable measure of arginine vasopressin (AVP) and an endogenous stress marker.

During pregnancy, copeptin levels rise; in preeclamptic pregnancies, this rise is more pronounced than in normal pregnancies. Copeptin levels during the first trimester may also be a predictor of gestational diabetes and preeclampsia in the future (5; 6).

The aim of this study was to evaluate the role of maternal serum copeptin levels in diagnosis of threatened preterm labor and prediction of preterm birth.

This was a prospective case control study that was conducted on 88 pregnant women at Obstetrics and Gynecology Department, Faculty of Medicine, Menoufia University. All pregnant women included in this study were divided into two groups: Group I (Case group n=58): including pregnant ladies who were admitted for threatened preterm labor. We depended on painful uterine contractions and the existence of changes in the cervix for the diagnosis of preterm labor. Group II (Control group n=30): including 30 healthy pregnant ladies matching cases in age, parity and gestational age.

In our study, the cervical length mean in cases group was 32.08±9.04 mm and ranged from 25 to 50 mm, and in controls it was 42.77±5.88 mm ranging from 30 to 52 mm which was significantly higher in controls than in cases. On the other hand, cervical dilatation mean in cases was 2.26±1.26 cm, and the range was from 1 to 6 cm, and in controls it was zero, cervical dilatation was significantly higher in cases than controls.

In accordance, Tulmac et al. (1) reported that cervical dilatation and length showed a significant difference between the groups, suggesting that an appropriate risk assessment was done while constructing the groups.

It was observed that women who had cervical dilatation had a higher risk of preterm delivery, and that preterm birth was independently correlated with short cervical length (7).

According to Ibrahim and Ahmed (8), full-term delivery is usually related to a cervical length of greater than 2.3 centimeters. Furthermore, Fuchs et al. (9) shown that in a group presenting with painful contractions (< 32 weeks), a cervical length of < 15 mm was associated with a 5.5-fold greater risk (44%) of delivery within a week, whereas a cervical length of ≥ 15 mm was associated with a 2% risk. Transvaginal cervical length (CL) measurement is a good indicator of increased risk of spontaneous preterm birth, according to Hamzaoğlu et al. (10).

In our study, serum copeptin was significantly higher in cases than controls. serum Copeptin mean was 641.29±167.87pg/ml, and the range was from 350 to 950 pg/ml in cases, and in controls it was 192.67±71.16 pg/ml ranging from 110 to 350 pg/ml.

This is in harmony with Tulmac et al. (1) who reported that, The threatened preterm labor group had a higher level of serum Copeptin 7.76(0.39–35.62) ng/mL compared to 6.23(1.64–36.88) ng/mL for control group.

Our findings were consistent with Foda and Abdel (11) who showed that level of copeptin was greater in patients in labor compared to those who are not in labor.

The level of copeptin in serum during pregnancy has been a subject of extensive research especially in the aspect of its relation to the complications of pregnancy (5). When it was initially examined in preeclamptic patients, it was discovered to be higher than in normotensive pregnant controls (12).

In our study, serum Copeptin mean was 642±163pg/dl, and the range was from 350 to 950 pg/dl in cases with term birth, was 750±170pg/dl, and the range was from 400 to 900 pg/dl in cases with preterm birth and in controls it was 192.67±71.16 pg/dl ranging from 110 to 350 pg/dl, serum copeptin was significantly higher in cases with preterm birth than term birth and controls.

A study by Yeung et al. (13) concluded that higher copeptin levels were associated with increased risk of preterm birth not affected by preeclampsia; however, the association did not persist after adjustment for race. Another study by Tulmac et al. (1) assessed the serum copeptin levels by categorizing the patients according to the state of their preterm and term deliveries. There was no difference between the groups. This may be due to larger sample size in that study.

In our study, serum copeptin was negatively correlated with age. This comes in agreement with Yeung et al. (13) who found that higher copeptin levels were significantly ($P<0.05$) related to younger maternal age. In contrary, Tuten et al (14) found that there was no correlation between copeptin level and maternal age.

In our study, serum copeptin was negatively correlated with BMI, while it was positively correlated with respiratory rate, Urea, Creatinine, ALT, AST, INR, and RBG. However, serum copeptin was not correlated with MBP, pulse and temperature.

Ghorab et al. (15) observed that serum copeptin levels have a positive correlation with the body mass index (BMI), blood pressure, serum creatinine, uric acid, ALT and AST.

Tuten et al (14) found that in women with preeclampsia, copeptin correlated positively with systolic and diastolic blood pressure, creatinine, AST, ALT. Also, Kehinde et al (16) showed that serum Copeptin level was positively correlated to serum transaminases.

ROC curve was used to determine the best cut off value of serum copeptin in predicting the threatened preterm labor. Our ROC results revealed that the serum copeptin cut-off value is $\geq$ 380 pg/ml and the area under the curve is equal to 1.00 which indicate that it is an excellent predictor. The sensitivity, specificity, positive predictive and negative predictive values of serum copeptin were 98.3%, 100%, 100% and 96.8% respectively.

No previous studies have been done to determine the cutoff point of serum copeptin level in diagnosis of preterm labor or prediction of preterm birth. However, copeptin levels in the diagnosis and prognosis of preeclampsia have been the subject of numerous other research, all of which found copeptin to be potentially helpful. (13; 17;18).

In a study by Niranjani (19), ROC analysis is used to evaluate the third trimester marker's sensitivity and specificity as well as the diagnostic performance of the serum Copeptin. Serum Copeptin levels between the Pre-eclampsia group and the control group may be distinguished using the optimal cutoff value of 313.57 pg/ml, which results in 82.35% specificity and 96.30% sensitivity. 93.33% is the negative predictive value and 89.66% is the positive predictive value.

Another study by Ola Sayed Mohamed et al., (20) found that the cut off value of serum Copeptin in discriminating preeclampsia and control group was 280 pg/ml, with 80% specificity and 73.33% sensitivity.

Despite these promising findings we have found of serum copeptin, it is essential to acknowledge some limitations, including the relatively small sample size and single-center design of the study. Further large-scale, multicenter research is needed to validate the utility of serum copeptin in a broader population and to assess its potential clinical implications in the management of preterm labor.

Conclusion

Maternal serum copeptin levels can serve as a valuable diagnostic and predictive marker in cases of threatened preterm labor and preterm birth. More reliable results can be obtained with a larger number of patients.

References

1. Tulmac, A., Sayan, O.B., Dag, Z.O., Oguz, Y., Gencosmanoglu, G., Caglar, T., Kisa, U. Serum Copeptin Levels in Threatened Preterm Labor. Fetal Pediatr Pathol 2021; 40(5): 414–422.
2. Slattery, M.M., Morrison, J.J. Preterm delivery. Lancet 2002; 360(9344): 1489–1497.
3. van Baaren, G.J., et al. Cost effectiveness of diagnostic testing strategies including cervical length measurement and fibronectin testing in women with symptoms of preterm labor. Ultrasound Obstet Gynecol 2018; 51(5): 596–603.
4. Dobsa, L., Edozien, K.C. Copeptin and its potential role in diagnosis and prognosis of various diseases. Biochem Med 2013; 23(2): 172–190.
5. Joosen, A.M., et al. Reference intervals and longitudinal changes in copeptin and MR-proADM concentrations during pregnancy. Clin Chem Lab Med 2018; 56(1): 113–119.
6. Ma, H.H., Yang, S.Y., Wang, P., Zhang, J.F. Evaluation of the value of plasma concentration of copeptin in the first prenatal visit to diagnose gestational diabetes mellitus. Acta Diabetol 2017; 54(12): 1123–1129.
7. Oskovi Kaplan, Z.A., Ozgu-Erdinc, A.S. Prediction of Preterm Birth: Maternal Characteristics, Ultrasound Markers, and Biomarkers: An Updated Overview. J Pregnancy 2018; 2018: 1–18.
8. Ibrahim, S.A., Ahmed, M.A. Prediction of Preterm Delivery in Pregnant Women with Threatened Preterm Labor Using Transvaginal Ultrasound and Neutrophils to Lymphocytes Ratio. Zagazig Univ Med J 2020; 26(4): 556–565.
9. Fuchs, I.B., Henrich, W., Osthues, K., Dudenhausen, J.W. Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor. Ultrasound Obstet Gynecol 2004; 24(5): 554–557.
10. Hamzaoğlu, K., Davutoğlu, E.A., Bulut, H., Madazli, R. Prediction of preterm delivery in threatened preterm labor with short cervical length. J Obstet Gynaecol 2022; 42(6): 1911–1916.
11. Foda, A.A., Aal, I.A. Maternal and neonatal copeptin levels at cesarean section and vaginal delivery. Eur J Obstet Gynecol Reprod Biol 2012; 165(2): 215–218.
12. Zulfikaroglu, E., et al. Circulating levels of copeptin, a novel biomarker in preeclampsia. J Obstet Gynaecol Res 2011; 37(9): 1198–1202.
13. Yeung, E.H., et al. Increased levels of copeptin before clinical diagnosis of preeclampsia. Hypertension 2014; 64(6): 1362–1367.
14. Tuten, A., Kucur, M., et al. Maternal serum copeptin concentrations -in early and late- onset preeclampsia. Taiwan J Obstet Gynecol 2015; 54(4): 350–354.
15. Ghorab, A.A., Al-Barshomy, S., Mahmoud, O.A., Shahein, M.S., Sakla, N.S. Value of serum copeptin estimation in the

diagnosis of kidney injury in preeclampsia. Zagazig Univ Med J 2023; 29(3): 753–760.

16. Akinlade, K.S., Adediji, I.O. Serum copeptin and pregnancy outcome in Preeclampsia. Niger Med J 2015; 56(5): 362–368.
17. Jadli, A., et al. Combination of copeptin, placental growth factor and total annexin V microparticles for prediction of preeclampsia at 10–14 weeks of gestation. Placenta 2017; 58: 67–73.
18. Cornelius, D.C. Copeptin: a new biomarker that is specific for preeclampsia? Hypertension 2014; 64: 1189–1191.
19. Niranjani, R. Correlation between Serum Copeptin and Related Biochemical Parameter Levels in assessing the Severity of Pre-Eclampsia. Doctoral dissertation, Tirunelveli Medical College, Tirunelveli 2020.
20. Mohamed, O.S. Copeptin in Pregnancy Induced Hypertension and Pre- eclamptic Egyptian Women: Relation with CD62p. A Case Control Study. Res Obstet Gynecol 2018; 6(2): 23–31.

Scoring System for the prediction of the Severity of Placenta Accrete Spectrum (PAS) in Women with Placenta Previa (PAS scoring system)

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Abstract

Background: Antenatal diagnosis of PAS and a multidisciplinary team approach are necessary to reduce maternal and fetal intrapartum complications.

Objectives: To establish a scoring system for the prediction of the severity of placenta accrete spectrum (PAS) in women with placenta previa.

Methods: This is prospective observational study was conducted on 35 pregnant females with sonographic confirmation of placenta previa, All patients were subjected to complete detailed personal and medical history, complete gynecologic and obstetric history, general examination including vital signs systems review including examination of different systems, laboratory investigations including preoperative routine investigations (CBC, liver function tests, kidney function tests, coagulation profile, virology, detailed ultrasound examination for placental lacunae, bladder uterus interface vascularity, bladder line, uterine muscle thickness, loss of demarcation between uterus and placenta and cervical length as parameters of PAS scoring system.

Results: The mean age of study group was 31.14±5.80 years with mean body weight was 85.57 ±7.96 Kg, 11 females experienced antenatal vaginal bleeding. The mean PAS score in females without PAS , Accreta, Increta, Percreta was 4.00 1±.4, 8.60 ±1.72,12.50 ±1.29, 13.50 ±0.71 which was significantly higher in females with PAS p value < 0.001. The scoring system of PAS has (AUC =0.986, SE= 0.015) with p value<0.001 with cutoff point 5.5, sensitivity of 100%, specificity of 86%.

Conclusion: Scoring System for severity prediction of PAS is simple and feasible modality to ascertain the presence of PAS in women with placenta previa.

Keywords: PAS, Placenta Previa, Prenatal Diagnosis, scoring system,

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Introduction

Placenta accreta spectrum (PAS) appears when the chorionic villi invade into the muscle layer of the uterus [1]. Depending on how deeply the placental villi invade into the uterine muscle, known as the basalis of the decidua of the myometrium, there are PAS 2 types: placenta accreta and placenta increta.[2]. Percreta placenta appears when villi penetrate the myometrium and spread beyond the serosa [2].

The most important factor that increases the placenta previa (PP) prospect is the location of placenta low in the uterus and blocks the internal cervical opening [3]. The frequency of cesarean sections (CS) is increasing in parallel with the incidence of postoperative scar tissue (PAS). This is because trophoblastic villi can penetrate the uterine scar, which is a weaker region of the myometrium [4].

In pregnancy, PAS in high-risk patients' early detection is crucial for planning the correct management at delivery. This is because the placenta may adhere to the myometrium without detaching, leading to severe bleeding that can be life-threatening [5]; Patients with PAS might need preventive uterine artery embolization and blood transfusions [6].

In addition to clinical risk factors (CRF), imaging performances a critical role in the early detection of placental accreta spectrum (PAS). Ultrasound (US) serves as the primary imaging technique for this purpose. Both grayscale and color Doppler ultrasound have proven increasingly valuable in identifying abnormal placental invasion. In the trimesters of second and third, PAS key ultrasonographic indicators include the following: placental lacunae, thinning of the myometrium, the bladder wall interruption, increased the placental bed vascularity, and the clear zone loss. PAS presence can be reliably suspected by these signs when assessed properly [4,7]. This study aimed to create a scoring system to assess placenta accreta spectrum (PAS) severity in women who have placenta previa.

Methods

This is a prospective observational study was conducted at department of obstetrics and Gynecology of Menoufia University hospitals from October 2023 to April 2024 conducted on 35 pregnant females with sonographic confirmation of placenta previa diagnosis.

Ethical consideration: The study protocol received approval from the ethical committee at the Faculty of Medicine, Menoufia University. Written informed consent was obtained from all participants prior to the start of the trial. Every participant knew what was going to happen and may withdraw from the research at any time without explanation.

Participants had to be between the ages of 19 and 44 and have a confirmation of sonography of placenta previa after 28 gestational weeks to be eligible for the study. Women who were excluded had to have undergone an emergency referral for severe vaginal bleeding and needed surgery without a previous routine ultrasonographic examination at our hospital. Methods: All patients were evaluated in great detail, with a full medical history, physical exam, abdominal exam, and vaginal exam. Laboratory investigations included a complete blood count, Rh typing, a coagulation profile (prothrombin time, partial thromboplastin time, and INR), liver function tests, serum creatinine levels, and liver function tests. An ultrasound scan was also performed.

Estimated score scale for PAS:

Here are some of the ultrasonographic parameters that were examined: placental lacunae, vascularity at the interface of uterus-bladder, the anterior wall myometrial thickness, the hypoechoic retroplacental zone, the line of bladder, length of cervix, and previous cesarean sections history.

These seven characteristics formed the basis of a score system for evaluating the spectrum of placenta accreta (PAS).

Placental lacunas were classified based on the study of Finberg [8] as follows: level one, no lacunae detected; level two, one and three lacunae, typically round and small, less than two cm in size; level three, four and six lacunae, usually irregular, ranging from 2 to 4 cm; and level 4, extensive irregular lacunae covering significant portions of the placenta or the entire placenta, four cm or larger. The main of uterine wall at the site of attachment of placental was categorized as: level one, posterior; level two, lateral; and level three, anterior.

The interface of uterus–bladder vascularity was graded according to the study of Luo et al. [9] showed that levels 1–3 are to be considered: low flow, moderate flow, and fewer than ten vessels (often less than 1 mm in diameter). Level 2 is higher flow, with more than ten small vessels and/or numerous visible main vessels. Level 3 is the interface completely filled with vessels or bridging vessels.

According to the evaluation of the hypoechoic retroplacental zone, the myometrial thickness was classified into three levels: level 1, myometrium ≥1 mm with a clear zone; level 2, myometrium ≥1 mm with an ambiguous or lost zone; and level 3, myometrium <1 mm with a lost zone.

A complete and clear bladder line is indicated by a level 1, an unclear or irregular line by a level 2, and a lost line by a level 3.

There were three levels of cervical length classifications: level 1, greater than 3 cm; level 2, between 1 and 3 cm; and level 3, less than 1 cm.

The measurements of the myometrial thickness were taken in the sagittal plane at the lower anterior region, close to the internal cervix. In order to evaluate vascularity and myometrial thickness, a trained sonographer used transvaginal ultrasound, color Doppler, transabdominal ultrasound, and grayscale imaging.

Clinical procedures: Our research shows that the surgical team was informed of the anticipated PAS scores. Obstetricians with expertise in PAS performed cesarean sections on patients whose scores were 4 or higher. Patients whose scores were 3 or lower were considered to have an extremely low likelihood of PAS, on the other hand. Skilled surgeons or, in the case of hysterectomy, histological examination verified the PAS level. The patient was deemed to not have PAS if the placenta was delivered spontaneously.

Study outcome

Primary Outcome: Develop a scoring system to assess spectrum of placenta accreta (PAS severity) in women having placenta previa.

Secondary outcome: Estimate the incidence of neonatal and maternal outcomes based on the different levels of placenta accreta spectrum (PAS).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 26 was utilized on an IBM compatible computer for data tabulation and analysis.

Normally distributed quantitative data was denoted by mean ($\bar{x}$) and standard deviation (SD), whereas qualitative data was denoted by number and percentage (No & %), and non-normally distributed quantitative data was depicted by median, interquartile range (IQR), and range.

The following test types are used in analytical statistics: chi-square test ($\chi 2$), one way ANOVA test (F), and the Kruskal Wallis test.

The receiver operator characteristic (ROC) curves were built with highest sensitivity and specificity cutoffs to assess the biomarker effectiveness. The test's accuracy is measured by the area under the ROC curve, or AUROC. A test's area of 0.5 is not meaningful, whereas a test's area of 1 is desired. For statistical significance, we set the cutoff at p-values less than 0.05.

Results

Demographic data and clinical characteristics were as follows: the study group had 31.14 years mean age, a mean body weight of 85.57 kg, and an average height of 165.06 cm. The children median number was 3, varying from 2 to 3. The mean age of gestation at recruitment was 33.74 weeks, and 11 pregnant women experienced antenatal vaginal bleeding. The details are illustrated in Table 1.

The frequency and distribution of the Placenta Accreta Spectrum (PAS) parameters, including grading scores related to placental lacunae, attachment of placental to the wall of utreus, factors such as the amount of prior cesarean sections, cervical length, myometrial thickness, and vascularity at the uterine-bladder contact, are shown in Table 2.

Table 3 showed the scoring system according to PAS, as a statistically substantial difference was found among without PAS females and with PAS females as regard placental lacunae grades as most of with PAS females had grade 3and 4 , also a statistically substantial difference was found among without PAS females and with PAS females as regard main uterine wall placental attachment, as most of with PAS females had level 3 placental attachment, also females with PAS significantly had more vascularity in the uterine bladder interface. Most females with PAS significantly had bladder line at level 2 and 3, Also, most females without PAS significantly had cervical length at level 1. Also females with PAS had significantly lower myometrial thickness and more times of CS,

Also as regard PAS score the mean score un females without PAS , Accreta, Increta, Percreta was 4.00 1±.4, 8.60 ±1.72,12.50 ±1.29, 13.50 ±0.71 which was significantly higher in females with PAS and was higher in patients having Percreta than Increta than Accreta p value < 0.001.

The outcome of maternal and fetal rendering to PAS are illustrated in table 4, no substantial difference was found among females without PAS, with accreta, with increta or placenta percreta females as regard uterine artery ligation, bladder injury, ICU admission, conservative CS, CS hysterectomy fetal outcome and the time of operation p value>0.05, While a statistically substantial difference was found as regard the need of hemostatic sutures and blood transfusion as females with PAS needed uterine hemostatic sutures and blood transfusion than without PAS p value 0.002 and 0.001 respectively. Also a statistically substantial difference was found regarding the type of CS as 85.7% females without PAS, 26.7% with accreta , had emergent CS. While one case with placenta percreta and no cases with placenta increta had emergent CS.

Diagnostic accuracy of scoring system in prediction of PAS is illustrated in table 5, the scoring system of PAS has (AUC =0.986, SE= 0.015) with p value<0.001 with cutoff point 5.5, sensitivity of 100%, specificity of 86%, accuracy of 94%, PPV of 91% and NPV of 100%.

Discussion

This was a prospective observational study included 35 pregnant women with placenta previa, aimed at developing a systemic score to predict the Placenta Accreta Spectrum likelihood.

Spectrum of Placenta Accreta (PAS) disorders involve several abnormal attachment types or trophoblastic cells invasion into the myometrium. Damage to the endometrial-myometrial interface is what causes this disorder to interfere with proper placentation. The outcome is an excessively deep penetration of the placental villi and an overabundance of trophoblastic infiltration due to insufficient decidualization at the uterine scar site [6].

Our study showed that our study group mean age was 31.14±5.80 years with mean

body weight was 85.57 ±7.96 Kg, the mean height was 165.06 ±6.25 cm, with median parity of 3 (2-3) offsprings, the age of gestation mean at recruitment was 33.74 ±2.56 weeks, there were 11 pregnant females experienced antenatal vaginal bleeding, Of the participants, 32 women had experienced at least 1 previous cesarean section.Which is in agreement with Shih et al.[10] his 170 women were included in the research, and their average age when they were diagnosed was 32.1 ± 4.7 years. One hundred twenty-two of them had undergone a caesarean section in the past, and forty-six had a history of uterine procedures like myomectomy or curettage. Twenty-one of the pregnant women in this study reported bleeding before the baby was born. At the time of sonographic diagnosis of placenta accreta, the mean age of gestation was 30.7 ± 2.2 weeks; at birth, it had increased to 34.3 ± 1.7 weeks. Also, Tovbin et al.[11] noticed that the average age of the mother at the ultrasound was 33.8 ± 4.5 years, and the mean age of gestation at diagnosis was 33.9 weeks of pregnancy. On average, there were 4.0 ± 1.6 gestations per mother, and 2.0 ± 1.2 live births per mother. There was a mean of gestational age of 37.7 ± 1.7 weeks at the delivery time. Zhang et al.[12] conducted a study that involve 532 women, whose ages ranged from twenty to fifty years and whose age of gestion at delivery ranged from 28 to 40.5 weeks. The aim was to validate a prenatal PAS score for diagnosing Placenta Accreta Spectrum (PAS). According to PAS classification there were 14(40%) pregnant females without PAS, 15 (42.9%) females with placenta accreta, 4 (11.4%) with placenta increta and 2(5.7%) with percreta. Among them there were 26 females had conservative CS while 9 had CS hysterectomy,16 females with PAS had uterine hemostatic sutures, Also the mean operative time was 35.71 ±1.56 minutes, also according to Neonatal APGAR score there were 23 neonates with good APGAR score, and 12 neonates were admitted to NICU. The study of Shih et al., [10] found that 39 patients were detected with Spectrum of Placenta Accreta (PAS) depend on criteria of antenatal sonographic. To prevent severe postpartum hemorrhage, cesarean hysterectomy was performed on 37 of these women. Final pathological analysis identified 6 cases (3%) of placenta accreta, 24 cases (24.6%) of placenta increta, and 9 cases (5.3%) of placenta percreta. Of the 170 patients, 131 (77%) were ultimately diagnosed with placenta previa without accrete. Saxena et al. [13] reported that 14.29% of cases with grade 1 PAS showed no invasion, while 85.71% exhibited invasion, including 9.52% with placenta percreta, 19.05% with placenta increta, and 57.14% with placenta accreta. Additionally, Luo et al. reported that 60 women (40%) were diagnosed with Placenta Accreta Spectrum (PAS). Within this group, placenta accreta was identified in 79 cases (20%), increta in 53 cases (13%), and percreta in 28 cases (7%). Also Saxena et al.[13] noticed that cesarean hysterectomy was performed on all women with PAS grades 1–3 (42%) due to placenta non-separation and the postpartum hemorrhage risk. In contrast, none of the women with PAS grade 0 (58%) required a hysterectomy; they underwent a cesarean section instead.

Regarding the PAS score, the average scores were 4.00 ± 1.4 for women without PAS, 8.60 ± 1.72 for those with accreta, 12.50 ± 1.29 for those with increta, and 13.50 ± 0.71 for those with percreta. Scores were significantly higher in women with PAS, with the highest scores observed in those with percreta, followed by increta and accreta, with a p-value of < 0.001. Moreover, all sonographic criteria used to determine the PAS score were significantly linked to the diagnosis of PAS, which aligns with the findings of Tovbin et al.[11] who observed a statistically substantial difference in the MAP prevalence across different probability groups based on the scoring system. The prevalence rates were 0.9% in the group of low probability, 29.4% in the group of moderate probability, and 84.2%

in the high probability group, with a p-value of < 0.0001. They also found that all criteria of sonography used in the scoring system were substantially related with MAP, with a p-value of < 0.0001.Which is also agreed with Ağaoğlu & Çağlar.[14] found that the mean PAS scores were 2.8 ± 1.4 for women without PAS, 3.6 ± 1.9 for those with accreta, 5.1 ± 2.4 for those with increta, and 9.8 ± 1.6 for those with percreta, with a p-value of 0.001. The score of PAS was significantly superior in the group of percreta related to the other groups (p = 0.000). However, there were no significant differences in scores of PAS among the no PAS, accreta, and groups of increta (p > 0.05).

Saxena et al.[13] observed that a substantial correlation was found among the prior cesarean sections number and the score of PAS (p = 0.004). The majority of women (52%) exhibited lacunae as an ultrasound finding, followed by loss of the clear zone (42%), bladder wall interruption (34%), uterovesical hypervascularity (16%), and increased vascularity in the inferior part of the placenta (8%).Additionally, a significant association was reported among the PAS score and the degree of placental invasion (p < 0.0001).Which is also agreed by Zhang et al.[12]and Del Negro et al.[14].

Gao et al.[15] found that a substantial correlation was discovered among sonographic criteria of PAS diagnosis and previous times of cesarean section with patients with PAS and its severity p value<0.05. Also, Zhang et al.[12] reported that a substantial correlation among PAS and factors such as placental location, placental thickness, the presence or absence of the retroplacental space, the thickness of the retroplacental myometrium, the presence of placenta lacunae, retroplacental myometrial blood flow, and a history of cesarean sections. However, there were no significant associations with the presence or absence of a cervical sinus, cervical morphology, or bladder line interruption.

The scoring system of PAS showed a high diagnostic performance with an AUC of 0.986 (SE = 0.015) and a p-value < 0.001 at a cutoff point of 5.5. It demonstrated 100% sensitivity, 86% specificity, 94% accuracy, 91% positive predictive value (PPV), and 100% negative predictive value (NPV). Shih et al. (2009) determined that 3D power Doppler, with a sensitivity of 97% and specificity of 92%, was the only criteria that provided the best accurate diagnosis of placenta accreta, as determined by ROC analysis. Although they had almost perfect specificities, the criteria "disrupted bladder mucosa" (18%) and "exophytic placenta invading the bladder" (10%) had low sensitivity for detecting placenta accreta, while the criteria "loss of retroplacental echolucent zone" and "abnormal lacunae" were less effective.

Which is consistent with Tobvin et al.[11] reported that for diagnosing MAP, a high probability score had 69.6 % overall sensitivity, 98.7% specificity , 84.2% positive predictive value, and 97.1%. negative predictive value When both high and moderate probability scores were considered, the sensitivity increased to 91.3% and the specificity was 93.6%, with an AUC of 0.94 (95% CI, 0.86–1.00).

Also consistent with Saxena et al.[13] reported that, using histopathology as the gold standard, the PAS score achieved 100% overall sensitivity, 90.62% specificity, 85.71%positive predictive value (PPV), 100% negative predictive value (NPV), and diagnostic accuracy of 94%.

Gao et al.[15] reported that the scoring system for diagnosing PAS had a sensitivity of 82.6%, specificity of 81.8%, positive predictive value of 82.6%, and negative predictive value of 81.8%. Clinical diagnosis indicated that 23 of the 45 patients in the scoring set had PAS, while 22 did not. The 37 cases where the diagnosis was in line with the "gold standard" resulted in a concordance rate of 82.2% (37/45).

Zhang et al.[12] found that using the final ultrasound scoring system, a total score of less than 3 points indicated no PAS. Placenta accreta was diagnosed with a score of 3 or higher, showing 84% sensitivity and 53% specificity. A score of 5 or higher identified PAS, with 69% sensitivity and 92% specificity. Placenta increta was diagnosed with a score of 7 or higher, yielding 58% sensitivity and 91% specificity. Finally, placenta percreta was identified with a score of 10 or more, with 74% sensitivity and 83% specificity.

In contrast to Yang et al.[16] discovered that the PAS scoring system had a sensitivity of 98.1%, specificity of 31.4%, and overall accuracy of 74.3% for detecting placenta percreta at a cutoff of 6 points. The prenatal ultrasound staging system and the placenta accreta scoring system both offered precise predictions for placenta percreta. When compared to clinical classification, their areas under the curve were 0.872 (95% CI: 0.793-0.951) and 0.864 (95% CI: 0.779-0.949), respectively, and the p-value was 0. 0001.

Luo et al.[9] found that using the threshold scores of <2.25, 2.25-6.20, 6.20-8.95, and ≥8.95 for diagnosing no PAS, accreta, increta, and percreta, respectively, the scoring system established a high positive predictive value (PPV) of 95.44% for no PAS and 81.81% for percreta. It also showed moderate PPVs of 80.26% for accreta and 75.47% for increta.

Del Negro et al.[14] found that when the PAS score was below 5.5, all patients were correctly classified as non-PAS (group 0). Conversely, patients with scores above 15.5 were accurately diagnosed with placenta percreta. However, a score of 13 showed an overlap between PAS and non-PAS cases. The analysis demonstrated strong performance metrics, with a 100% sensitivity, 89% specificity, 92% accuracy, and 0.94 AUC. To corroborate these findings and further verify the PAS score for prenatal prediction of morbidly adherent placenta, multicenter studies are needed, as this study had significant limitations, such as a limited sample size and being done at a single site.

Conclusion

The scoring system for predicting the severity of Placenta Accreta Spectrum (PAS) is a straightforward and practical method for determining the presence of PAS in women with placenta previa.The scoring system for predicting the severity of Placenta Accreta Spectrum (PAS) is a straightforward and practical method for determining the presence of PAS in women with placenta previa.

References

1. Silver RM, Barbour KD . Placenta accreta spectrum. Obstet Gynecol Clin North Am ;2015;42:381–402.
2. Cahill AG, Beigi R, Heine RP, Silver RM, Wax JR. Placenta Accreta Spectrum. Am J Obstet Gynecol. 2018 Dec;219(6):B2-B16
3. Carusi DA, The placenta accreta spectrum: Epidemiology and risk factors. Clin Obstet Gynecol ,2018,61:733–742.
4. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. Am J Obstet Gynecol. 2018;218(1):75-87
5. Leyendecker JR, DuBose M, Hosseinzadeh K, Stone R, Gianini J, Childs DD, Snow AN, Mertz H. MRI of pregnancy-related issues: abnormal placentation. AJR Am J Roentgenol. 2012;198(2):311-20.
6. Jauniaux E, Bhide A, Kennedy A, Woodward P, Hubinont C, Collins S; FIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel. FIGO consensus guidelines on placenta accreta spectrum disorders: Prenatal diagnosis and screening. Int J Gynaecol Obstet. 2018;140(3):274-280.

7. Jauniaux E, Bunce C, Grønbeck L, Langhoff-Roos J. Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(3):208-218.
8. Finberg HJ, Williams JW. Placenta accreta: prospective sonographic diagnosis in patients with placenta previa and prior cesarean section. J Ultrasound Med. 1992 ;11(7):333-43
9. Luo L, Sun Q, Ying D, Wu X, Yan P, Yang Y, Chen Z. Scoring system for the prediction of the severity of placenta accrete spectrum in women with placenta previa: a prospective observational study. Arch Gynecol Obstet. 2019 ;300(3):783-791
10. Shih JC, Palacios Jaraquemada JM, Su YN, Shyu MK, Lin CH, Lin SY, Lee CN. Role of three-dimensional power Doppler in the antenatal diagnosis of placenta accreta: comparison with gray-scale and color Doppler techniques. Ultrasound Obstet Gynecol. 2009 Feb;33(2):193-203.
11. Tovbin J, Melcer Y, Shor S, Pekar-Zlotin M, Mendlovic S, Svirsky R, Maymon R. Prediction of morbidly adherent placenta using a scoring system. Ultrasound Obstet Gynecol. 2016;48(4):504-510.
12. Zhang J, Li H, Feng D, Wu J, Wang Z, Feng F. Ultrasound scoring system for prenatal diagnosis of placenta accreta spectrum. BMC Pregnancy Childbirth. 2023 ;23(1):569
13. Saxena U, Rana M, Tripathi S, Misra RN, Khambra P. Prediction of Placenta Accreta Spectrum by Prenatal Ultrasound Staging System in Women with Placenta Previa with Scarred Uterus. J Obstet Gynaecol India. 2023 ;73(Suppl 2):191-198
14. Del Negro V, Aleksa N, Galli C, Ciminello E, Derme M, Vena F, Muzii L, Piccioni MG. Ultrasonographic Diagnosis of Placenta Accreta Spectrum (PAS) Disorder: Ideation of an Ultrasonographic Score and Correlation with Surgical and Neonatal Outcomes. Diagnostics (Basel). 2020 ;11(1):23.
15. Gao Y, Gao X, Cai J, Han F, Xu G, Zhang X, Zhang T, Yu L. Prediction of placenta accreta spectrum by a scoring system based on maternal characteristics combined with ultrasonographic features. Taiwan J Obstet Gynecol. 2021;60(6):1011-1017
16. Yang X, Zheng W, Yan J, Yang H. Comparison between placenta accreta scoring system, ultrasound staging, and clinical classification. Medicine (Baltimore). 2022 ;101(46):e31622.

Table (1): Maternal characteristics of studied participants (n=35)

Variable	No. of studied participants=35
Age (Years) Mean ±SD Range	 31.14 ±5.80 20-44
Weight (Kg) Mean ±SD Range	 85.57 ±7.96 69-105
Height (cm) Mean ±SD Range	 165.06 ±6.25 150-179
BMI (Kg/m^2) Mean ±SD Range	 31.48 ±3.34 25.04-42.22
Parity Median (IQR) Range	 3 (2-3) 0-6
Gestational age (Weeks) Mean ±SD Range	 33.74 ±2.56 28-37
Previous vaginal deliveries Median (IQR) Range	 0 (0-0) 0-4
Previous abortions Mean ±SD Range	 0 (0-1) 0-4
Antenatal vaginal bleeding (No& %) Present Absent	 11 (31.4%) 24 (68.6%)

SD: Standard deviation, IQR: Interquartile range, BMI: Body Mass Index

Table (2): Scoring system for prediction of PAS

Variable	No. of studied participants=35	
	No.	**%**
Placental lacunes 1 2 3 4	 1 20 11 3	 2.9 57.1 31.4 8.6
Main uterine wall of placental attachment 1 2 3	 8 7 20	 22.9 20 57.1

Vascularity in uterus-bladder interface 1 2 3	 18 14 3	 51.4 40 8.6
Bladder line 1 2 3	 17 11 7	
Cervical length 1 2 3	 23 11 1	
Myometrial thickness and hypoechoic retro-placental zone 1 2 3	 12 16 7	
Times of previous CS 0 1 2 ≥3	 3 6 9 17	
Total score Median (IQR) Range	7 (4-11) 2-14	

IQR: Interquartile range

Table (3): Scoring system according to PAS (n=35)

Variables	Without PAS (n=14)		Accreta (n=15)		Increta (n=4)		Percreta (n=2)		Test of significance	p-value
	No.	%	No.	%	No.	%	No.	%		
Placental lacunes										
1 2 3 4	1 12 0 1	7.1 85.7 0 7.1	0 8 6 1	0 53.3 40 6.7	0 0 4 0	0 0 100 0	0 0 1 1	0 0 50 50	χ2=22.36	**0.008***
Main uterine wall of placental attachment										
1 2 3	5 6 3	35.7 42.9 21.4	3 0 12	20 0 80	0 1 3	0 25 75	0 0 2	0 0 100	χ2=14.91	**0.018***
Vascularity in uterus-bladder interface										
1 2 3	13 1 0	92.9 7.1 0	5 10 0	33.3 66.7 0	0 3 1	0 75 25	0 0 2	0 0 100	χ2=40.43	**<0.001***
Bladder line										
1 2 3	13 1 0	92.9 7.1 0	4 8 3	26.7 53.3 20	0 2 2	0 50 50	0 0 2	0 0 100	χ2=27.03	**<0.001***

Cervical length										
1 2 3	8 5 1	57.1 35.7 7.1	14 1 0	93.3 6.7 0	0 4 0	0 100 0	1 1 0	50 50 0	χ2=15.31	**0.018***
Myometrial thickness and hypoechoic retro-placental zone										
1 2 3	12 2 0	85.7 14.3 0	0 11 4	0 73.3 26.7	0 3 1	0 75 25	0 0 2	0 0 100	χ2=34.78	**<0.001***
Times of previous CS										
0 1 2 ≥3	3 5 4 2	21.4 35.7 28.6 14.3	0 1 4 10	0 6.7 26.7 66.7	0 0 0 4	0 0 0 100	0 0 1 1	0 0 50 50	χ2=17.42	**0.036***
Total score										
Mean ±SD Range	4.00 1±.4 2-7		8.60 ±1.72 6-11		12.50 ±1.29 11-14		13.50 ±0.71 13-14		F=51.12	**<0.001***

*: Statistically significant, SD: Standard deviation, χ2: Chi-squared test, F: One Way ANOVA test

Table (4): Maternal and fetal outcome according to PAS (n=35)

Variables	Without PAS (n=14)		Accreta (n=15)		Increta (n=4)		Percreta (n=2)		Test of significance	p-value
	No.	%	No.	%	No.	%	No.	%		
Uterine artery ligation										
Yes No	12 2	85.7 14.3	15 0	100 0	4 0	100 0	2 0	100 0	χ2=3.18	0.468 (NS)
Hemostatic sutures Or uterine remodeling										
Yes No	2 12	14.3 85.7	12 3	80 20	3 1	75 25	1 1	50 50	χ2=13.53	**0.002***
Bladder injury										
Yes No	1 13	7.1 92.9	1 14	6.7 93.3	1 3	25 75	0 2	0 100	χ2=1.67	0.573 (NS)
Blood transfusion (Units)										
Median (IQR) Range	0.5 (0-1) 0-5		2 (1-2) 1-4		3.5 (2.25-4.75) 2-5		4.5 (4-5) 4-5		K=16.76	**0.001***
ICU admission										
Yes No	1 13	7.1 92.9	3 12	20 80	2 2	50 50	1 1	50 50	χ2=4.82	0.156 (NS)
Maternal outcome										
Conservative CS CS hysterectomy	13 1	92.9 7.1	9 6	60 40	3 1	75 25	1 1	50 50	χ2=4.75	0.184 (NS)
Fetal outcome										
Good APGAR NICU admission	10 4	71.4 28.6	10 5	66.7 33.3	3 1	75 25	0 2	0 100	χ2=4.20	0.306 (NS)

Type of operation										
Elective Emergent	2 12	14.3 85.7	11 4	73.3 26.7	4 0	100 0	1 1	50 50	$\chi 2$=14.39	**0.001***
Time of operation (Minutes)										
Mean ±SD Range	35.71 ±1.33 33-37		35.67 ±2.02 29-38		36.00 ±0.82 35-37		35.50 ±0.71 35-36		F=0.06	0.982 (NS)

*: Statistically significant, IQR: Interquartile range, SD: Standard deviation, $\chi 2$: Chi-squared test, K: Kruskal Wallis test, F: One Way ANOVA test

Table (5): Diagnostic accuracy of scoring system in prediction of PAS

Scoring system	
AUC	0.986
SE	0.015
p-value	**<0.001***
95% CI	0.957-1.000
Cutoff point	5.5
Sensitivity	100%
Specificity	86%
Accuracy	94%
PPV	91%
NPV	100%

AUC: Area under curve, SE: Standard error, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Single Pedicle Ligation; A New Surgical Technique to Lower Hospital Cost of Abdominal Hysterectomy among Developing Countries – A Pilot Study

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Abstract

Background: Although minimally invasive approaches to hysterectomy are the preferred route, an open abdominal hysterectomy remains an important surgical option for some patients.

Objective: Assessment of single pedicle ligation as a new surgical technique aiming to decrease abdominal hysterectomy related bleeding and costs among developing countries compared with conventional sutures.

Patients and Methods: A total of 40 women candidates for elective total abdominal hysterectomy and/or bilateral salpingio-oophorectomy were enrolled and divided into two equal groups. Group A (control group) was subjected to classic technique and group B (study group) subjected to single pedicle ligation technique. After surgery, both groups were compared regarding number of polyglactin 910 suture ampoules used all over the surgery and estimated blood loss.

Results: The study revealed that although there were differences favouring this new surgical technique over classic surgical technique, as drop 0.78% less in Hematocrit value, 4%less in mean estimated blood loss , 25% less in drain use and 25% less blood transfusion.But these results had no statistical significant difference.

Conclusion: In women undergoing abdominal hysterectomy single pedicle ligation surgical technique help in lowering surgical related blood loss and costs with no statistically significant difference compared with traditional methods.

Keywords: Single Pedicle Ligation; Abdominal Hysterectomy; Developing Countries.

INTRODUCTION

The surgical operation known as hysterectomy is often performed on a global scale. Hysterectomy is most often performed for symptomatic uterine leiomyomas (51.4%), abnormal uterine hemorrhage (41.7%), endometriosis (30%), and prolapse (18.2%), but there may be some in-

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stances when these criteria overlap (Huang et al., 2020).

Hysterectomies may be performed by several methods, including vaginal, laparoscopic approaches (such as complete laparoscopic hysterectomy with or without robotic assistance or laparoscopically assisted vaginal hysterectomy), or abdominal approaches (Eggemann et al., 2018).

Analysis of U.S. surgical data between 1998 and 2010 sheds light on evolving practice patterns in this area and underscores a trend of the decreasing number of hysterectomies performed through the abdominal route—from 65% to 54% during this period—in favor of minimally invasive techniques (Lin et al., 2021).

The obstetrician–gynecologist should discuss the options with the patient and make clear recommendations on which route of hysterectomy will maximize benefits and minimize risks given the specific clinical situation (Higgins et al., 2022).

Although minimally invasive approaches to hysterectomy are the preferred route, open abdominal hysterectomy remains an important surgical option for some patients (Polen-De et al., 2021).

Open abdominal hysterectomy may be necessary when the vaginal or laparoscopic approach is not appropriate to manage the patient's clinical situation, when facilities cannot support less invasive surgical approaches, or when an attempt at a minimally invasive route to hysterectomy fails intraoperatively (Ali et al., 2019).

The occurrence of bleeding issues after a hysterectomy is influenced by many factors. The median range of expected blood loss during abdominal hysterectomy, as determined by randomized studies, is 238-660.5 ml. There exists a correlation between various blood loss parameters, such as transfusion, decline in hemoglobin, hematoma, and vascular injury. Additionally, numerous variables have been identified as contributing to the escalation of bleeding complications. These variables encompass the proficiency of the surgeon, the volume of the surgeon's practice, the surgical volume of the hospital, and the surgical technique employed (Naveiro-Fuentes et al., 2018).

AIM OF THE WORK

This study aims to assess single pedicle ligation as a new surgical technique aiming to decrease abdominal hysterectomy related bleeding and to reduce of the surgery Cost in developing countries as decrease vicryl ampoules numbers and keeping all the pedicles by the same knot reduces the incidence of bleeding in-between the pedicles and double securing of the pedicles.

PATIENTS AND METHODS

This interventional study (pilot study) was conducted at Obstetrics and Gynecology Department, Faculty of Medicine, Ain Shams University Hospitals from April 2023 till February 2024. A total of 40 women were enrolled and divided into two equal groups. To achieve the objective, pilot study was conducted on at least 40 women; they were subdivided into 2 equal groups (20 women in the standard abdominal hysterectomy and 20 women in the single pedicle ligation group) including (the dropout rate.

Inclusion criteria:
Age: 40-60 years old, Women candidate for elective total abdominal hysterectomy and/or bilateral salpingio-oophorectomy for any cause as abnormal uterine bleeding due to uterine fibroids or endometrial hyperplasia or dysfunctional uterine bleeding resistant to medical treatment, adenomyosis resistant to medical treatment.

Exclusion criteria:
Women unfit for surgery, women with chronic debilitating disease, women with bleeding

tendency or taking anticoagulant therapy, women refusing to participate or sign informed consent, pelvic inflammatory disease (PID), endometriosis, diffuse intra-abdominal adhesions necessitating extensive dissection, gynecological cancer/ sarcoma.

Study interventions and procedures:

a) Complete history taking of clinical importance including:

Personal history: age, residence, occupation, marital status and special habits as smoking, alcohol, etc, **present history** of bleeding or pain including onset, duration, and criteria of pattern, **menstrual history:** day of last menstrual period, regularity and amount of bleeding, **obstetric history:** gravidity, parity, previous miscarriages or obstetric complications, **contraceptive history:** type, duration of use before pregnancy, **medical history:** medical comorbidities with pregnancy as hepatic, renal, endocrinal, psychosocial condition, cardiovascular, diabetes, chronic hypertension, **surgical history:** Previous cesarean sections and its neonatal outcomes, **family history** of maternal or fetal complications with pregnancy.

b) Clinical examination with special emphasis on:

General (pulse, blood pressure and temperature), cardiac, chest, neurological, abdominal, lower limb and pelvic examinations in a form of bimanual and speculum examination to detect any abnormal findings and to exclude any local cause of bleeding or pain.

c) Investigation:

Routine investigations as complete blood picture, liver and kidney function tests, coagulation profile "prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR)", viral hepatitis markers: hepatitis B and C viruses, Blood group (ABO) and Rh, urinalysis, ECG and chest X-ray examination, cervical Pap smear, endometrial sampling if indicated.

d) **Imaging:** Transvaginal and pelvic ultrasounds were done by Samsung HS60 ultrasound device in Ain Shams University Maternity Hospital to detect conditions such as uterine fibroids, adenomyosis, and endometriosis.

e) All ultrasound examinations were done by an expert and professional medical personnel to ensure the accuracy of examination results.

1. A total of 2 units of packed RBCs were reserved after making ABO matching.
2. Surgical procedure in both groups:

- The procedure team was lecturer and assistant lecturer or senior resident. The surgery team was fixed to avoid variation in the technique.
- The patient was positioned supine on the operation table and spinal anesthesia was used unless contraindicated.
- Sterilization, catheterization and toweling.
- Laparotomy and development of the visual field.
- Clamping and cutting of the round ligament.
- Double clamping, cutting, and ligation of the ovarian ligament and Fallopian tube (or the infundibulopelvic ligament) using coated, synthetic, absorbable, polyglactin 910, braided, 0 or 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery.
- Mobilization of the bladder.

► Then in group A:

- Clamping, cutting, and ligation of the uterine artery and vein using coated, synthetic, absorbable, polyglactin 910, braided, 0 or 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery
- Pushing down the cutting stump with gauze.

- Clamping, cutting, and ligation of the sacrouterine ligament and the posterior half of the cardinal ligament using coated, synthetic, absorbable, polyglactin 910, braided, 0 or 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery.
- Clamping, cutting, and ligation of the vesicouterine ligament and the anterior half of the cardinal ligament using coated, synthetic, absorbable, polyglactin 910, braided, 0 or 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery.
- Clamping of the boundary between the portio vaginalis and the vagina
- Incision of the vagina and removing the uterus.
- Disinfection of the vagina and closure of the vaginal cuff using coated, synthetic, absorbable, polyglactin 910, braided, 0 or 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery.

► While in group B 'single pedicle ligation': Aiming to use 2 ampoules of coated, synthetic, absorbable, polyglactin 910, braided, 1, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt) all over the surgery.

- Clamping, division and ligation of uterine vessels with Vicryl 1 suture (keeping the Vicryl threads intact).
- Clamping, division and ligation of Mackenrodt's ligament to the previous knot (keeping the Vicryl threads intact).
- Clamping, division and ligation of paravaginal tissue to the previous knot (keeping the Vicryl threads intact).
- Opening of vaginal cuff, removal of the uterus and closure of vaginal vault with the previous Vicryl 1 threads.

► Then in both groups;

- Hemostasis
- Closure of the abdominal wall:
- Closing the rectus sheath with a continuous looped suture using of coated, synthetic, absorbable, polyglactin 910, braided, 1, dyed, 75 cm, curved rounded needle (Vicryl ; EGYSORB, Egypt).
- Subcutaneous wound closure using interrupted technique of suturing using of coated, synthetic, absorbable, polyglactin 910, braided, 0, dyed, 75 cm, curved rounded needle (Vicryl®; EGYSORB, Egypt).
- Closing the skin using Ethicon®; PROLENE Polypropylene Suture, 8411H, Synthetic Non-absorbable, CT-2 (26 mm), 1/2 Circle needle.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test. The p-value was considered significant as the following: P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant, P-value >0.05 was considered insignificant.

RESULTS

Table 1: Comparison between Group A: Control group and Group B: Study group according to Demographic data.

Demographic data	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
Age "years"					
Mean±SD	47.00±4.40	46.45±3.72	0.182	0.672	NS
Range	42-56	40-53			
BMI [wt/ ht^2]					
Mean±SD	28.30±6.23	27.69±4.71	0.124	0.727	NS
Range	20-44	23-41			
Wt. (kg)					
Mean±SD	81.45±15.98	78.85±10.78	0.364	0.550	NS
Range	60-120	65-105			
Height (cm)					
Mean±SD	1.63±0.06	1.63±0.04	0.000	1.000	NS
Range	1.5-1.7	1.6-1.7			

Using: t-Independent Sample t-test for Mean±SD;
NS: Non significant

Table 2: Comparison between group A: Control group and Group B: Study group according to premenopause, postmenopause, myoma, adenomyosis and endometrial hyperplasia without atypia.

	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
Premenopause	19 (95.0%)	19 (95.0%)	0.000	1.000	NS
Postmenopause	1 (5.0%)	1 (5.0%)	0.000	1.000	NS
Myoma	17 (85.0%)	14 (70.0%)	1.290	0.256	NS
Adenomyosis	2 (10.0%)	6 (30.0%)	2.500	0.114	NS
Endometrial hyperplasia without atypia	2 (10.0%)	0 (0.0%)	2.105	0.147	NS

Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate
NS: Non significant

Table 3: Comparison between Group A: Control group and Group B: Study group according to Hematocrit (Hct) before and after operation& Drop of Hematocrit.

AAW	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
Before operation					
Mean±SD	35.22±2.88	35.44±5.75	0.022	0.882	NS
Range	29-39.8	28.6-54			

After operation					
Mean±SD	30.01±3.07	31.00±5.40	0.508	0.480	NS
Range	23-34	24-45			
Drop of HCT					
Mean±SD	5.22±2.88	4.44±1.88	1.016	0.320	NS
Range	1.1-11	1.2-9			

Using: t-Independent Sample t-test for Mean±SD;
NS: Non significant.

This table shows drop of Hematocrit 0.78% less in group B but without statistically significant difference between both groups, with p-value (p>0.05).

Table 4: Comparison between Group A: Control group and Group B: Study group according to Estimated Blood loss.

Estimated Blood loss	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
Mean±SD	243.30±131.13	221.85±78.04	0.395	0.533	NS
Range	60-455	59-354			

Using: t-Independent Sample t-test for Mean±SD;
NS: Non significant

This table shows 4% less in the mean estimated blood loss in group B, but without statistically significant difference between both groups with p-value(p>0.05).

Table 5: Comparison between Group A: Control group and Group B: Study group according to No. of vicryl 0, No. of vicryl 1.

	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
No. of vicryl 0					
Median (IQR)	3 (3-4)	3 (3-4)	0.428	0.517	NS
Range	1-5	1-4			
No. of vicryl 1					
Median (IQR)	5 (4-6)	5 (4-7)	0.631	0.432	NS
Range	1-8	3-8			

Using: Mann-Whitney test
NS: Non significant.

Table 6: Comparison between Group A: Control group and Group B: Study group according to Drain.

Drain	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
No	9 (45.0%)	14 (70.0%)	2.558	0.110	NS
Yes	11 (55.0%)	6 (30.0%)			

Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate
NS: Non significant.

This table shows 25% less in drain use in group B, but without statistically significant difference with p-value (p>0.05).

Table 7: Comparison between Group A: Control group and Group B: Study group according to Blood transfusion after operation.

Blood transfusion	Group A: Control group (n=20)	Group B: Study group (n=20)	Test value	p-value	Sig.
No	**13 (65.0%)**	**18 (90.0%)**	3.584	0.058	NS
Yes	**7 (35.0%)**	**2 (10.0%)**			

Using: x2: Chi-square test for Number (%) or Fisher's exact test, when appropriate
NS: Non significant.

This table shows 25% less blood transfusion in group B, but without statistically significant difference with p-value (p>0.05).

DISCUSSION

Hysterectomy is the second most frequently performed surgical procedure for women of reproductive age (Gartner et al., 2018). Regardless of the surgical technique used, it is associated with short- and long-term (Lin et al., 2021).

Consequently, this study was conducted to assess efficacy of single pedicle ligation as a new surgical technique in decreasing bleeding, related number of polyglactin 910 suture ampoules used and costs of abdominal hysterectomy among developing countries.

This interventional pilot study was conducted at Ain Shams University Maternity Hospital during period from April 2023 till February 2024. A total of 40 participates candidate for elective total abdominal hysterectomy and/or bilateral salpingio-oophorectomy were enrolled and divided into 2 equal groups. Group A (control group) was subjected to classic surgical technique and group B (study group) subjected to single pedicle ligation suturing technique. After surgery, both groups were compared regarding estimated blood loss and total number of polyglactin 910 suture ampoules used all over the surgery.

Our study revealed that although there were differences favouring this new surgical technique over classic surgical technique; as drop 0.78% less in Hematocrit value,4% less in mean estimated blood loss , 25% less in drain use and 25% less blood transfusion.But these results had no statistical significant difference.

Regarding our knowledge, no previous studies assessed the efficacy of single pedicle ligation as a new surgical technique in decreasing abdominal hysterectomy related bleeding and costs.

Dutta and Dutta (2014) in acomparative prospective study that was undertaken at Multicare hospital and J.N.M hospital, Kalyani West- Bengal, India during the period from January 2000 to December 2009. During this period 1000 abdominal hysterectomy operation were performed by this procedure (Group A) and 450 (Group B) by conventional method, reported that ligation of uterine and ovarian arteries, prior to conventional abdominal hysterectomy procedures is found to be extremely safe procedure thereby reducing the risk of intra-operative and post- operative complications such as haemorrhage caused by trauma or slipping and retraction of uterine arteries and ovarian arteries are of great concern to a gynecologist working especially in rural settings where there infrastructure and facilities like blood transfusion etc are not available easily.

In this method, no traumatic injury of left and right ovarian vessels were reported, only 0.4% cases which had traumatic injury to left

uterine vessel and 0.3% cases with right uterine vessel which was managed immediately. This has got no significance statistically.

Aziz et al. (2022) showed in a randomized single blind controlled trial was carried on 70 women undergoing total abdominal hysterectomy. They were randomly allocated in two equal groups: misoprostol group: patients received two tablets of Misoprostol (=200 μg) 30 minutes before operation and a control group (placebo group): patients received two tablets of Placebo 30 minutes before operation.

Haemoglobin and Haematocrit reductions were significantly lower among misoprostol group than among placebo group.

Regarding preoperative haemoglobin and haematocrit, the study discovered no significant variation among the studied groups,but postoperative haemoglobin and haematocrit were significantly elevated among the misoprostol group rather than the placebo group . Regarding blood loss(ml), it was significantly decreased among the misoprostol group in contrast to placebo group. Regarding side effects among the studied groups, Nausea & vomiting were significantly more frequent among the misoprostol group than the placebo group while diarrhea, headache, fever and shivering were non-significantly prevalent with the misoprostol group in contrast to the placebo group.

That agrees with Tabatabai and colleagues (2015) in double blind randomized clinical trial was conducted with 80 candidates for abdominal hysterectomy, used a 400-microgram rectal dose before TAH and demonstrated that a single rectal misoprostol dose significantly reduced peri-operative bleeding in comparison to a placebo.

This disagree with Chai and colleagues (2011) who designed a pilot study on 64 TAH women and didn't give any significant decrease in intraoperative blooding during TAH when compared to placebo (570 mL vs 521 mL; P = 0.904); This may be due to not excluding females with major adhesions and a fewer sample.

Parashi & Astaraei (2022) aimed to investigate the effect of a single preoperative dose of sublingual misoprostol on reducing blood loss during total abdominal hysterectomies.

In a single-blind randomized controlled trial (RCT), The statistical population included all women who were candidates of hysterectomy in 2017 and 2018. A total of 132 patients were randomly selected and classified into two groups of misoprostol (N=66) and placebo (N=66). Examining intraoperative blood loss was considered a primary outcome. Moreover, levels of hemoglobin before and 24 hours after the surgery, the need for a blood transfusion, febrile morbidity, and the duration of hospitalization were regarded as secondary outcomes. The mean of hemoglobin values was lower in the placebo group compared to the misoprostol one, and this difference was statistically significant ($P < 0.001$). There was a significant difference in intraoperative blood loss between the two groups, and it was significantly higher

Topsoee et al. (2015) showed in adouble-blinded randomized placebo-controlled trial conducted on atotal of 332 women, that the primary outcome of intraoperative total blood loss was reduced in the group treated with tranexamic acid compared to the placebo group when estimated both subjectively by the surgeon and objectively by weight (98.4 mL vs 134.8 mLand 100.0 mL vs 166.0 mL). The incidence of blood loss ≥500 mL was also significantly reduced (6 vs 21), as well as the use of open-label tranexamic acid (7 vs 18). Furthermore, the risk of reoperations owing to postoperative hemorrhage was significantly reduced in the tranexamic acid group compared to the placebo group (2 vs 9). This corresponds to an absolute risk reduction of 4.2% and number needed to treat of 24. No incidence of thromboembolic events or death was observed in any of the groups.

This reported that prophylactic treatment with tranexamic acid reduces the overall total blood loss, the incidence of substantial blood loss, and the need for reoperations owing to postoperative hemorrhage in relation to benign hysterectomy. No incidences of serious adverse events occurred.

Nivedhana et al. (2018) in arandomized, double-blind, placebo-controlled study that conducted on hundred patients undergoing abdominal hysterectomy. Group T (n = 50)-received TXA 15 mg/kg in 100 ml Normal saline and Group N (n = 50) received the same volume of Normal saline infused over 15 minutes. Estimated blood loss, need for blood transfusion, duration of surgery, postoperative hemoglobin and incidence of adverse events were noted.

There was statistically significant reduction in mean blood loss in group T when compared to group N (360 ml versus 540 ml). Accordingly, there was significant difference in the number of patients requiring blood transfusion (12% versus 42%) and also the postoperative hemoglobin levels. The group T patients had a significantly shorter operating time (127.86 versus 148.64 minutes). None of the patients developed any major adverse events.

CONCLUSION

In women undergoing abdominal hysterectomy, single pedicle ligation surgical technique help in lowering surgical related estimated blood loss and costs although no statistically significant difference compared with classic traditional method.

References

1. Ali SA, Farahat MM, ElShafei MA (2019): Surgical approach to hysterectomy for benign gynecological diseases. The Egyptian Journal of Hospital Medicine; 77(3):5279-86.
2. Aziz AEA, Sokary AASE, Borg HMES, Marey SK. (2022). Effect of preoperative single dose misoprostol on intraoperative blood loss during abdominal hysterectomy: a randomized controlled trial. Journal of Advances in Medicine and Medical Research, 34(1), 127.
3. Chai J, Hon E, Li CF, Pun T, Yeung S and Ho P (2011): A pilot study of pre-operative misoprostol in reducing operative blood loss during hysterectomy. Eur J Obstet Gynecol Reprod Biol., 158: 72.
4. Dutta DK and Dutta I (2014). Abdominal hysterectomy: a new approach for conventional procedure. Journal of Clinical and Diagnostic Research: JCDR, 8(4), OC15.
5. Eggemann H, Ignatov A, Frauchiger-Heuer H, Amse T, Costa SD (2018): Laparoscopic-assisted vaginal hysterectomy versus vaginal hysterectomy for benign uterine diseases: a prospective, randomized, multicenter, double-blind trial (LAVA). Archives of gynecology and obstetrics; 297:479-85.
6. Gartner DR, Doll KM, Hummer RA, Robinson WR (2018): Contemporary geographic variation and socio-demographic correlates of hysterectomy rates among reproductive aged women. Southern medical journal; 111(10):585.
7. Higgins C, Mcdonald R, Mol BW (2022): Indications and surgical route for hysterectomy for benign disorders: a retrospective analysis in a large Australian tertiary hospital network. Archives of Gynecology and Obstetrics; 306(6):2027-33.
8. Huang CC, Lo TS, Huang YT, Long CY, Law KS, Wu MP (2020): Surgical trends and time frame comparison of surgical types of hysterectomy: A nationwide, population-based 15-year study. Journal of Minimally Invasive Gynecology; 27(1):65-73.

9. Lin CH, Long CY, Huang KH, Lo TS, Wu MP (2021): Surgical trend and volume effect on the choice of hysterectomy benign gynecologic conditions. Gynecology and minimally invasive therapy; 10(1):1-9.
10. Naveiro-Fuentes M, Rodrfguez-Oliver A, FernSndez-Parra J, GonzSIez- Paredes A, Aguilar-Romero T, Mozas-Moreno J (2018): Effect of surgeon's experience on complications from laparoscopic hysterectomy. Journal of gynecology obstetrics and human reproduction; 47(2):63.
11. Nivedhana AP, Jalakandan B, Gunaseelan S (2018): Effect of prophylactic tranexamic acid on blood conservation in Indian women undergoing abdominal hysterectomy. International journal of reproduction, contraception, obstetrics and gynecology; 7(9):3538-46.
12. Parashi S, Astaraei V, Vahdat M, Dini P, Mohammadianamiri M (2022): The Effect of a Single Preoperative dose of sublingual misoprostol in reducing intraoperative blood loss after total abdominal hysterectomy: a single-blind randomized controlled trial. Journal of Obstetrics, Gynecology and Cancer Research, 3(4), 143-147.
13. Polen-De C, Bakkum-Gamez J, Langstraat C (2021): Route of Hysterectomy for Benign Disease: Abdominal Hysterectomy. Journal of Gynecologic Surgery; 37(2):116-21.
14. Tabatabai A, Mojgan K, Bahare M and Marzie V (2015): Effects of a single rectal dose of Misoprostol prior to abdominal hysterectomy in women with symptomatic leiomyoma: a randomized double blind clinical trial. Electronic Physician, 76: 1372.
15. Topsoee MF, Bergholt T, Ravn P, Schouenborg L, Moeller C, Ottesen B, Settnes A (2016): Anti-hemorrhagic effect of prophylactic tranexamic acid in benign hysterectomy—a double-blinded randomized placebo-controlled trial. American journal of obstetrics and gynecology; 215(1):72-e1.

Role of Ultrasonography in Intrauterine Contraceptive Device Utilization in Mansoura University Hospital

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Abstract

Background: More often than any other type of contraception, intrauterine contraceptive devices (IUCDs) are used in Egypt. In most cases, a non-guided procedure is used to insert IUCDs in office settings. Blind insertion possibly causes various complications including perforation. It is recommended to conduct TVUS prior to insertion in order to determine the uterus's size and orientation, as well as to rule out the possibility of pregnancy or pathology. Moreover use of TVUS during regular follow up may improve outcomes and help reduce IUCD related complications.

Aim of the work: Compare ultrasound-guided and non-ultrasound-guided IUCD insertion techniques for proper placement, problems, time, and patient satisfaction during insertion and follow-up.

Patients and methods: The study recruited 200 women using copper TCu-380A that were randomly divided into two groups (Each of 100 females), subgroup U (where ultrasound guided technique before insertion, during insertion and follow up and subgroup B (with non-ultrasound guided technique for IUCD insertion). The primary outcome was measuring the proper device placement post-insertion and after the next menstruation. Secondary outcomes included measuring the incidence of complications including perforation, expulsion, cervical problems, bradycardia, syncope, measuring patient satisfaction, assessment of difficult IUCD insertion and pain scores.

Results: The overall incidence of complications was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound group. The duration for insertion was statistically significantly longer in the non-ultrasound guided technique group as compared to the ultrasound group. The Pain score during insertion was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound group. The degree of satisfaction was statistically significantly higher in the ultrasound technique group.

Conclusions: Several positive outcomes were linked to the use of TVUS during the insertion of IUCD, including a shorter insertion duration, lower pain levels, a higher degree of satisfaction, and a smaller frequency of problems. Also, TVUS scan during regular follow up substantially help reduce IUCD related complications and improve continuity of the method.

Key words: IUCD, Ultrasound, Blinded, Insertion, Satisfaction.

Introduction

Negative effects on maternal and fetal health can result from unwanted pregnancies in a number of ways, including unsafe abortion, postponed prenatal care, negative consequences for children, and diminished educational and economic possibilities for the pregnant woman [1].

The Intrauterine Device (IUCD) is the most used reversible contraception worldwide with a prevalence usage rate of 15%. IUCDs offer simple, efficient, safe, and low-cost reversible and long-term contraception [2].

Traditional technique of IUCD insertion and lack of regular follow up approach may result from problems, failure, or difficulties associated with intrauterine contraceptive device insertion [3]. Five to fifteen percent of women will have their IUCD removed in the first year following insertion due to irregular uterine bleeding caused by device-endometrium contact and uterine muscle pressure. Most bleeding problems are caused by the IUCD's disharmonious interaction with the uterus, hence inappropriate position should be ruled out before switching birth control methods [4].

TVUS is the gold standard choice for guidance of insertion and assessing IUCD position and consequences [5].

Researchers have conducted a comparison between ultrasound guided and blind IUCD insertion techniques in terms of the correct placement of the IUCD in the uterus, the occurrence of problems, the time required for the procedure, and patient satisfaction. According to their findings, ultrasonography-guided IUCD insertion is superior to blind techniques in terms of achieving the desired fundal position of the device with a lower risk of problems, less discomfort, and higher patient satisfaction [6, 7].

It is intended in this current study to compare both techniques and use of TVUS during follow up visits.

Patients and Methods

Over the course of a year, researchers at Mansoura University Hospital's Obstetrics and Gynecology Department performed a prospective randomized interventional trial.

The study included 200 women using copper TCu-380A in Reproductive and Fertility Unit at Mansoura University Hospitals. The females were randomly divided into two groups (Each of 100 females), **subgroup U** (Ultrasound guided technique before insertion , during insertion and follow up and **subgroup B (Blind technique)**

The current study included regularly menstruating women before IUCD insertion in the age between 20 and 45 years who didn’t receive non-steroidal anti-inflammatory at 24 hours before the examination.

The cases with the following criteria were excluded; septic abortion, unexplained abnormal vaginal bleeding, cervical cancer, malignant, benign gestational trophoblastic disease, uterine cancer, uterine anomalies, endometrial polyps and uterine fibroids, pelvic infection within the past three months and presence of pelvic pathology as ovarian cysts, pelvic endometriosis.

All procedures adhere to the 2013 Helsinki Declaration [8]. All subjects provided written informed consent after the study was approved by the Mansoura university faculty of medicine's institutional review board.

Full medical history, detailed physical examination and routine laboratory investigations were conducted to all the included females.

Ultrasound

TVUS was conducted before insertion for both subgroups (B and U) for measurements of dimension of the uterus, determination of the position of the uterus (RVF, lateral position) and to detect any associated abnormalities (cervical, uterine or adnexal). Ultrasound was also used during the insertion for U subgroup to assure proper fundal placement of the device. US guidance helps prevent uterine perforation.

Technique for IUCD insertion:

- Encourage women to micturate for emptying the bladder.
- Placing women in a lithotomy position.
- Under aseptic and antiseptic measures the cervix was seen with sterile Cusco's speculum.
- We used a vulsellum to tract the cervix and introduce uterine sound to assess uterine length and orientation.
- TVUS scan was performed to confirm uterus position and its measurments .
- Inserting IUCD in the uterine cavity without touching it. Safety is best with "no-touch" implantation. This includes keeping the loaded IUCD and uterine sound away from unsterile surfaces.
- The no-touch technique involves:
  - IUCDs should be loaded into the inserter when still in their sterile package to avoid direct contact.
  - Prior to inserting the IUCD, make sure to clean the cervix well with antiseptic.
  - When using the uterine sound or loaded IUCD inserter, avoid touching the vaginal wall or speculum blades.
  - Making just one trip through the cervical canal with the uterine sound and the loaded intrauterine contraceptive device (IUCD) inserter.
- Following insertion, TVS was performed to verify proper placement of the IUCD.

Follow up was performed for both groups at the following time points, after one month or next menstruation, after 3 regular cycles or 3 months, after 6 months, after 9 months and after 12 months for both groups or when complications occur as bleeding, pain, pregnancy, malposition and missed threads.

Study outcomes

The main outcomes after insertion and following the subsequent menstruation, measure the appropriate positioning of the device.

The secondary outcomes were to asess the incidence of the associated complications included perforation, expulsion, cervical problems, bradycardia, syncope, measuring patient satisfaction, identification of difficult IUCD insertion and assesment of pain score during insertion.

Difficulty of IUCD insertion was measured by whether uterine sound with a diameter of 4 mm or smaller can pass through the internal cervical os or not. Internal cervical os resistance as a measure of IUCD insertion difficulties. Using the following scale, researchers were to ascertain how challenging it was to pass both the sound and the IUCD: Easy (1-2) Normal (3-4) Mild difficulty (5-6), Severe difficulty (9-10).

All women were taught how to express their pain (during insertion) on an eleven-point scale (VAS), from 0 to 10, with 0 for no pain, and 10 for the maximum pain ever felt [9].

Any intrauterine contraceptive device (IUCD) that was more than 3 mm away from the fundal endometrial surface was deemed misplaced [10]. It was determined that expulsion had occurred if the intrauterine contraceptive device had passed through the external cervical os, even marginally [10].

Statistical analysis

Coding, processing, and analysis of the data

were carried out using the SPSS 26 for Windows® application. The qualitative data was presented in percentage and number form. To compare groups, researchers used the Chi-Square test, which is also known as Fischer's Exact test or the Monte-Carlo test. Quantitative data was examined for normalcy using the Kolmogorov-Smirnov test. The range and mean ± SD were the ways the data was shown.

A Mann Whitney U test was employed in the event that the data did not follow a normal distribution, and an independent samples t-test was utilized to compare the two groups with normally distributed quantitative variables. P values <0.05 are considered significant.

Results

The study included 200 women using copper TCu-380A in Reproductive and Fertility Unit at Mansoura University Hospitals. The females were randomly divided into two groups (Each of 100 females), **subgroup U** (Ultrasound guided technique) before insertion, during insertion and follow up and **subgroup B (Blind technique)**.

Table (1) shows that there was no statistically significant difference between the two study groups regarding the Age, BMI, parity, previous vaginal delivery, and previous CS. The mean age in the ultrasound technique group was 31.02 ± 7.20 years while in the non-ultrasound guided technique group, the mean age was 33.15 ± 8.26 years. The mean BMI in the ultrasound technique group was 30.26 ± 4.90 kg/m2 while in the non-ultrasound guided technique group, the mean BMI was 31.04 ± 6.54 kg/2.

Table (1): Demographic characteristics among the studied groups

Variables		Groups		P value
		Ultrasound technique (Subgroup U) (N=100)	Non ultrasound guided technique (Subgroup B) (N=100)	
Age (years)	Mean ± SD	31.02 ± 7.20	33.15 ± 8.26	**0.153**
	Range	19 - 42	19 – 41	
BMI (Kg/m^2)	Mean ± SD	30.26 ± 4.90	31.04 ± 6.54	**0.340**
	Range	20.48 – 34.15	20.28 – 35.12	
Parity	Mean ± SD	2.76 ± 1.14	2.93 ± 1.27	**0.352**
	Range	1- 6	1- 6	
Previous vaginal delivery	Mean ± SD	1.71 ± 0.92	1.95 ± 0.97	**0.137**
	Range	0 - 5	0 – 6	
Previous CS	**Mean ± SD**	**1.36 ± 0.90**	**1.24 ± 0.92**	**0.234**

Table (2) reveals that there was no statistically significant difference between the two study groups regarding the sounding status. Successful sounding was reported in 97% and 94% in the ultrasound technique group and blinded technique group respectively

Table (2): Sounding status among the studied group

	Groups				Test of significance
	Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Sounding status					
Success	97	97 %	94	94 %	0.306
Failure	3	3 %	6	6 %	

Table (3) discloses that at the baseline, the fundal distance was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound technique group (5.70 ± 3.40 mm versus 3.30 ± 1.02 mm respectively).

Table (3): Fundal Distance (D) immediately after insertion among the studied groups

		Groups				Test of significance
		Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Fundal distance	Mean ± SD	3.30 ± 1.02		5.70 ± 3.40		0.001*
	Range	1.5 – 5		-4 – 12.4		
Fundal distance grades						
0 – 3 mm		41	41 %	27	27 %	
3.1 – 10 mm		59	59 %	68	68 %	0.001*
> 10 mm		0	0 %	5	5 %	

Table (4) records that at one month follow up, the fundal distance was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound technique group (6.68 ± 2.58 mm versus 5.75 ± 2.32 mm respectively).

Table (4): Fundal distance (D) at follow up postmenstrual after one month among the studied groups.

Variables		Groups				Test of significance
		Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Fundal distance	Mean ± SD	5.75 ± 2.32		6.68 ± 2.58		0.014*
	Range	2.7 - 10		2.7 – 13.3		
Fundal distance grades						
0 – 3 mm		22	22 %	15	15 %	0.016*
3.1 – 10 mm		78	78 %	78	78 %	
> 10 mm		0	0 %	7		7 %

Table (5) demonstrates that follow up downward displacement (mm) postmenstrual after one month didn't show a statistically significant difference between the two groups.

Table (5): Follow up downward displacement (mm) postmenstrual after one month among the studied groups.

		Groups				Test of significance
		Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Displacement	Mean ± SD	2.74 ± 1.75		2.80 ± 1.89		z = - 0.310 p= 0.756
	Range	- 0.6 – 5.4		- 1.5 – 5.9		
Displacement > 5 mm		9	9 %	14	14 %	c^2 = 1.228 P = 0.268

Table (6) reveals that the overall incidence of complications was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound group (12% versus 2%). In the ultrasound group, complications were bradycardia in 2% while in the non-ultrasound guided technique group, complications were bradycardia 4%, partial perforation 6%, Low lying IUCD in 6%, cervical displacement in 2% and expulsion in 2%.

Table (6): Complications in the two studied groups

	Groups				Test of significance
	Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Bradycardia	2	2 %	4	4 %	FET = 0.338 P = 0.561
Syncope	0	0 %	0	0 %	----------
Partial perforation	0	0 %	6	6 %	FET= 3.046 P = 0.081
Low lying IUCD	0	0 %	6	6 %	FET= 3.046 P = 0.081
Cervical displacement	0	0 %	2	2 %	FET= 1.005 P = 0.316
Expulsion	0	0 %	2	2 %	FET= 2.020 P = 0.155
Overall	2	2 %	12	12 %	FET= 5.664 P = 0.002*

Table (7) the following table discloses that the duration for insertion was statistically significantly longer in the non-ultrasound guided technique group as compared to the ultrasound group (7.58 ± 0.90 minutes and 5.94 ± 1.19 minutes respectively).

The Pain score during insertion was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound group (1.77 ± 0.72 and 0.98 ± 0.65 respectively). The degree of satisfaction was statistically significantly higher in the ultrasound technique group.

Table (7): Evaluation of pain and patients' satisfaction in the two study groups.

		Groups				Test of significance
		Ultrasound technique (Subgroup U) (N=100)		Non ultrasound guided technique (Subgroup B) (N=100)		
Time (minutes)	Mean ± SD	5.94 ± 1.19		7.58 ± 0.90		t = - 11.001 p < 0.001*
	Range	4 - 8		6 – 9		
Pain score during insertion	Mean ± SD	0.98 ± 0.65		1.77 ± 0.72		z= - 6.920 p < 0.001*
	Range	1 (0 -2)		2 (1 – 3)		
Degree of satisfaction						
Dissatisfied	16	16 %	38	38 %		C^2 = 15.742 P < 0.001*
Satisfied	84	84 %	62	62 %		

Discussion

The purpose of this research was to evaluate the efficacy of ultrasonography-guided versus non-ultrasound-guided intrauterine contraceptive device insertion procedures with respect to the following: correct fundal positioning of the IUCD, frequency of problems, time required for insertion and follow-up, and patient satisfaction.

The study included 200 women using copper TCu-380A and were randomly divided into two groups (Each of 100 females), subgroup U (where ultrasound guided technique before insertion, during insertion and follow up and subgroup B (with non-ultrasound guided technique for IUCD insertion).

The current study showed that both groups are comparable regarding demographic data as Age, BMI, parity, previous vaginal delivery, and previous CS.

This was similar to the trial that randomized 300 eligible women for IUCD insertion into two groups of 150 women, TAS-guided IUCD insertion versus non-TAS-IUCD insertion (no ultrasonography). The mean age, parity, number of previous CSs, BMI, and IUCD insertion time did not differ between the two groups (P=0.9, P=0.08, P=0.1, and P=0.9, respectively) [11].

This was also confirmed by another study (Abbas), who randomly assigned 102 female IUCD implantation patients to the TAS-guided and traditional groups (51 in each group). Compared to age, gravidity, parity, BMI, previous deliveries, IUCD history and duration, and IUCD-associated problems, there was no statistical significance [6].

This indicates the process of effective randomization to avoid the selection bias and exclude this effect on the results.

In this study, sounding status did not differ statistically between groups. Successful sounding was reported in 97% and 94% in the ultrasound technique group and non-ultrasound guided technique group respectively.

According to Elhoussieny et al., the ultrasound-guided and non-ultrasound-guided method groups had 98% and 96% success rates, respectively, with no statistically significant difference [7]

In contrast, El-Bahnasy et al. found that 3% of women who had ultrasound-guided IUCD insertion had failed insertion and 96% had it in place, while in traditional IUCD insertion, 6% had failed insertion, 80% had it in place, and 14% had it low lying. High statistical differences existed between groups (P<0.001) [12].

Elsedeek examined the effectiveness of trans-abdominal ultrasonography guidance in IUCD insertion identification in her cohort study. She evaluated 80 parous women's IUCD after the operation and one week later. Proper IUCD fitting and placement were accomplished in 32 (80%) and 27 (68%) women compared to 39 (98%) and 38 (95%) women in the non-ultrasound guided and ultrasound guided groups (P = 0.04 and 0.02). Ultrasound guidance improved IUCD placement and fit compared to non-ultrasound guidance [13].

In the current study, the fundal distance was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound technique group (5.70 ± 3.40 mm versus 3.30 ± 1.02 mm respectively). At one month follow up, the fundal distance was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound technique group (6.68 ± 2.58 mm versus 5.75 ± 2.32 mm respectively).

According to Elhoussieny et al., fundal distance (distance between the IUCD and inner uterine wall) 0.0 -0.3 mm was substantially more prevalent in group U than group B (P=0.009) shortly after insertion [7].

The current results showed that the Pain score during insertion was statistically significantly higher in the non-ultrasound guided technique group as compared to the ultrasound

group (1.77 ± 0.72 and 0.98 ± 0.65 respectively).

This matches a recent meta-analysis of seven RCTs involving 1267 subjects. In the ultrasound-guided group, IUCD insertion reduced VAS pain (P = 0.001) [14].

In agreement with Samaha et al., TAS-IUCD insertion resulted in considerably decreased mean pain scores (1.3 ± 1.02 vs. 1.6 ± 0.76, P=0.0001) [11].

According to El-Bahnasy et al., ultrasound-guided IUCD insertion patients reported discomfort between 1-5 with Median (IQR). 4 (3–5); conventional IUCD insertion group: 3-8 (IQR). 7 (6 – 8). Significant differences were found between groups (P<0.001) [12].

Elhoussieny et al. showed that pain perception (VAS-100) was significantly lower among group ultrasound guided group than among group non ultrasound guided technique group [7]

Abbas observed that TAS-IUCD insertion was statistically superior to regular IUCD insertion in participant pain assessments (P<0.001) [6].This is because ultrasound-guided IUCD insertion eliminates unwanted manipulations (touch/push) of the cervix or uterus, which can cause additional pain.

In this study, the duration for insertion was statistically significantly longer in the non-ultrasound guided technique group as compared to the ultrasound group (7.58 ± 0.90 minutes and 5.94 ± 1.19 minutes respectively).This supported Baradwan et al.'s finding that ultrasonography guided reduced procedure insertion time compared to control (P < .001) [14].

El-Bahnasy et al. found that ultrasound-guided IUCD insertion took 25-45 seconds, with a mean ±S.D. of 35.56 ±6.323, while traditional IUCD insertion took 56-110 seconds, with a mean ±S.D. of 82.44±17.545. Significant differences (P < 0.001) were found between groups, supporting our findings [12]. This also was in the same line with Abbas who reported that the mean time for IUCD insertion in the TAS-guided IUCD insertion was 32.2 ± 14.8 seconds versus 77.7 ± 30.6 seconds in the traditional group (p < 0.001) [6].

In agreement with our findings, Elsedeek et al. (2016) found that US-guided procedures were shorter [13].

A key distinction between the two techniques, in favor of the new methodology, was the number of stages and instruments needed by the old method. When a patient is in a lot of pain, they tend to move around a lot, which makes the treatment more difficult and takes longer.

However, according to Ali et al. (2019). Examined the time and pain of intrauterine contraceptive device insertion using trans-abdominal ultrasound (US-guided) and the Uterine Sounding Sparing Approach (USSA). According to their research, USSA is a superior method that significantly reduces treatment time and pain while increasing patient satisfaction [15].

Our results showed that the degree of satisfaction was statistically significantly higher in the ultrasound technique group. According to El-Bahnasy et al., there was no statistically significant difference between groups (P=0.436) in patient satisfaction, with 89% satisfied and 11% unsatisfied in the ultrasound-guided IUCD insertion group and 41% with 59% in the traditional group [12]. Additionally, the ultrasound-guided group had a higher rate of satisfied women, according to Baradwan et al. [14].

According to Elhoussieny et al., there was a marked decrease in patient dissatisfaction in the group that had ultrasonography guidance compared to the group that did not [7]

In the current study, the overall incidence of complications was statistically significantly higher in the non-ultrasound guided

technique group as compared to the ultrasound group (12% versus 2%) (p= 0.002). This agrees with the findings of Baradwan et al., who demonstrated that problems and misplaced IUCDs were significantly reduced when the insertion was guided by ultrasonography [14].This aligns with El-Bahnasy et al.'s findings of substantial differences (P< 0.001) in IUCD insertion complications between groups. Ultrasound-guided IUCD side effect 71% of IUCD-inserted women had no complications, 16% suffered bleeding, 7% pelvic pain, and 6% backache. In traditional IUCD insertion, 69% of women experienced no complications, 20% bleeding, 9% pelvic pain, and 2% backache [12].

Maged et al. found that ultrasound-guided group ladies had fewer problems, including bleeding and procedure failure, than controls. In terms of other problems, such as infection and perforation, both groups were comparable [16].

The overall complication rate was much lower in the group who underwent ultrasonography guidance compared to the group that did not.

With just two cases recorded in the group using the non-ultrasound guided approach, there was no statistically significant difference in the incidence of expulsion between the two groups (p= 0.155).This was in line with the findings of Samaha et al., who found no statistically significant difference in the rate of IUCD expulsion between the groups who had TAS-IUCD insertion and those that did not (0.7% (1/150) versus 1.3% (2/150), respectively, P=0.6) [11].

A number of complications, including uterine colic, bleeding, unplanned pregnancies, expulsion, and IUCD displacement, can arise from the use of IUCDs [17, 18]. In this study, one-month postmenstrual downward displacement (mm) did not differ between groups statistically. The incidence of cervical displacement was not statistically significant (p= 0.155) and only two cases of expulsion were documented in the non-ultrasound guided method group. This contradicted Samaha et al., who found that TAS-IUCD insertion considerably reduced cervical IUCD displacement (0% (0/150) versus 2% (3/150), P=0.03) [11].

Also, TAS-guided IUCD insertion enables for correct IUCD placement and decreases the danger of expulsion and mal-positioning, according to Balica et al., Which could lead to fewer cases of unwanted pregnancies, less pain after the procedure, and happier patients who get intrauterine device [19].

In a study by McCool, 21% of symptomatic women needed IUCD removal (19% due to incorrect IUCD position) and 18% of asymptomatic women needed it based on ultrasound findings.

While perforation of the uterus during intrauterine device insertions occurs in 0.6–16% of all insertions, it is more likely to occur if the device is inserted within four to six weeks following either the delivery of the baby or an elective abortion [20].Neither the incidence of low-lying IUCD (p=0.081) nor the incidence of partial perforation (p=0.081) differed significantly between the two groups in the present work. The non ultrasound guided technique group, complications were bradycardia 4%, partial perforation 6%, Low lying IUCD in 6%.

Samaha et al. did not find any perforations, pregnancies, or mal-positioned IUCDs in their investigation, which is in line with the current findings [11].

The main limitation of the study is that is a single center study that couldn't reflect the variations in the technical skills of the operator that could affect the results.

Conclusion

The use of ultrasound during the insertion of IUCD was associated with some favorable outcomes such as shorter duration of insertion, less pain scores and higher degree

of satisfaction lesser incidence of complications. Although the overall success rate was higher in the ultrasound group, it showed no statistically significant difference compared to the non-ultrasound guided technique group. A multicentric study is recommended based on regular follow up of IUCD,being guided by TVUS scan.

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References

1. Tsui AO, McDonald-Mosley R, Burke AE. Family planning and the burden of unintended pregnancies. Epidemiologic reviews. 2010;32(1):152-74.
2. Ahmadi F, Haghighi H, Irani S, et al. Presentation of intrauterine device in a didelphic uterus. Iran J Radiol. 2015;12(3).
3. Bahamondes L, Makuch MY, Monteiro I, et al. Knowledge and attitudes of Latin American obstetricians and gynecologists regarding intrauterine contraceptives. Int J Womens Health. 2015:717-22.
4. Kroon Cd, Houwelingen Jv, Trimbos J, et al. The value of transvaginal ultrasound to monitor the position of an intrauterine device after insertion. A technology assessment study. Human Reproduction. 2003;18(11):2323-7.
5. Nowitzki KM, Hoimes ML, Chen B, et al. Ultrasonography of intrauterine devices. Ultrasonography. 2015;34(3):183.
6. Abbas AM. Ultrasound-guided intrauterine device insertion: a step closer to painless insertion: a randomised control trial. Eur. J. Contracept. Reprod. Health Care. 2018;23(2):165.
7. Elhoussieny AS, Ibrahim AM, Hassanin AS, et al. Efficacy and Safety of Ultrasound Guided versus Blind Technique for Office Insertion of Intrauterine Contraceptive Device: A Randomised Clinical Trial. J Evid Based Health. 2019;9(2):432-40.
8. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.
9. Chiarotto A, Maxwell LJ, Ostelo RW, et al. Measurement properties of visual analogue scale, numeric rating scale, and pain severity subscale of the brief pain inventory in patients with low back pain: a systematic review. J. Pain. 2019;20(3):245-63.
10. Salama S, ElTemamy EAER, Abdel-Rasheed M, et al. Role of vaginal misoprostol prior to levonorgestrel-releasing IUD insertion. Al-Azhar Intern. Med. J. 2022;3(2):28-33.
11. Chitturi S, Hui J, Salisbury E, et al. Abdominal pain in an intrauterine contraceptive device user. Postgrad. Med. J. 2001;77(911):602-.
12. S El-Bahnasy H, Hanafy M, El-Mallah S. Role of ultrasound technique in woman satisfaction during placement of intrauterine contraception (a randomized clinical trial). Al-Azhar. Med. J. 2022;51(1):135-46.
13. Elsedeek MS. Comparison between the traditional non-guided and a novel ultrasound-guided technique for office fitting of intrauterine contraceptive devices. Int. J. Gynecol. Obstet. 2016;133(3):338-41.
14. Baradwan S, Alshahrani MS, Alnoury A, et al. Does Ultrasound Guidance Provide Pain Relief During Intrauterine Contraceptive Device Insertion? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J. Med. Ultrasound. 2023;42(7):1401-11.
15. Ali MK, Abbas AM, Ramadan A, et al. A randomized clinical trial between ultrasound-guided and uterine sound-sparing approach for copper intrauterine device insertion. Fertility and Sterility.

2019;112(3):e9.

16. Maged AM, Nada AM, Abdelwahab H, et al. The value of ultrasound guidance during IUD insertion in women with RVF uterus: A randomized controlled trial. J Gynecol Obstet Hum Reprod. 2021;50(4):101875.
17. Fadiloglu S, Dilbaz B, Fadiloglu E, et al. Relationship between copper IUD complications and ultrasonographic findings. Arch. Gynecol. Obstet. 2018;297:989-96.
18. Ariadi A, Aulia A. Effect of fixation suture of the intrauterine contraceptive device at cesarean section on the continuity of trans-cesarean post-partum contraception. J Obstet Gynaecol Res. 2017;10:17-21.
19. Balica AC, Kim CS, Egan S, et al. Sonographically guided insertion of intrauterine device: Indications and results. J.Clin. Ultrasound. 2018;46(2):132-5.
20. Averbach S, Hofler L. Long-acting reversible contraception with contraceptive implants and intrauterine devices. JAMA. 2022;327(20):2013-4.

Pilot Study to Assess Endometrial Compaction as a Tool to Predict Successful Pregnancy Outcomes in IVF and ICSI Cycles

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Abstract

Background : Accurately predicting the possibility of pregnancy during an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle has long been challenging.

Aim of the Work : to determine whether the clinical pregnancy rate in IVF and ICSI cycles is affected by the alteration in endometrial thickness, volume, and perfusion between the end of the estrogen phase and the day of embryo transfer.

Patients and Methods: The present study was a prospective observational study conducted in the obstetrics and gynecology department of Mansoura University Hospitals, Mansoura, Egypt. The present study was conducted on 25 subfertile women undergoing IVF and ICSI cycles. Endometrial preparation with the use of progesterone was done for all patients. In these 25 women candidates for ICSI, endometrial thickness and sub-endometrial perfusion were measured with a trans-vaginal 2-dimensional ultrasound (2D U/S) and 3-dimensional power Doppler ultrasound (3D PD U/S), respectively, on the day of human chorionic gonadotrophin (hCG) trigger and embryo transfer (ET).

Results: When comparing instances with positive pregnancy tests to those with negative pregnancy tests, there is a notable increase in endometrial volume and sub-endometrial vascularization flow index (VFI), corresponding to the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. The average uterine resistance index (RI) on the day of embryo transfer in positive pregnancy cases is considerably higher than in negative pregnancy instances, and it is also significantly higher on the day of embryo transfer compared to the day of HCG trigger in positive pregnancy cases. By contrasting cases in which pregnancies were positive with those in which they were negative, there is a significant increase in the average uterine pulsatility index (PI) on the days of embryo transfer and HCG trigger as well as on the day of embryo transfer when compared to the day of HCG trigger in positive pregnancy cases.

Conclusion: Endometrial volume, sub-endometrial VFI, uterine RI, and uterine PI had an impact on the pregnancy outcome and clinical pregnancy rate in IVF and ICSI cycles.

Keywords: Compaction, endometrial, IVF and ICSI cycles, pregnancy.

Introduction

Endometrial receptivity is the term used to characterize the complex process by which the uterine lining gets ready for an embryo's implantation. The success of embryo apposition, adhesion, invasion, and ongoing pregnancy depends on the synchronization of endometrial preparation and embryo growth, which are independent but contemporaneous processes. [1].

Endometrial compaction can be defined as an increase in endometrial vascular density associated with the progressive coiling of the spiral arteries during the luteal phase. This feature is a characteristic of the late luteal phase, in which endometrial thickness is different from that at the end of the estrogen phase [2].

The term "assisted reproductive technology" (ART) describes techniques that manipulate oocytes outside of the body; the most popular kind of these techniques is in vitro fertilization (IVF). The phrase "in vitro" refers to fertilizing oocytes outside of a living creature in a petri dish, whereas embryos grow into pregnancy in the uterus and oocytes mature in vivo in the ovary. [3].

Advances in in vitro fertilization (IVF) and embryo transfer (ET) have come about as a consequence of examining every stage of the procedure, comparing the effects of various approaches, and assessing the outcomes to determine which approach is best. This includes patient preparation, stimulation protocol selection, culture technique, embryo selection, transfer mechanics, and post-transfer management. [4].

Age, the quality of the embryo, and endometrial receptivity are the primary factors that determine whether an assisted reproductive technology cycle is successful. An essential condition for embryonic implantation is the synchronization of endometrial and embryonic development. Most couples can now acquire high-quality embryos owing to advancements in laboratory technology. As a result, determining the patient's anticipated course of treatment depends greatly on the endometrial receptivity.

While endometrial receptivity has a significant guiding role in therapy that can significantly increase the success rate of in vitro fertilization (IVF), one of the primary issues is the dearth of real clinical trials to assess endometrial receptivity. [5].

Endometrial compaction, which is the change in endometrial thickness between the end of the estrogen-only phase and the day of embryo transfer, has been the subject of recent research evaluating its predictive power for success after frozen embryo transfer (FET). The endometrium's compaction upon progesterone initiation suggests that it is receptive to the hormone, suggesting that it may serve as a surrogate for endometrial receptivity. There have been inconsistent findings from three cohort studies on the connection between endometrial compaction and clinical outcomes after ET. [2, 6].

However, when Bu et al. evaluated 1334 natural cycle blastocyst FETs as well as 1757 medicated FETs, they discovered that cycles in which the endometrial lining expanded following the onset of progesterone had a higher clinical pregnancy rate (CPR) than cycles in which the lining either compacted or remained unchanged in both medicated and natural cycle FET. In this investigation, every embryo was a high-quality, untested blastocyst. [7].

The current study set out to determine if the clinical pregnancy rate and pregnancy outcome in IVF and ICSI cycles were affected by changes in endometrial thickness, vol-

ume, and perfusion between the end of the estrogen phase and the day of embryo transfer.

Patients and Methods

The current study was a prospective observational study conducted at the obstetrics and gynecology department of Mansoura University Hospitals in Mansoura, Egypt.

Before their involvement in the study, all women who were chosen for participation provided written informed consent. The Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) granted approval.

Twenty-five subfertile women having IVF/ICSI cycles participated in the current study. We excluded from our study any patient who was less than 20 years old or more than 40 years old, had a body mass index (BMI) of less than 18.5 kg/m2 or more than 30 kg/m2, had lesions in the uterus, had poor quality embryos, and had chronic hypertension, lung disease, diabetes mellitus, renal disease, liver disease, endocrine disorder, or autoimmune disease.

If the endometrial thickness is not sufficient, estrogen treatment is continued, and ultrasound evaluation is done repeatedly until the endometrium becomes apparent to be sufficient. Following ovulation induction and oocyte retrieval, in every patient, progesterone was utilized to prepare the endometrium. Patients whose endometrial thickness at the end of the estrogen phase was less than 7 mm had their cycles cancelled and were not included in the analysis. Any naturally occurring or artificially created cycles were not included in this research.

On the day of the hCG trigger and embryo transfer (ET), endometrial thickness and sub-endometrial perfusion were examined in these 25 women who were eligible for ICSI using a transvaginal 2-D ultrasound and a 3-D power Doppler ultrasound, respectively. The endometrial volume (EV), thickness, and other angiographic power Doppler indexes (vascularization index (VI), flow index (FI), and vascularization flow index (VFI), which stand for the number of vessels, blood flow, and endometrial perfusion, respectively, plus uterine resistance index (RI) and pulsatility index (PI), were measured by utilizing the Samsung UGEO H60 device.

Endometrial compaction is assessed by ultrasound measurements of endometrial thickness, endometrial volume, and sub-endometrial perfusion using a trans-vaginal 2-D ultrasound and 3-D power Doppler on the day of triggering and the day of embryo transfer.

The main outcome measure is modifications to endometrial thickness, volume, perfusion, and ongoing pregnancy rate.

Results

Pregnancy rates were 40% (table 1).

Between instances with positive and negative pregnancy tests, there was not a significant difference in endometrial thickness based on the incidence of pregnancy on the day of the hCG trigger and the day of embryo transfer ($p > 0.05$). (table 2).

The endometrial volume significantly increases in cases of positive pregnancy tests compared to negative pregnancy tests on the day of embryo transfer and the day of the hCG trigger occurs. However, in both the positive and negative pregnancy groups, there is no discernible difference in endometrial volume between both the day of the embryo transfer and the HCG trigger. (table 3).

Regarding sub-endometrial VI, there was no discernible difference between instances with positive and negative pregnancy tests based on the occurrence of pregnancy on the day of the embryo transfer and the hCG trigger ($p > 0.05$). Between cases with positive pregnancy tests and negative pregnancy tests, there was no discernible change in sub-en-

dometrial FI according to the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer ($p > 0.05$). When compared to negative pregnancy tests, there is a notable increase in sub-endometrial VFI in cases of positive pregnancy tests based on the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. In contrast, there is no discernible variation in sub-endometrial VFI in the groups of women who did not become pregnant between the day of the embryo transfer and the HCG trigger. Comparing the day of embryo transfer to the current HCG trigger in the group of women who became pregnant, there is a significant rise in sub-endometrial VFI (table 4).

Regarding the average uterine RI, there was no discernible difference between instances with positive and negative pregnancy tests based on the incidence of pregnancy on the day of the hCG trigger ($p > 0.05$). The average uterine RI on the day of embryo transfer in positive pregnancy instances is significantly higher than in negative pregnancy instances, and it is also significantly higher on the day of embryo transfer compared to the day of HCG trigger in positive pregnancy cases. By comparing instances with positive pregnancies to those with negative pregnancies, there is a significant increase in the average uterine PI on the days of embryo transfer and HCG trigger and on the day of embryo transfer when compared to the day of HCG trigger in positive pregnancy cases (table 5).

Discussion

Since the first IVF was created in 1978, the processes used in assisted reproductive technologies (ART) have undergone significant change. [8]. There are currently methods for determining high-quality embryos and evaluating endometrial health. Additionally, ART procedures are always being improved to boost the number of successful pregnancies, reduce the number of multiple births, and produce healthier offspring from genetically modified progenitors. [9]. The birth rate has not increased significantly over the past ten years, despite these improvements. This suggests that the low implantation rates in stimulated cycles will persist [10].

a variety of female reproductive processes, including implantation, endometrial expansion, the formation of the corpus luteum, and the development of a dominant follicle, are undoubtedly influenced by angiogenesis. Therefore, in attempts to forecast the success of IVF treatment, a lot of research has concentrated on ovarian and endometrial vascularization. Given that embryonic implantation occurs in the endometrium, endometrial blood flow provides a realistic representation of uterine receptivity. [11]. Nonetheless, the pregnancy rate increases when vessels are visible, reaching the endometrium and the sub-endometrial halo. [12].

This research project sought to ascertain if changes in the thickness of the endometrium, volume, and perfusion the day of embryo transfer and the completion of the estrogen phase possess an effect on the clinical pregnancy rate and pregnancy outcome in IVF/ICSI cycles.

This study, which included 25 subfertile women having IVF/ICSI cycles, was a prospective observational study performed in the obstetrics and gynecology department at Mansoura University Hospitals, Mansoura, Egypt. Progesterone was utilized in every case to prepare the endometrium.

Most of the cases under investigation are urban dwellers, with an average age of 29.2 ± 3.38 and a mean BMI of 25.69 ± 2.22. These findings were compared to those of Hashad et al., who found that women in the research cohort had a mean age of 26, whereas women in the control group had a mean age of 27. [14]. El-Shourbagy et al. concluded that there was no discernible age difference between the groups that were fertile and infertile [15]. The mean age of the study group was 26.9 ± 3.8 years, and the mean age of the

control group was 28.5 ± 4.9 years, neither group's differences were statistically different. (P = 0.194) as regards age [16].

Pregnancy rates were 40%, according to the current study. This was comparable to other research, as live births occur in about one-third of IVF and ICSI cycles [17, 18]. 44.8% was calculated to be the overall 1-year continuing pregnancy rate [19].

In terms of endometrial thickness, the current study observed not a noticeable statistical difference between instances with positive and negative pregnancy tests based on the occurrence of pregnancy on the day of embryo transfer and the day the hCG trigger occurs ($p > 0.05$).

Comparable to our results, other research revealed no association between endometrial thickness on the day of the hCG application and pregnancy rates [20–23] or a distinction that is statistically significant in mean endometrial thickness between groups who were pregnant and those who were not pregnant [24–26].

On the other hand, prior research by Kehila and colleagues revealed a statistically significant correlation between the total pregnancy rate (PR) and endometrial thickness, which is evaluated before triggering ovulation. They contend that if the endometrium measures more than 12 mm in width, the likelihood of a successful pregnancy increases by around three times. [27]. Roughly the same conclusion is drawn from the Bozdag et al. study, which discovered a considerably higher clinical PR in individuals whose endometrial thickness was greater than 14 mm on the day that hCG was administered [28].

The current study found that, in cases with positive pregnancy tests compared to negative pregnancy tests, there is a considerable increase in endometrial volume in accordance with the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. However, in both the positive and negative pregnancy groups, there is no discernible alteration in endometrial volume between the day of the embryo transfer and the HCG trigger.

Comparable to this, Kovachev et al. looked at the endometrial volume as determined by 3-D ultrasound on the day of ET and discovered that an endometrial volume of less than 2 ml was associated with significantly lower implantation rates, while an endometrial volume of more than 2 ml was positively correlated with a successful outcome of ART. [29].

Additionally, a study found that women who were successful in becoming pregnant had a considerable increase in endometrial volume following hCG treatment, but not those who were unsuccessful. Nevertheless, they disagreed with our findings since they demonstrated that no variation was observed in endometrial volume between conception and non-conception cycles on the day of oocyte aspiration. [30].

Additionally, Mercé et al. discovered that patients who became pregnant had a noticeably larger endometrial volume. [26].

According to our research, there was no discernible change in sub-endometrial FI or VI between instances with positive and negative pregnancy tests on the day of the embryo transfer and the hCG trigger ($p > 0.05$).

In keeping with what we discovered, on the day of embryo transfer, Kim et al. conducted a prospective observational study on 234 women (n = 113 pregnant group and n = 121 nonpregnant group) having their first IVF-ET utilizing a GnRH-long protocol with stimulation by recombinant follicular stimulating hormone (rFSH). The women had color Doppler ultrasonography and 3D power Doppler-US scans. While sub-endometrial region VI and FI did not vary throughout the groups, the group of pregnant women showed increased endometrial VI, FI, and VFI values than the nonpregnant group ($p = 0.001$, $p = 0.000$, and $p = 0.021$, respectively) [31].

These findings contrast with a study by Kupesic et al. that included 89 patients and revealed that, on the day of embryo transfer, pregnant patients had considerably higher sub-endometrial FI compared to non-pregnant patients, whereas sub-endometrial VI and VFI were equivalent in both groups [32]. In addition, Vohra et al. demonstrated that endometrial VI was substantially higher in the pregnant group than in the non-pregnant group. [33].

The current study demonstrated that, in cases with positive pregnancy tests compared to negative pregnancy tests, there is a considerable rise in sub-endometrial VFI in accordance with the occurrence of pregnancy on the day of the hCG trigger and the day of embryo transfer. In contrast, there is no discernible variation in sub-endometrial VFI in the negative pregnancy groups between the day of embryo transfer and the HCG trigger. There is a discernible increase in sub-endometrial VFI when the day of embryo transfer is compared to the day of HCG trigger in the pregnant positive group.

Consistent with our results, Mishra et al. proved that there was a substantial difference in endometrial VI, FI, and VFI between the pregnant and non-pregnant groups. While sub-endometrial FI was identical between the two groups, there was a substantial difference in sub-endometrial VI and VFI [34].

More than half of pregnancies that are successfully achieved in the absence of endometrial and sub-endometrial flow on the day of embryo transfer end in spontaneous miscarriage, indicating that the development of the endometrial vascular tree is crucial for supporting the early stages of gestation [35].

According to Ng et al., the pregnant group had considerably higher levels of uterine RI, endometrial VI, and VFI than the non-pregnant group. [36].

According to our research, the average uterine RI did not show any significant difference between the cases of positive and negative pregnancy tests on the day of the hCG trigger ($p > 0.05$). The mean uterine RI on the day of embryo transfer in cases of positive pregnancy is considerably higher than in cases of negative pregnancy; additionally, in cases of positive pregnancy, it is significantly higher on the day of embryo transfer in comparison to the day of HCG trigger.

These results might be related to the impact of elevated serum estradiol and the hormonal state during ovarian-controlled stimulation. When using recombinant HCG (rhCG) as a trigger, all parameters for both groups significantly decreased; flowmetry parameters then recovered on the day of embryo transfer. Due to its up-regulation effect on vascular endothelial growth factors, the rhCG effect on vascularization may be linked to a decrease in both resistance and pulsatility flow. [37].

Consistent with our findings, Ragheb et al. show that sub-endometrial RI does not differ statistically between pregnant and non-pregnant groups [38].

However, in contrast, a study conducted in Turkey by Adkan et al. used transvaginal color Doppler ultrasonography on the day of the hCG injection to compare uterine and arcuate blood flow parameters in 46 women having IVF therapy with and without a good outcome. They showed that women who had successful IVF had considerably lower mean uterine artery PI and RI as well as arcuate artery RI than those who had unsuccessful operations. [39].

The outcomes of the current investigation exhibited that there was a significantly higher increase in the average uterine PI on the days of embryo transfer and HCG trigger in positive pregnancy instances than in negative pregnancy instances. Additionally, in cases of positive pregnancy tests, the average uterine PI on the day of embryo transfer is greater than the day of the HCG trigger.

Conversely, Zollner et al. showed that in cryo cycles, no distinction was made. in the uterine artery blood flow parameters (PI [3.2 vs.

3.0], RI [0.9 vs. 0.9], and peak systolic velocity (PSV) (53.2 vs. 51.2) between patients who were pregnant and those who were not. [13].

Furthermore, Ng and colleagues examined the impact of smoking, female age, different forms of infertility and parity, reasons for infertility, and estradiol (E2) serum levels on Doppler ultrasound during IVF treatment. All the previously described parameters were discovered to have no effect on the endometrial and sub-endometrial Doppler flow indices. assessed on the day of the hCG injection during ICSI treatment. [40].

A study performed in 2011 demonstrated that in cases of recurrent miscarriage, there is a requirement for both healthy blood flow to the uterus and endometrium, as evidenced by decreased endometrial blood flow and increased uterine artery blood flow resistance. Additionally, women who experience unexplained recurrent pregnancy loss may exhibit abnormalities in both uterine and endometrial blood flow. [41]. However, Alcázar and Ruiz Perez found no statistically significant variations in Doppler parameters between patients who had a threatened first-trimester abortion and those who did not. [42].

Conclusion

Endometrial volume, sub-endometrial VFI, uterine RI, and uterine PI all impact the clinical pregnancy rate and pregnancy outcome in IVF/ICSI cycles.

Table (1): Pregnancy rate in the study cases.

Variables	Study cases. n= 25	
	Number	Percent
Pregnancy		
Negative pregnancy	15	60
Positive pregnancy	10	40

Categorical data expressed as number (%)

Table (2): Analysis of endometrial thickness according to the occurrence of pregnancy

Variables	Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
On the day of the hCG trigger	10.27 ± 1.51	10.32 ± 2.05	t = - 0.075 P= 0.957
On the day of embryo transfer	10.31 ± 1.51	10.44 ± 2.04	t = - 0.186 P= 0.854
P1	0.638	0.116	

t: Paired samples t-test

*: Statistically significant (p< 0.05)

P1: Comparison between the value on the day of embryo transfer and the hCG trigger

Table (3): Analysis of Endometrial Volume according to the occurrence of pregnancy

Endometrial Volume	Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
On the day of the hCG trigger	3.14 ± 0.85	4.29 ± 1.25	t = - 2.746 P= 0.012*
On the day of embryo transfer	2.96 ± 0.84	4.16 ± 1.26	t = -2.862 P= 0.009*
P1	0.308	0.426	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

Table (4): Analysis of sub-endometrial VI, FI and VFI according to the occurrence of pregnancy

		Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
Sub-endometrial VI	On the day of the hCG trigger	1.39 ± 0.63	1.74 ± 0.92	t = - 1.128 P= 0.271
	On the day of embryo transfer	1.65 ± 0.63	2 ± 0.92	t = -1.119 P= 0.275
	P1	0.284	0.280	
Sub-endometrial FI	On the day of the hCG trigger	28 ± 4.84	30.42 ± 2.57	t = - 1.444 P= 0.162
	On the day of embryo transfer	28.60 ± 4.83	30.84 ± 2.56	t = -1.340 P= 0.193
	P1	0.457	0.695	
Sub-endometrial VFI	On the day of the hCG trigger	0.35 ± 0.18	0.71 ± 0.29	t = - 3.745 P= 0.001*
	On the day of embryo transfer	0.52 ± 0.18	0.99 ± 0.29	t = - 4.961 P < 0.001*
	P1	0.106	0.045*	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

Table (5): Analysis of average uterine RI and PI according to the occurrence of pregnancy

		Negative pregnancy (n= 15)	Positive pregnancy (n= 10)	Test of significance
average uterine RI	On the day of the hCG trigger	0.81 ± 0.03	0.80 ± 0.06	t = 0.221 P= 0.827
	On the day of embryo transfer	0.82 ± 0.03	0.88 ± 0.06	t = -3.829 P= 0.003*
	P1	0.642	0.001*	
average uterine PI	On the day of the hCG trigger	1.86 ± 0.36	2.27 ± 0.51	t = - 2.369 P= 0.027*
	On the day of embryo transfer	2.01 ± 0.35	2.50 ± 0.51	t = -2.864 P= 0.009*
	P1	0.124	0.041*	

t: Paired samples t-test
*: Statistically significant (p< 0.05)
P1: Comparison between the value on the day of the hCG trigger and the day of embryo transfer

References

1. Teh, W.T., J. McBain, and P. Rogers, What is the contribution of embryo-endometrial asynchrony to implantation failure? J Assist Reprod Genet, 2016. 33(11): p. 1419-1430.
2. Haas, J., R. Smith, E. Zilberberg, D. Nayot, J. Meriano, E. Barzilay, and R.F. Casper, Endometrial compaction (decreased thickness) in response to progesterone results in optimal pregnancy outcome in frozen-thawed embryo transfers. Fertil Steril, 2019. 112(3): p. 503-509.e1.
3. Zhao, Y., P. Brezina, C.C. Hsu, J. Garcia, P.R. Brinsden, and E. Wallach, In vitro fertilization: four decades of reflections and promises. Biochim Biophys Acta, 2011. 1810(9): p. 843-52.
4. Friedler, S., In Vitro Fertilization: Innovative Clinical and Laboratory Aspects. 2012: BoD– Books on Demand.
5. Zhang, Q., X. Wang, Y. Zhang, H. Lu, and Y. Yu, Nomogram prediction for the prediction of clinical pregnancy in Freeze-thawed Embryo Transfer. BMC Pregnancy Childbirth, 2022. 22(1): p. 629.
6. Riestenberg, C., M. Quinn, A. Akopians, H. Danzer, M. Surrey, S. Ghadir, and L. Kroener, Endometrial compaction does not predict live birth rate in single euploid frozen embryo transfer cycles. J Assist Reprod Genet, 2021. 38(2): p. 407-412.
7. Bu, Z., X. Yang, L. Song, B. Kang, and Y. Sun, The impact of endometrial thickness change after progesterone administration on pregnancy outcome in patients transferred with single frozen-thawed blastocyst. Reprod Biol Endocrinol, 2019. 17(1): p. 99.
8. Wang, J. and M.V. Sauer, In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological ad-

vancement. Therapeutics and clinical risk management, 2006. 2(4): p. 355-364.

9. Davidson, L.M., Y. Liu, T. Griffiths, C. Jones, and K. Coward, Laser technology in the ART laboratory: a narrative review. Reproductive BioMedicine Online, 2019. 38(5): p. 725- 739.
10. Levi-Setti, P.E., I. Zerbetto, A. Baggiani, E. Zannoni, L. Sacchi, A. Smeraldi, E. Morenghi, R. De Cesare, A. Drovanti, and D. Santi, An observational retrospective cohort trial on 4,828 IVF cycles evaluating different low prognosis patients following the POSEIDON criteria. Frontiers in Endocrinology, 2019. 10: p. 282.
11. Adamczyk, M., E. Wender-Ozegowska, and M. Kedzia, Epigenetic factors in eutopic endometrium in women with endometriosis and infertility. International Journal of Molecular Sciences, 2022. 23(7): p. 3804.
12. Garhy, I.T.E., A.H. Mohamed, and A.S. Sultan, Uterine and subendometrial arteries Doppler in patients with recurrent first trimestric abortion. The Egyptian Journal of Hospital Medicine, 2018. 73(5): p. 6683-6690.
13. Zollner, U., M.-T. Specketer, K.-P. Zollner, and J. Dietl, Uterine artery blood flow in the periimplantation period in embryo transfer cycles. Asian Pacific Journal of Reproduction, 2012. 1(3): p. 177-182.
14. Elkholy, H.A.N.K., A.M.N.-E. Hashad, I.M. Ibrahim, and M.K. Etman, A study of endometrial perfusion in unexplained infertility. The Egyptian Journal of Hospital Medicine, 2018. 72(6): p. 4673-4680.
15. El-Shourbagy, S., A.M. Ossman, and A. El-Mohamady, The role of sildenafil citrate (viagra) suppositories on endometrial response (thickness and mean resistance index of endometrial spiral artery) in cases of unexplained infertility. Menoufia Medical Journal, 2017. 30(2): p. 343.
16. Ali zarad, C., M.H. Mohamed, and W.S.A. Shanab, Role of uterine artery Doppler in assessment of unexplained infertility. Egyptian Journal of Radiology and Nuclear Medicine, 2021. 52(1): p. 59.
17. De Geyter, C., C. Calhaz-Jorge, M.S. Kupka, C. Wyns, E. Mocanu, T. Motrenko, G. Scaravelli, J. Smeenk, S. Vidakovic, and V. Goossens, ART in Europe, 2015: results generated from European registries by ESHRE. Human reproduction open, 2020. 2020(1): p. hoz038.
18. Sunderam, S., D.M. Kissin, Y. Zhang, A. Jewett, S.L. Boulet, L. Warner, C.D. Kroelinger, and W.D. Barfield, Assisted reproductive technology surveillance—United States, 2017. MMWR Surveillance Summaries, 2020. 69(9): p. 1.
19. Lintsen, A.M.E., M.J.C. Eijkemans, C.C. Hunault, C.A.M. Bouwmans, L. Hakkaart, J.D.F. Habbema, and D.D.M. Braat, Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. Human Reproduction, 2007. 22(9): p. 2455-2462.
20. Corbacioğlu, A. and B. Baysal, Effects of endometrial thickness and echogenic pattern on assisted reproductive treatment outcome. Clin Exp Obstet Gynecol, 2009. 36(3): p. 145- 7.
21. Laasch, C. and E. Puscheck, Cumulative embryo score, not endometrial thickness, is best for pregnancy prediction in IVF. J Assist Reprod Genet, 2004. 21(2): p. 47-50.
22. Yoeli, R., J. Ashkenazi, R. Orvieto, M. Shelef, B. Kaplan, and I. Bar-Hava, Significance of increased endometrial thickness in assisted reproduction technology treatments. J Assist Reprod Genet, 2004. 21(8): p. 285-9.
23. Rashidi, B.H., M. Sadeghi, M. Jafarabadi, and E.S. Tehrani Nejad, Relationships between pregnancy rates following in vitro fertilization or intracytoplasmic sperm

injection and endometrial thickness and pattern. Eur J Obstet Gynecol Reprod Biol, 2005. 120(2): p. 179-84.

24. Okohue, J.E., S.O. Onuh, P. Ebeigbe, I. Shaibu, I. Wada, J.I. Ikimalo, and E.E. Okpere, The effect of endometrial thickness on in vitro fertilization (IVF)-embryo transfer/intracytoplasmic sperm injection (ICSI) outcome. Afr J Reprod Health, 2009. 13(1): p. 113-21.
25. Kinay, T., Y. Tasci, S. Dilbaz, O. Cinar, B. Demir, and A. Haberal, The relationship between endometrial thickness and pregnancy rates in GnRH antagonist down-regulated ICSI cycles. Gynecol Endocrinol, 2010. 26(11): p. 833-7.
26. Mercé, L.T., M.J. Barco, S. Bau, and J. Troyano, Are endometrial parameters by threedimensional ultrasound and power Doppler angiography related to in vitro fertilization/embryo transfer outcome? Fertil Steril, 2008. 89(1): p. 111-7.
27. Kehila, M., S. Kebaili, I. Bougmiza, S. Meddeb, S. Boughizane, H. Khairi, and M. Ajina, [Endometrial thickness in in vitro fertilization. A study of 414 cases]. Tunis Med, 2010. 88(12): p. 928-32.
28. Bozdag, G., I. Esinler, and H. Yarali, The impact of endometrial thickness and texture on intracytoplasmic sperm injection outcome. J Reprod Med, 2009. 54(5): p. 303-11.
29. Kovachev, E., Z. Ganchev, S. Cherneva, E. Zokhav, and A. Shperberg, [Measurement of endometrial volume and endometrial thickness for assessment of endometrial receptivity in assisted reproductive techniques]. Akush Ginekol (Sofiia), 2005. 44 Suppl 2: p. 27-33.
30. Järvelä, I.Y., P. Sladkevicius, S. Kelly, K. Ojha, S. Campbell, and G. Nargund, Evaluation of endometrial receptivity during in-vitro fertilization using three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol, 2005. 26(7): p. 765-9.
31. Vickers, N.J., Animal communication: when i'm calling you, will you answer too? Current biology, 2017. 27(14): p. R713-R715.
32. Kupesic, S., I. Bekavac, D. Bjelos, and A. Kurjak, Assessment of endometrial receptivity by transvaginal color Doppler and three-dimensional power Doppler ultrasonography in patients undergoing in vitro fertilization procedures. J Ultrasound Med, 2001. 20(2): p. 125-34.
33. Vohra, R., M. Pandurangi, S.R. Nellepalli, R. Vembu, and S. Nagireddy, 3D Vascularity: A Novel Predictor of FET Success? International Journal of Infertility & Fetal Medicine, 2022. 13(2): p. 65-69.
34. Mishra, V.V., R. Agarwal, U. Sharma, R. Aggarwal, S. Choudhary, and P. Bandwal, Endometrial and Subendometrial Vascularity by Three-Dimensional (3D) Power Doppler and Its Correlation with Pregnancy Outcome in Frozen Embryo Transfer (FET) Cycles. J Obstet Gynaecol India, 2016. 66(Suppl 1): p. 521-7.
35. Chien, L.-W., H.-K. Au, P.-L. Chen, J. Xiao, and C.-R. Tzeng, Assessment of uterine receptivity by the endometrial-subendometrial blood flow distribution pattern in women undergoing in vitro fertilization-embryo transfer. Fertility and sterility, 2002. 78(2): p. 245-251.
36. Ng, E.H., C.C. Chan, O.S. Tang, W.S. Yeung, and P.C. Ho, The role of endometrial and subendometrial blood flows measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during IVF treatment. Hum Reprod, 2006. 21(1): p. 164- 70.
37. Silva Martins, R., A. Helio Oliani, D. Vaz Oliani, and J. Martinez de Oliveira, Subendometrial resistence and pulsatility index assessment of endometrial receptivity in assisted reproductive technology cycles. Reproductive Biology and Endocrinology, 2019. 17(1): p. 62.

38. Ragheb, S.R., S.M. Sharara, M.S. Aly, M.M. El-Sherbiny, H.F. Mohammad, and H.A. Badran, ROLE OF 2D DOPPLER ULTRASOUND ON THE DAY OF EMBRYO TRANSFER IN PREDICTING PREGNANCY IN ICSI. Ain Shams Medical Journal, 2019. 70(10, 11 & 12): p. 565-577.

39. Adakan, S., T. Yoldemir, E. Tavmergen, E. Goker, and R. Killi, Predictivity of uterine artery, arcuate artery, and intraovarian artery Doppler indices measured on the day of human chorionic gonadotropin injection on pregnancy outcomes. Fertil Steril, 2005. 84(2): p. 529-32.

40. Ng, E.H.Y., C.C.W. Chan, O.S. Tang, W.S.B. Yeung, and P.C. Ho, The role of endometrial blood flow measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during in vitro fertilization treatment. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2007. 135(1): p. 8-16.

41. Anwar, A., E. BaraKat, A. Bendary, A. Biomy, and F. Elebiary, Uterine Artery Doppler and Sub Endometrial Blood Flow in Patients with Unexplained Recurrent Miscarriage. Benha Journal of Applied Sciences, 2022. 7(5): p. 165-172.

42. Alcázar, J.L. and M.L. Ruiz-Perez, Uteroplacental circulation in patients with first-trimester threatened abortion. Fertility and sterility, 2000. 73(1): p. 130-135.

Transvaginal Ultrasonography for Evaluation of Endometriotic Adhesions

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Abstract

Background: Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus, is a frequent gynaecological disease. Accurate diagnosis and staging of endometriosis by imaging is essential to accurately guide the clinician in disease management. Transvaginal sonography (TVS) is a cost-effective method compared to MRI in the diagnosis of endometriosis specifics.

Aim: To evaluate the accuracy of TVS in the detection of pelvic adhesions caused by endometriosis.

Methods: This prospective cohort study enrolled 80 cases diagnosed with endometriosis were subjected to laparoscopy. Transvaginal ultrasonography was done using 2D and 3D scan without any bowel preparation and was guided by Adhesion scoring system. Transvaginal ultrasonography was used to detect the presence or absence of adhesions using the sliding sign approach.

Results: Concerning the severity of endometriosis based on the r-ASRM classification, the number of cases with disease stages I and II, stage III and stage IV were 3 (2.3%), 32 (24.4%) and 96 (73.3%), respectively. There was statistical significance difference between TVS Technique versus laparoscopy as regard detection of mid anterior adhesion, up anterior adhesion, up posterior adhesion, mid posterior adhesion, Rt-O-Ut adhesion, Inter O-O adhesion, Rt-O-side adhesion, Lt-O-Ut adhesion, Lt-O-side adhesion and Low posterior adhesion ($P<0.05$).

Conclusion: Adhesion scoring system could simply and noninvasively predict the degree of endometriosis adhesions. As a result, we could assess the actual condition of endometriotic adhesions with this approach both presurgically and postoperatively.

Keywords: Transvaginal, Ultrasonography, Endometriosis, Adhesions, Sliding Sign.

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INTRODUCTION

Endometriosis is a frequent gynecological disorder described by the existence of extrauterine stroma and ectopic endometrial glands. It has been a frequent and es-

sential problem in females of reproductive age, presenting with pain and loss of fertility [1]. Endometriosis affects around 6–10% of childbearing females who are fertile, with peak prevalence among those in their 25–30s. Endometriosis can have a broad spectrum of manifestations which include irregular menstrual periods, chronic pelvic pain (CPP), painful menstruation, dyspareunia, dysphasia, dysuria, subfertility, and a poor life quality [2].

The most frequent site of endometriosis are the ovaries and the pelvic peritoneum, followed by deep masses in pelvic subperitoneal space, the gut, and the genitourinary system [3]. Endometrioma has been considered a frequent adnexal mass in premenopausal females, and it is often accompanied by adhesions, which could make the operation more difficult with a subsequent increase in the operating time [4]. US could be utilized in the presurgical diagnosis of females with suspected endometriosis to decrease the number of unwarranted laparoscopies (negative laparoscopy) [5].

The sliding sign approach using TVS is a non-invasive and efficient approach for detection of endometriosis adhesions at the Douglas' pouch [6]. Unluckily, the size of an endometrioma measured by TVS assessment doesn't correlate with the degree of adhesive disease. Additionally, small cysts may be associated with a considerable degree of pelvic adhesions [7]. Numerous other approaches, which include the Enzian score, US mapping and endometriosis fertility index (EFI) approach are suggested as diagnostic procedures for endometriosis [8].

A possible need for presurgical assessment has to be the recognition of extensive pelvic adhesions to allow referral to an appropriate surgeon with adequate experience in conducting difficult laparoscopy. In fact, pelvic adhesions could limit the proper laparoscopic surgery and have been considered the primary cause for conversion to laparotomy [9].

Aim of Study

This study aimed to evaluate the accuracy of TVS in the detection of pelvic adhesions caused by endometriosis.

PATIENTS AND METHODS

This prospective cohort study was conducted in Mansoura University Hospital Obstetrics and Gynecology Department on (80) cases diagnosed with endometriosis. This study was performed within 1 year years January 2021 to January 2022. This study enrolled patients aged from 18 to 45 years old with clinical diagnosis of pelvic endometriosis and were subjected to laparoscopy. Patients with pelvic tumors whether benign or malignant, patients with history of Pelvic Inflammatory Disease, patients have unilateral or bilateral adnexectomy at the time of surgery and patients refused to participate in the study were ruled out from this study.

Methods

Entire cases were subjected to history taking and general examination that included age, body mass index, previous medical treatment or previous surgery for endometriosis, operation time, blood loss. Abdominal and local examinations were also done for all patients.

Transvaginal ultrasound was guided by Adhesion scoring system [8] and this system includes 2 components, the adhesion mapping phase and the scoring phase. The total number of sites showing adhesions in the two images was directly described as an adhesion score ranging from zero to ten.

The adhesion mapping phase was used to detect adhesions to measure the extent of the endometriosis adhesions. The presence or absence of adhesions was evaluated in a total of 10 sites: five in the uterus–ovarian cross-section (transverse) and five in the sagittal section of the uterus (sagittal). Five sites included in the transverse plane were the spac-

es between the right ovary and the uterus (Rt O-Ut) and between the left ovary and the uterus (Lt O-Ut), the space between the left and right ovary (Inter O-O), the spaces between the right ovary and the right pelvic sidewall (Rt O Side) and between the left ovary and the left pelvic sidewall (Lt O-Side).

While the five sites included in the sagittal plane were the upper 1/2 (Up Ant) and the lower half (Mid Ant) of the anterior side of the uterus, ranging from the upper uterine part to the vesicouterine pouch and the upper 3rd (Up Post), the middle 3rd (Mid Post) and the lower 3rd (Low Post) of the posterior uterine aspect, ranging from the upper uterine part to Douglas' pouch.

Transvaginal ultrasonography was used to detect the presence or absence of adhesions using the sliding sign approach. The same ten areas were assessed by TVS and are assessed under laparoscopy of the pelvis to detect whether the adhesions exist or not to confirm the accuracy of adhesion mapping detected before operation.

The existence of adhesions was evaluated by assessing the mobility between an object and its nearby adjacent structures according to the pressure on the laparoscopic forceps (when mobility could be detected between two structures, it has to be judged as a site negative for adhesion; otherwise, it should be judged as a site positive for adhesion). The overall number of areas revealing adhesions could be defined as an intraoperative adhesion score ranging from zero to ten. The adhesion scoring phase included calculating the score according to the lesions determined.

Transvaginal ultrasonography was done using 2D and 3D scan without any bowel preparation. The region-of-interest was detected in US using a B-mode scan and a transvaginal volume transducer. The sliding sign approach consisted of detecting whether an object is sliding against its surroundings by pushing it with the examiner's hand over the abdominal wall by using TVS.

Ethical Consideration

Approval from the hospital's ethical committee (IRB) was obtained. Informed consent was obtained from all the studied women. Personal privacy was respected. The collected data was not used for any other purpose.

Statistical Analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25. Armonk, NY). Qualitative data were expressed as frequency and percentage. Qualitative data for two groups were compared by Chi-Square test (or Fishers exact test). Quantitative data were initially tested for normality using Kolmogorov-Smirnov and Shapiro-Wilks tests with data being normally distributed if $p>0.05$. Quantitative data were expressed as mean±SD if normally distributed or median and IQR if not. Quantitative data between two groups were compared by Independent- Samples t test or the non-parametric alternative Mann-Whitney U test according to the distribution of data. Results were considered as statistically significant if p value ≤ 0.050.

RESULTS

Table (1) represents analysis of the laparoscopic findings in the cases of the study in which positive adhesions (mid anterior, up anterior, up posterior, mid posterior, low posterior, Rt-O-Ut, Rt-O-side, Inter O-O, Lt-O-Ut, Lt-O-side) represents the following ratios respectively (5%, 2.5%, 22.5%, 51.3%, 60%, 50%, 40%, 41.3%, 68.8%, 48.8%). Table (1): Analysis of the laparoscopic findings in the

Table (1): Analysis of the laparoscopic findings in the cases of the study

Items	Study subjects N = 80	
Positive adhesions	**Number**	**Percent**
Mid anterior	**4**	**5**
Up anterior	**2**	**2.5**
Up posterior	18	22.5
Mid posterior	**41**	**51.3**
Low posterior	**48**	**60**
Rt-O-Ut	**40**	**50**
Rt-O-side	**32**	**40**
Inter O-O	**33**	**41.3**
Lt-O-Ut	**55**	**68.8**
Lt-O-side	**39**	**48.8**

Table (2) shows predictive value of TVS Technique versus laparoscopy in detection of mid anterior adhesion, there is statistical significance difference between both methods. TVS Sensitivity represents 25%, TVS specificity represents 98.7%, TVS accuracy represents 25%, TVS PPV is 50% and NPV is 96.25.

Table (2): Predictive value of TVS Technique versus laparoscopy in detection of Mid anterior adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 76)		**Positive (n= 4)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=78)	75 (TN)	98.7	3 (FN)	75	8.754	0.003*
Positive (N= 2)	1 (FP)	1.3	1 (TP)	25		
Sensitivity	25 %					
Specificity	**98.7 %**					
Accuracy	**95 %**					
PPV	**50%**					
NPV	**96.2%**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (3): Predictive value of TVS Technique versus laparoscopy in detection of Up anterior adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 78)		**Positive (n= 2)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=75)	75 (TN)	96.2	0 (FN)	0	30.769	< 0.001*
Positive (N= 5)	3 (FP)	3.8	2 (TP)	100		

Sensitivity	100 %
Specificity	**96.2 %**
Accuracy	**96.2 %**
PPV	**40%**
NPV	**100%**

c^2 : Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (4) shows predictive value of TVS Technique versus laparoscopy in detection of Up posterior adhesion, in which statistical significance difference is found between them (p< 0.001*). TVS sensitivity is 83.3%, TVS specificity is 87.1%, TVS accuracy 86.2%, TVS PPV is 65.2%, TVS NPV is 94.7%.

Table (4): Predictive value of TVS Technique versus laparoscopy in detection of Up posterior adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 62)		**Positive (n= 18)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=57)	54 (TN)	87.1	3 (FN)	16.7	33.781	< 0.001*
Positive (N= 23)	8 (FP)	12.9	15 (TP)	83.3		
Sensitivity	83.3 %					
Specificity	**87.1 %**					
Accuracy	**86.2 %**					
PPV	**65.2%**					
NPV	**94.7 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (5) shows predictive value of TVS Technique versus laparoscopy in detection of Mid posterior adhesion with statistical significance difference between them p< 0.001*. TVS Sensitivity is 95.1%, TVS Specificity is 76.1%, TVS Accuracy is 86.2%, TVS PPV is 81.3%, TVS NPV is 93.8%.

Table (5): Predictive value of TVS Technique versus laparoscopy in detection of Mid posterior adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 39)		**Positive (n= 41)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=32)	30 (TN)	76.9	2 (FN)	4.9	43.227	< 0.001*
Positive (N= 48)	9 (FP)	23.1	39 (TP)	95.1		
Sensitivity	95.1 %					

Specificity	**76.9 %**
Accuracy	**86.2 %**
PPV	**81.3%**
NPV	**93.8 %**

c^2 : Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (6) shows predictive value of TVS Technique versus laparoscopy in detection of Low posterior adhesion with statistical significance difference between them (p< 0.001*). TVS sensitivity is 89.6%, TVS specificity is 78.1%, TVS accuracy is 85%, TVS PPV is 86%, TVS NPV is 83.3%.

Table (6): Predictive value of TVS Technique versus laparoscopy in detection of Low posterior adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 32)		**Positive (n= 48)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=30)	25 (TN)	78.1	5 (FN)	10.4	37.556	< 0.001*
Positive (N= 50)	7 (FP)	21.9	43 (TP)	89.6		
Sensitivity	89.6 %					
Specificity	**78.1 %**					
Accuracy	**85 %**					
PPV	**86%**					
NPV	**83.3 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (7) shows predictive value of TVS Technique versus laparoscopy in detection of Rt-O-Ut adhesion with statistical significance difference between them (p< 0.001*). TVS sensitivity is 85%, TVS specificity is 82.5%, TVS accuracy is 83.8%, TVS PPV is 84.6%, TVS NPV is 82.9%.

Table (7): Predictive value of TVS Technique versus laparoscopy in detection of Rt-O-Ut adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 40)		**Positive (n= 40)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=39)	33 (TN)	82.5	6 (FN)	15	36.473	< 0.001*
Positive (N= 41)	7 (FP)	17.5	34 (TP)	85		
Sensitivity	85 %					
Specificity	**82.5 %**					
Accuracy	**83.8 %**					

PPV	**84.6%**
NPV	**82.9 %**

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (8) shows predictive value of TVS Technique versus laparoscopy in detection of Rt-O-side adhesion with statistical significance difference between them p=0.003*. TVS sensitivity is 50%, TVS specificity is 81.2%, TVS accuracy is 68.8%, TVS PPV is 64%, TVS NPV is 70.9%.

Table (8): Predictive value of TVS Technique versus laparoscopy in detection of Rt-O-side adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 48)		**Positive (n= 32)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=55)	39 (TN)	81.2	16 (FN)	50	8.727	0.003*
Positive (N= 25)	9 (FP)	18.8	16 (TP)	50		
Sensitivity	50 %					
Specificity	**81.2 %**					
Accuracy	**68.8 %**					
PPV	**64%**					
NPV	**70.9 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (9) shows predictive value of TVS Technique versus laparoscopy in detection of Inter O-O adhesion with statistical significance difference between them (p< 0.001*). TVS sensitivity is 81.8%, TVS specificity is 81.5%, TVS accuracy is 87.5%, TVS PPV is 87.1%, TVS NPV is 87.8%.

Table (9): Predictive value of TVS Technique versus laparoscopy in detection of Inter O-O adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 47)		**Positive (n= 33)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=49)	43 (TN)	91.5	6 (FN)	18.2	43.898	< 0.001*
Positive (N= 31)	4 (FP)	8.5	27 (TP)	81.8		
Sensitivity	81.8 %					
Specificity	**91.5 %**					
Accuracy	**87.5 %**					
PPV	**87.1%**					
NPV	**87.8 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (10) shows predictive value of TVS Technique versus laparoscopy in detection of Lt-O-Ut adhesion in which there is statistical significance difference between them p< 0.001*. TVS sensitivity is 85.5%, TVS specificity is 72%, TVS accuracy is 65%, TVS PPV is 87.1%, TVS NPV is 69.2%.

Table (10): Predictive value of TVS Technique versus laparoscopy in detection of Lt-O-Ut adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 25)		**Positive (n= 55)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=26)	18 (TN)	72	8 (FN)	14.5	25.863	< 0.001*
Positive (N= 54)	7 (FP)	28	47 (TP)	85.5		
Sensitivity	85.5 %					
Specificity	**72 %**					
Accuracy	**65 %**					
PPV	**87.1%**					
NPV	**69.2 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

Table (11) shows predictive value of TVS Technique versus laparoscopy in detection of Lt-O-side adhesion in which there is statistical significance difference between both methods (p< 0.001*). TVS sensitivity represents 74.4%, TVS specificity represents 78%, TVS accuracy represents 76.2%, TVS PPV represents 76.3%, TVS NPV represents 46.2%.

Table (11): Predictive value of TVS Technique versus laparoscopy in detection of Lt-O-side adhesion

	Laparoscopic findings				**c^2/FET**	**P**
	Negative (n= 41)		**Positive (n= 39)**			
	No	**%**	**No**	**%**		
Transvaginal ultrasondraphy findings						
Negative (N=42)	32 (TN)	78	10 (FN)	25.6	25.863	< 0.001*
Positive (N= 38)	9 (FP)	22	29 (TP)	74.4		
Sensitivity	74.4 %					
Specificity	**78 %**					
Accuracy	**76.2 %**					
PPV	**76.3%**					
NPV	**46.2 %**					

c^2: Chi-square test
FET: Fischer's exact test *: Statistically significant
PPV: Positive predictive value NPV: Negative predictive value

DISCUSSION

Endometriosis presents as different pathologies including endometrioma, deep infiltrating endometriosis (DIE) and endometriosis adhesions. Thus, it isn't easy to expansively assess all such pathologies with a single test. As a result, focusing on one pathologic state and totally grasping its distribution and extent is important in terms of endometriosis management (10). Endometriosis adhesions are accompanied by loss of fertility. In addition, the presence of severe adhesions has been accompanied by with low pregnancy rates. Open surgery with colorectal excision for endometriosis apparently stimulated the development of extensive adhesions, which ultimately ended in worse pregnancy rates compared to laparoscopy [(11)].

As a result, it is clinically linked to precisely diagnose endometriosis adhesion to predict the likelihood of upcoming pregnancy. As a result, the traditional r-ASRM classification (reliant on surgical outcomes) is the only approach to totally describe the endometriosis adhesion condition, and no conclusive noninvasive approach to describe endometriosis adhesions was confirmed [(12)].

Ultrasound could be utilized in the presurgical diagnosis of females with suspected endometriosis to decrease the number of unwarranted laparoscopies (negative laparoscopy) (5). In addition, presurgical assessment could recognize precisely the existence of endometrioma and other adnexal masses responsible for pain (13). The sliding sign approach using TVS is a noninvasive and efficient approach for detection of endometriosis adhesions within the Douglas' pouch [(6)].

Unlikely, the endometrioma size measured by TVS doesn't correlate with the degree of adhesion. Additionally, small cysts might be accompanied by a substantial degree of pelvic adhesions [(7)]. Our study aimed to assess the accuracy of TVS in the detection of pelvic adhesions caused by endometriosis.

The demographic and clinical data in the cases of the study were stated as the mean age was 27.54 ± 7.78 ranging from 19-40 yrs, BMI mean was 29.53 ± 5.6 ranging from 19-54, gravidity mean was 3.06 ± 1.84 ranging from 1-6, parity mean was 1.68 ± 1.25 ranging from 0-5, abortion range from 0-3. Positive Family history of endometriosis was 37.5%. Menstrual history in the cases of the study is stated as mean age of menarche is 27.54 ± 7.78 ranging from 19-40, cycle length was represented as (normal: 71.3 %, frequent: 20%, infrequent: 8.8%), cycle amount was represented as (heavy: 55%, normal: 36.3%, scanty: 8.8%), and regular cycle represented 80%. In our study analysis of history of endometriosis in the cases in which symptoms (CPP, Dysmenorrhea, Menstrual disturbances) was represented as (36.6%, 58.8%, 5%). Previous medical therapy accounts for 35%, previous surgical treatment accounts for 11.3%. Distribution of Endometrioma in studied cases as (unilateral: 56.3%, bilateral: 38.8%, no: 5%). Staging (r-ASRM) was classified as (I: 3.8%, II: 5%, III: 23.8%, IV: 67.5%). Likewise, Ichikawa et al. stated in his study that 48.1% had received oral therapy for endometriosis and 9.2% had undergone preceding surgery for endometriosis [(8)]. On the other hand, Ichikawa et al. demonstrated in his research that 46.6% had unilateral endometriomas and 51.9% had bilateral endometriomas [(8)].

With regard to the severity of endometriosis based on the r-ASRM classification, the number of cases with disease stages I and II, stage III and stage IV were three (2.3%), 32 (24.4%) and 96 (73.3%), respectively. In This study, analysis of the TVS findings in the cases of positive adhesions (mid anterior, up anterior, up posterior, mid posterior, low posterior, Rt-O-Ut, Rt-O-side, Inter O-O, Lt-O-Ut, Lt-O-side) represented the following ratios respectively (3.8%, 6.3%, 28.8%, 60%, 62.5%, 51.3%, 31.3%, 38.8%, 67.5%, 47.5%). Total adhesions mean represented 3.96 ± 1.60 ranging from 1-8.

Similarly, Ichikawa et al. demonstrated in

their study that the percentages of adhesion were 70.5%, 61.1%, and 56.5% in Lt O-Ut, Low Post, and Mid Post, respectively. The sensitivity, specificity, PPV, NPV, LR+, LR− and accuracy of the adhesion mapping were 80.4%, 86%, 78.8%, 87%, 5.8, 0.23 and 83.9%, respectively [8].

Analysis of the laparoscopic findings in the cases of the study in which positive adhesions (mid anterior, up anterior, up posterior, mid posterior, low posterior, Rt-O-Ut, Rt-O-side, Inter O-O, Lt-O-Ut, Lt-O-side) represented the following ratios respectively (5%, 2.5%, 22.5%, 51.3%, 60%, 50%, 40%, 41.3%, 68.8%, 48.8%). In This study, predictive value of TVS Technique versus laparoscopy in detection of mid anterior adhesion, there was statistical significance difference between both methods. TVS Sensitivity represents 25%, TVS specificity represents 98.7%, TVS accuracy represents 25%, TVS PPV is 50% and NPV is 96.25, predictive value of TVS Technique versus laparoscopy in detection of Up anterior adhesion in which there is statistical significance difference between them ($p< 0.001$*). TVS sensitivity is 100%, TVS specificity 96.2%, TVS accuracy is 96.2%, TVS PPV is 40%, TVS NPV is 100%. The predictive value of TVS Technique versus laparoscopy in detection of Up posterior adhesion, in which statistical significance difference is found between them ($p< 0.001$*). TVS sensitivity is 83.3%, TVS specificity is 87.1%, TVS accuracy 86.2%, TVS PPV is 65.2%, TVS NPV is 94.7%. In our study, predictive value of TVS Technique versus laparoscopy in detection of Mid posterior adhesion showed statistical significance difference between them $p< 0.001$*. TVS sensitivity is 95.1%, TVS specificity is 76.1%, TVS accuracy is 86.2%, TVS PPV is 81.3%, TVS NPV is 93.8%, predictive value of TVS Technique versus laparoscopy in detection of Rt-O-Ut adhesion with statistical significance difference between them ($p< 0.001$*). TVS sensitivity is 85%, TVS specificity is 82.5%, TVS accuracy is 83.8%, TVS PPV is 84.6%, TVS NPV is 82.9%. predictive value of TVS Technique versus laparoscopy in detection of Inter O-O adhesion with statistical significance difference between them ($p< 0.001$*). TVS sensitivity is 81.8%, TVS specificity is 81.5%, TVS accuracy is 87.5%, TVS PPV is 87.1%, TVS NPV is 87.8%. Moreover, in this study, predictive value of TVS Technique versus laparoscopy in detection of Rt-O-side adhesion showed statistical significance difference between them $p=0.003$*. TVS sensitivity is 50%, TVS specificity is 81.2%, TVS accuracy is 68.8%, TVS PPV is 64%, TVS NPV is 70.9%, predictive value of TVS Technique versus laparoscopy in detection of Lt-O-Ut adhesion in which there is statistical significance difference between them $p< 0.001$*. TVS sensitivity is 85.5%, TVS specificity is 72%, TVS accuracy is 65%, TVS PPV is 87.1%, TVS NPV is 69.2%.

In accordance, when the diagnostic accuracy of adhesions in each site was assessed in Ichikawa et al. study, the diagnostic accuracy of Mid Post, Rt O-Ut and Inter O- O was considered very high. On the other hand, the adhesion diagnostic accuracy at Rt O-Ut and Lt O-Side, which are extra-uterine areas, were to some extent lower than that of the former [8].

Our study revealed that predictive value of TVS Technique versus laparoscopy in detection of Low posterior adhesion showed statistical significance difference between them ($p< 0.001$*). TVS sensitivity is 89.6%, TVS specificity is 78.1%, TVS accuracy is 85%, TVS PPV is 86%, TVS NPV is 83.3% and predictive value of TVS Technique versus laparoscopy in detection of Lt-O-side adhesion in which there is statistical significance difference between both methods ($p< 0.001$*). TVS sensitivity represents 74.4%, TVS specificity represents 78%, TVS accuracy represents 76.2%, TVS PPV represents 76.3%, TVS NPV represents 46.2%.

Similarly, Fedele et al. and Shalev et al. recorded a high accuracy of TVS in terms of uterine

adhesion diagnosis [14, 15]. In contrast, Niknejadi et al. study showed TVS failed to detect adhesions in 67% of the studied cases [16].

CONCLUSIONS

The adhesion scoring system can simply and noninvasively predict the extent and severity of endometriosis adhesions. As a result, we could assess the actual condition of endometriotic adhesions with such approach presurgically and postoperatively.

With regard to the issues with the adhesion scoring system, we have to consider the potential measurement error among the investigators. In addition, any examiner who is familiar with TVS should be able to give outcomes that are comparable because both this system and the sliding sign approach are simple to use. Another problem is that various endometriosis presentations, including endometriomas or DIE, may not be adequately assessed using the adhesion grading system alone.

Recommendations

This work represented a small sized sample of Egyptian population. So, additional studies with larger number of patients would be useful to confirm the importance of TVS in the detection of pelvic adhesions caused by endometriosis.

Declarations

Ethics approval and consent to participate Mansoura University's Faculty of Medicine's Ethical Committee gave its approval for the study and the patients' participation. Ethics of Humanity was given the all-clear by the Mansoura University Faculty of Medicine's Ethics Committee.

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REFERENCES

1. Bourgioti C, Preza O, Panourgias E, Chatoupis K, Antoniou A, Nikolaidou M, Moulopoulos L. MR imaging of endometriosis: spectrum of disease. Diagn. Interv. Imaging. 2017;98(11):751-67.
2. La Rosa VL, Barra F, Chiofalo B, Platania A, Di Guardo F, Conway F, Di Angelo Antonio S, Lin L-T. An overview on the relationship between endometriosis and infertility: the impact on sexuality and psychological well-being. J Psychosom Obstet Gynaecol. 2020;41(2):93-7.
3. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat. Rev. Endocrinol. 2019;15(11):666-82.
4. Matalliotakis M, Matalliotaki C, Trivli A, Zervou MI, Kalogiannidis I, Tzardi M, Matalliotakis I, Arici A, Goulielmos GN. Keeping an eye on perimenopausal and postmenopausal endometriosis. Diseases. 2019;7(1):29.
5. Chen Y-H, Wang D-B, Guo C-S. Accuracy of physical examination, transvaginal sonography, magnetic resonance imaging, and rectal endoscopic sonography for preoperative evaluation of rectovaginal endometriosis. Ultrasound Quarterly. 2019;35(1):54-60.
6. Reid S, Lu C, Casikar I, Reid G, Abbott J, Cario G, Chou D, Kowalski D, Cooper M, Condous G. Prediction of pouch of Douglas obliteration in women with suspected endometriosis using a new real-time dynamic transvaginal ultrasound technique: the sliding sign. J Ultrasound Obst Gyn. 2013;41(6):685-91.
7. Reid S, Condous G. Update on the ultrasound diagnosis of deep pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol. 2017;209:50-4.
8. Ichikawa M, Akira S, Kaseki H, Wata-

nabe K, Ono S, Takeshita T. Accuracy and clinical value of an adhesion scoring system: A preoperative diagnostic method using transvaginal ultrasonography for endometriotic adhesion. J. Obstet. Gynaecol. Res. 2020;46(3):466-78.

9. Holland TK, Cutner A, Saridogan E, Mavrelos D, Pateman K, Jurkovic D. Ultrasound mapping of pelvic endometriosis: does the location and number of lesions affect the diagnostic accuracy? A multicentre diagnostic accuracy study. BMC women's health. 2013;13:1-9.
10. Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, Abrao MS, Bush D, Kiesel L, Tamimi R, Sharpe-Timms KL. World Endometriosis Society consensus on the classification of endometriosis. Human reproduction. 2017;32(2):315-24.
11. Krämer B, Andress J, Neis F, Hoffmann S, Brucker S, Kommoss S, Höller A. Adhesion prevention after endometriosis surgery - results of a randomized, controlled clinical trial with second-look laparoscopy. Langenbecks Arch Surg. 2021;406(6):2133-43.
12. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67(5):817-21.
13. Turocy JM, Benacerraf BR. Transvaginal sonography in the diagnosis of deep infiltrating endometriosis: a review. J Clin Ultrasound. 2017;45(6):313-8.
14. Fedele L, Bianchi S, Dorta M, Vignali M. Intrauterine adhesions: detection with transvaginal US. Radiology. 1996;199(3):757-9.
15. Shalev J, Meizner I, Bar-Hava I, Dicker D, Mashiach R, Ben-Rafael Z. Predictive value of transvaginal sonography performed before routine diagnostic hysteroscopy for evaluation of infertility. Fertility and sterility. 2000;73(2):412-7.
16. Niknejadi M, Haghighi H, Ahmadi F, Niknejad F, Chehrazi M, Vosough A, Moenian D. Diagnostic accuracy of transvaginal sonography in the detection of uterine abnormalities in infertile women. Iran J Radiol. 2012;9(3):139-44.

Antifungal susceptibility patterns of vulvovaginal Candida species among Pregnant and Non Pregnant Women

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Abstract

Objectives: Determination of different Candida species present in vagina of pregnant and non-pregnant women with recurrent vaginal candidiasis, and the susceptibility patterns of vaginal Candida to antifungal drugs.

Patients & Methods: This study included 93 women with recurrent clear clinical picture of Candida vaginitis. Divided equally into 3 groups: 31 pregnant women in the third trimester, 31 non-pregnant women in the period of fertility using combined pills and 31 non-pregnant women not using contraception. Two high vaginal swabs were taken by sterile cotton wool swabs soaked in sterile saline. One swab was examined by Gram stain and the second swab was streaked onto a plate of sabouraud dextrose agar (SDA) with chloramphenicol. Identified Candida species were tested for susceptibility to antifungal drugs (Fluconazole, Itraconazole, Caspofungin, Voriconazole, Econazole and Nystatin) by disc diffusion method.

Results: In this study, Candida albicans and Candida glabrata were the most common species isolated from vaginal specimen followed by Candida krusei. There was a statistically significant increase in the percentage of Candida krusei among non-pregnant not using oral contraception group than other groups. The resistance to Econazole, fluconazol and Itraconazole were significantly increased in C. non albicans more than their resistance in C.albicans.

Conclusion: Although Candida albicans was the most prevalent species causing vaginal candidiasis in pregnant and non-pregnant using contraception women, candida non albicans are also incriminated in high percentage, e.g. C.glabrata, and C. krusei. Both C. albicans and C. non albicans were highly sensitive to voriconazole and Caspofungin in contrast to other drugs tested.

Keywords: Candida, antifungal drugs, susceptibility, Vulvovaginal Candidiasis.

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INTRODUCTION

When Candida is found in the vagina without immunosuppression or mucosal damage, it is typically not accompanied by any symptoms and is therefore called colonization. Vulvovaginal Candidiasis (VVC), as opposed to asymptomatic colonization, is characterized by inflammatory signs and symptoms when Candida species are present but no other pathogenic cause is present. Ten years ago, VVC was divided into simple and complex cases; this division has now been adopted and recognized globally (1).

An antifungal drug is a type of pharmaceutical fungicide that is used to treat and prevent dangerous systemic infections such cryptococcal meningitis, ringworm, athlete's foot, and candidiasis (thrush). These medications are typically only accessible with a prescription from a doctor, while some are over-the-counter (OTC) (2).

According to studies, the most common species responsible for pregnant women's vaginal candidiasis were Candida albicans. Most vaginal Candida species isolates showed a high level of azole drug susceptibility. In contrast to azole medications, topical nystatin had a propensity to decrease the sensitivity of certain isolates (3).

It has also been noted that non-albicans species, particularly Candida krusei, are becoming more resistant to medications. This is the case with the exception of itraconazole. With the exception of topical nystatin, the continued use of antifungal medications for the treatment of vaginal candidiasis in pregnant women is supported by the observed susceptibility of vaginal Candida species to azole medicines. To find any new medication resistance, however, ongoing monitoring of antifungal resistance to Candida species is necessary (4).

AIM OF WORK

To determine the different Candida species present in the vagina of pregnant and non-pregnant women, and the susceptibility patterns of vaginal isolates of Candida to antifungal drugs.

PATIENTS AND METHODS

This observational cross-section study was conducted at the Obstetrics and Gynecology department of Benha University Hospitals after receiving approval by the Research Ethical Committee of Benha Faculty of Medicine with the code RC 42-1-2024. Written informed consent was obtained from all participants prior to commencing the study. This study enrolled 93 women divided into 3 groups.

- Group 1: Pregnant women in the 3rd trimester (n=31).
- Group 2: Non-pregnant women in the fertility period using combined pills (n=31).
- Group 3: Non-pregnant women not using contraception (n=31).

Inclusion criteria:

1. Female patients with recurrent clear clinical picture of Candida vaginitis.
2. Age of female patients within the range of 20 to 38 years.

Exclusion criteria:

1. Women who did not consent and those who reported a history of vaginal bleeding, diabetic, hypertensive and thyroid problems.
2. Women used antifungal treatment, vaginal douches, lubricant or any local vaginal medication for at least 24 hours before sampling.

Methods

A- History taking:

Each patient was subjected to full history taking which involve name, age, last normal

menstrual period, gravidity&parity state, residence, occupation and past history of preterm labor.

B-Sampling procedure:

Women were selected and recruited into the study after a health talk about the study which was given by the principal investigator or the nurse on duty. Two high vaginal swabs were taken one after the other by inserting a sterile vaginal speculum into the vagina, and then a sterile cotton wool swab soaked in sterile saline was inserted into the posterior vaginal fornix and rotated gently before withdrawing. Each swab was inserted back into the tube from which it was taken. The tube containing the swab was labelled with the patient study number and date.

C- Microscopic examination:

One swab was examined by Gram stain to give the preliminary results to the clinician for patient management.

D- Cultivation and isolation of yeast

The second swab was streaked onto a plate of sabouraud dextrose agar (SDA) (Difco laboratories, USA) with chloramphenicol and incubated at 37°C for 48 hours. Pure yeast colonies (pasty, yellow-white) were isolated, and a Gram stained film was prepared.

E-Subculture and species identification:

Subculture of preserved yeasts was done twice on SDA with chloramphenicol medium, and inoculated plates were incubated at 37°C for 18 to 24 hours. Identification of Candida was then carried out by the germ tube test and subcultured on chromoagar media.

F-Antifungal susceptibility testing:

Antifungal susceptibility testing was done by disc diffusion method, Antifungal discs ;Fluconazole (FLU)(25µg), Itraconazole (ITC) (10µg), Caspofungin (CAS) (5 mg) and Voriconazole(Vo) (1µg), Econazole(ECN) (10µg) and Nystatin (NY) (100 IU) (LIOFILCHEM s.r.i –Italy) were used. Mueller-Hinton Agar supplemented with 2%w/v glucose and 0.5µg/ml methylene blue dye was used as recommended by CLSI document M44A.

Statistical analysis:

Data were entered checked and analyzed using SPSS version 22

RESULTS

Candida albicans (40, 43 %) and Candida glabrata (39, 41.9 %) were the most common species isolated from vaginal specimen followed by Candida krusei (14, 15.1 %). There was statistical significance increase in the percentage of Candida krusei (32.2 %) among non-pregnant not using contraception methods group than other groups Table (1). There were statistical significant differences in sensitivity of Candida albicans to different antifungal drugs with increased sensitivity to Caspofungin&Voriconazole, increased resistance to Econazole (67.5%), Fluconazole (55%), and increased percentage of dose dependent to Itraconazole (40%) and Nystatin(52.5%) Table (2). That there were statistical significant differences in sensitivity of Candida krusei to different antifungal drugs with increased sensitivity to Caspofungin(100%) & Voriconazole (71.4%), increased resistance to Econazole, Fluconazole (100% each) &Itraconazole (71.4%) and increased percentage of dose dependent to and Nystatin (71.4%) Table (3). There were statistical significance differences in sensitivity of Candida glabrata to different antifungal drugs with increased sensitivity to Caspofungin (76.9%) &Voriconazole(84.6%), increased resistance to Fluconazole, (66.7%) Econazole (84.6%) &Itraconazole (53.8%) and increased percentage of dose dependent to Nystatin (69.2%) Table (4). There was statistical significance increase in Econazole and fluconazol resistance in Candida krusei (100% each) compared to Candida glabrata (84.6% & 66.7% respectively) and Candida albicans (67.5% & 55% respectively). Also,

there was highly statistical significant increase in Itraconazole resistance among Candida krusei (71.4%) and Candida glabrata (53.8 %) compared to Candida albicans (30%). There was statistical significant increase in Voriconazole resistance in Candida krusei (28.6%) compared to Candida glabrata (15.4%) and Candida albicans (7.5%). Finally, there was statistical significant increase in Caspofungin resistance in Candida glabrata (23.1 %) compared to Candida krusei (0%) and Candida albicans (7.5%) Table (5). There was statistical highly significant increase in Econazole resistance in Candida non albican (88.7%) more than C. albicans species (67.5%). Also, there was statistical highly significant increase in Itraconazole resistance in Candida non albicans species (58.5%) more than C. albicans species (30%). There was statistical non-significant increase in Fluconazole resistance in Candida non albican (75.5%) more than C. albicans species (55%). Finally, there was statistical highly significant increase in voriconazole resistance in Candid non- albicans species (18.9%) more than C. albicans species (7.5%) Table (6).

Table (1): Candida species among the studied groups:

Candida species(n)	Non pregnant using Contraception methods (n=31)		Non pregnant not using Contraception methods (n=31)		Pregnant in the third trimester (n=31)		χ^2	P
	No	**%**	**No**	**%**	**No**	**%**		
Candida albicans(40)	15	48.4	9	29	16	51.6		
Candida krusei(14)	4	12.9	10	32.2	0	0	**13.5**	**0.009 ****
Candida glabrata(39)	12	38.7	12	38.7	15	48.4		

χ^2: Chi square test **: Highly Significant (P<0.01) n:number

Table (2): Susceptibility of Candida albicans to antifungal drugs.

Variable	**Candida albicans (n=40)**	
	No	**%**
Nystatin:		
Dose dependent	21	52.5
Resistant	12	30
Sensitive	7	17.5
Econazole:		
Dose dependent	6	15
Resistant	27	67.5
Sensitive	7	17.5
Itraconazole:		
Dose dependent	16	40
Resistant	12	30
Sensitive	12	30
Fluconazole:		
Dose dependent	14	35
Resistant	22	55
Sensitive	4	10

Voriconazole:		
Dose dependent	6	15
Resistant	3	7.5
Sensitive	31	77.5
Caspofungin:		
Resistant	3	7.5
Sensitive	37	92.5
P	**<0.001****	

**: Very highly Significant (P<0.001)

Table (3): Susceptibility of Candida krusei to different antifungal drugs.

Variable	Candida Krusei (n=14)	
	No	**%**
Nystatin:		
Dose dependent	10	71.4
Sensitive	4	28.6
Econazole:		
Resistant	14	100
Itraconazole:		
Resistant	10	71.4
Sensitive	4	28.6
Flucanazole:		
Resistant	14	100
Voricanazole:		
Resistant	4	28.6
Sensitive	10	71.4
Caspofngin:		
Resistant	0	0
Sensitive	14	100
P	**<0.001****	

**: Very highly Significant (P<0.001)

Table (4) : Susceptibility of Candida glabrata to antifungal drugs in all studied groups.

Variable	Candida glabrata (n=39)	
	No	**%**
Nystatin:		
Dose dependent	27	69.2
Resistant	6	15.4
Sensitive	6	15.4
Econazole:		
Resistant	33	84.6
Sensitive	6	15.4
Itraconazole:		
Dose dependnat	6	15.4
Resistant	21	53.8
Sensitive	12	30.8

Fluconazole: Dose dependnat Resistant Sensitive	 10 26 3	 25.6 66.7 7.7
Voriconazole: Resistant Sensitive	 6 33	 15.4 84.6
Caspofungin: Resistant Sensitive	 9 30	 23.1 76.9
P	**<0.001****	

**:Very highly Significant (P<0.001)

Table (5): Difference in susceptibility between three species of Candida to antifungal drugs.

Variable	Candida albicans (n=40)		Candida krusei (n=14)		Candida glabrata (n=39)		χ^2	P
	No	%	No	%	No	%		
Nystatin: Dose dependent Resistant Sensitive	 21 12 7	 52.5 30 17.5	 10 4 0	 71.4 28.6 0	 27 6 6	 69.2 15.4 15.4	**7.48**	**0.11 NS**
Econazole: Dose dependent Resistant Sensitive	 6 27 7	 15 67.5 17.5	 0 14 0	 0 100 0	 0 33 6	 0 84.6 15.4	**11.90**	**0.02***
Itraconazole: Dose dependnat Resistant Sensitive	 16 12 12	 40 30 30	 0 10 4	 0 71.4 28.6	 6 21 12	 15.4 53.8 30.8	**13.66**	**0.008 ****
Fluconazole: Dose dependnat Resistant Sensitive	 14 22 4	 35 55 10	 0 14 0	 0 100 0	 10 26 3	 25.6 66.7 7.7	**9.45**	**0.05***
Voriconazole: I Resistant Sensitive	 6 3 31	 15 7.5 77.5	 0 4 10	 0 28.6 71.4	 0 6 33	 0 15.4 84.6	**11.60**	**0.02***
Caspofungin: Resistant Sensitive	 3 37	 7.5 92.5	 0 14	 0 100	 9 30	 23.1 76.9	**6.71**	**0.04***

χ^2: Chi square test **: Highly Significant (P<0.01)

*:Significant (P<0.05) NS: Non significant (P>0.05)

Table (6): Difference in susceptibility between Candida albicans and Candida non albicans to antifungal drugs.

Variable	Candida albicans (n=40)		Candida non albicans (n=53)		χ^2	P
	No	%	No	%		
Nystatin: Dose dependent Resistant Sensitive	21 12 7	52.5 30 17.5	37 10 6	69.8 18.9 11.3	5.23	0.07 NS
Econazole: Dose dependent Resistant Sensitive	6 27 7	15 67.5 17.5	0 47 6	0 88.7 11.3	**9.86**	**0.007** **
Itraconazole: Dose dependnat Resistant Sensitive	16 12 12	40 30 30	6 31 16	11.3 58.5 30.2	**11.93**	**0.003** **
Fluconazole: Dose dependnat Resistant Sensitive	14 22 4	35 55 10	10 40 3	18.8 75.5 5.7	4.30	**0.11** NS
Voriconazole: I Resistant Sensitive	6 3 31	15 7.5 77.5	0 10 43	0 18.9 81.1	**10.10**	**0.006** **
Caspofungin: Resistant Sensitive	3 37	7.5 92.5	9 44	17 83	1.82	0.18 NS

χ^2: Chi square test **: Highly Significant (P<0.01) NS: Non significant (P>0.05)

DISCUSSION

In women who are still in the reproductive age, vulvovaginitis, or inflammation of the vulva and vagina, is typically caused by infectious organisms; approximately one-third of cases are caused by Candida vulvovaginitis (5).

Candida vulvovaginitis is a result of an infection with Candida species, most frequently Candida albicans, which causes inflammatory alterations in the vulval and vaginal epithelium. Many women have Candida as part of their regular flora, and it is frequently asymptomatic. Consequently, in order for Candida vulvovaginitis to occur, there must be Candida in the vagina or vulva in addition to discomfort, itching, dysuria, or inflammation (6).

Candida albicans is an endogenous commensal that is dimorphic and has been identified as the causative cause of most female lower reproductive tract infections. Even though they are less common than Candida albicans, other non-Candida species including Candida glabrata and Candida krusei can nonetheless result in serious opportunistic infections and show increased resistance to some antifungal drugs (7).

Our findings from this investigation indicate that Candida albicans significantly outnumbered Candida species that are not albicans. About 43% were made up of C. albicans, followed by C. glabrata (41.9%) and C. krusei (15.1%). The total prevalence of Candida species other than Candida albicans

(57%) was nearly equal to that Candida albicans (43%) and is somewhat comparable to the findings of Do Ngoc et al. (2019), who reported a very high proportion of non-albicans Candida species (60%) with Candida glabrata being almost as frequent as Candida albicans. Candida tropicalis accounted for 10.84 percent of all isolated cases, with C. krusei coming in second (8.43%) (8).

Additionally, our findings align with a study that reported a high prevalence of Candida albicans in China, with Candida glabrata, Candida tropicalis, and Candida parapsilosis following closely behind. Comparing isolated Candida species in Iran to non-albicans species, C. albicans was the most common species (9).

Our findings indicate that there was a significant predominance of Candida albicans over non-albicans Candida species in pregnant women. These findings are consistent with other studies that found Candida albicans to be the most common species causing vaginal candidiasis in pregnant women (4). Additionally, it was shown that Candida albicans predominated species in pregnant women with Candida vaginitis, accounting for 69.23 percent, followed by Candida glabrata (23.07%) and Candida andida tropicalis (7.69%) (10).

Knowing the antifungal susceptibility patterns of pathogenic fungus is essential for selecting the right treatment for mycoses. Testing for antifungal susceptibility can also be used to estimate the efficacy of antifungals, guaranteeing a positive course of therapy, tracking the emergence of drug resistance, and evaluating the therapeutic potential of novel drugs (11).

Treatment options for vulvovaginal candidiasis include polyene antifungals like amphotericin B and nystatin as well as azoles like fluconazole, ketoconazole, itraconazole, voriconazole, and clotrimazole. But the best medications for treating vaginal candidiasis in both pregnant and non-pregnant women are topical nystatin and azole antifungal medications (fluconazole, ketoconazole, itraconazole, and clotrimazole) (12).

Based on our findings, it was shown that Candida albicans was much more resistant to fluconazole (55%) and econazole (67.5%) and more susceptible to the antifungal medications casofungin (92.5%) and variconazole (77.5%).

Concerning Candida species other than Candida albicans, C. krusei and C. Glabrata showed susceptibility to antifungal drugs such as capsofungin (100%, 76.9% respectively) and voriconazole (71.4%, 84.6% respectively), but resistance to fluconazole (100% & 66.7% respectively), econazole (100%, 84.6% respectively), and itraconazole (71.4%, 53.8% respectively). All Candida species showed increased percentage of dose dependent sensitivity to Nystatin (52.2% for C. albicans, 71.4% for C. krusie and 69.2% for C. glabrata).

Both Candida albicans and non-Albicans (C. krusie, C. glabrata) exhibited considerable resistance to fluconazole (55%, 100%, and 66.7%, respectively). Regarding econazole, C. krusie (100%) and C. glabrata (84.6%) demonstrated greater resistance than C. albicans (67.5%). Furthermore, C. krusie and C. glabrata had higher levels of resistance to itraconazole (71.4% and 53.8%, respectively) than did C. albicans (30%). Additionally, resistance to voriconazole began to emerge, and it was more common in C. non albicans (28.6% in C. krusie and 15.4% in C. glbrata) than in C. albicans (7.5%).

The findings align with the findings of Satora et al. (2023), who reported that the isolates of Candida found in the vagina were extremely resistant to fluconazole. Conversely, another study revealed that C. albicans had a very high susceptibility to fluconazole (96%) (12).

A study using in vitro antifungal susceptibility analysis revealed that 41.7% of the C. krusei isolates were resistant to fluconazole.

Furthermore, a resistance to fluconazole has been observed in Candida glabrata. Furthermore, 100% resistance to itraconazole was demonstrated by C. glabrata and C. krusei. There was little resistance to nystatin and voriconazole (13).

The majority of the non-Candida albican species, including Candida krusei and Cadida albican, were shown to be susceptible to itraconazole, which is in contrast to our findings (11).

Consequently, fungal infections are frequently difficult to treat; antifungal medications must be used carefully to prevent further resistance development, and they can only be taken as directed by a physician.

CONCLUSION

In contrast to Candida non albicans species, which showed greater resistance to Itraconazole, the majority of vaginal Candida species isolates showed low susceptibility to the azole medications (Fluconazole, Econazole, and Itraconazole). Furthermore, susceptibility to the drug increased with increasing dosage. There was also a trend to find that topical nystatin, particularly at higher doses, was more effective at suppressing both Candida albicans and non-Albicans. Unlike other medicines examined, voriconazole and capsaicin showed a significant degree of sensitivity for both Candida albicans and Candida non albicans.

REFERENCES

1. Pappas PG, Kauffman CA, Andes D, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-e50.
2. Baginski M, Czub B. Amphotericin B and its new derivatives - mode of action. Curr Drug Metab. 2009;10(5):459-469.
3. Farr A, Effendy I, Frey Tirri B, Hof H, Mayser P, Petricevic L, Ruhnke M, Schaller M, Schaefer APA, Sustr V, Willinger B, Mendling W. Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k). Mycoses. 2021;64(6):583-602.
4. Nelson M, Wanjiru W, Margaret MW. "Prevalence of vaginal candidiasis and determination of the occurrence of Candida species in pregnant women attending the antenatal clinic of Thika District Hospital, Kenya." Open Journal of Medical Microbiology 2013.
5. Buggio L, Somigliana E, Borghi A, Vercellini P. Probiotics and vaginal microecology: fact or fancy?. BMC Womens Health. 2019;19(1):25.
6. Farhan MA, Moharram AM, Salah T, Shaaban OM. Types of yeasts that cause vulvovaginal candidiasis in chronic users of corticosteroids. Med Mycol. 2019;57(6):681-687.
7. Ito F, Okubo T, Yasuo T, Mori T, Iwasa K, Iwasaku K, Kitawaki J. Premature delivery due to intrauterine Candida infection that caused neonatal congenital cutaneous candidiasis: a case report. J Obstet Gynaecol Res. 2013;39(1):341-343.
8. Do Ngoc Anh, Nguyen Duy B, Le Tran A, Le Bach Q, Nguyen Khac L,Trinh The Son, Hoang Anh Tuan, Do Quyet. Prevalence of Candida species isolated from vaginal discharge of women undergoing in vitro fertilization-embryo transfer in Vietnam. Biomedical Journal of Scientific & Technical Research, 2019; 14(5):1-4.
9. Hedayati MT, Taheri Z, Galinimoghadam T, Aghili SR, Yazdani Cherati J, Mosayebi E. Isolation of different species of Candida in patients with vulvovaginal candidiasis from sari, iran. Jundishapur J Microbiol. 2015;8(4):e15992.

10. Kanagal DV, Vineeth VK, Kundapur R, Shetty H, Rajesh A. New technology and clinical applications. Infect. Dit al. Prevalence of vaginal candidiasis in pregnancy among coastal south Indian women. J Womens Health, Issues Care, 2014;3(6): 2.
11. Pfaller MA, Yu WL. Antifungal susceptibility testing. New technology and clinical applications. Infect Dis Clin North Am. 2001;15(4):1227-1261.
12. Satora M, Grunwald A, Zaremba B, Frankowska K, Żak K, Tarkowski R, Kułak K. Treatment of Vulvovaginal Candidiasis—An Overview of Guidelines and the Latest Treatment Methods. Journal of Clinical Medicine. 2023; 12(16):5376.
13. Mukasa KJ, Herbert I, Daniel A, Sserunkuma KL, Joel B, Frederick B. Antifungal Susceptibility Patterns of Vulvovaginal Candida species among Women Attending Antenatal Clinic at Mbarara Regional Referral Hospital, South Western Uganda. Br Microbiol Res J. 2015;5(4):322-331.

Association between hospital admission and maternal depression

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Abstract

Background : Maternal mental health is a very important issue. A great proportion of pregnant women are at risk of antenatal depression. Hospital admission would be a contributing factor to develop depression.

Objectives: To determine the association between hospital admission and maternal depression among pregnant women.

Study design: This cross- sectional study was conducted at the obstetrics and gynecology department at a tertiary hospital. The study recruited hospitalized pregnant women for variable causes. A control group including women attending for routine antenatal care was recruited. Screening for depression was done using Arabic validated form of the Edinburgh Postnatal Depression Scale. Comparison between both groups was done regarding depression scores, prevalence of depression, and suicidal thoughts.

Results: There was no difference between both groups but for employment, BMI, and parity. The study group was admitted for a mean duration of 7.3 ± 3.3 days. Only 1 patient (0.9%) in the study group had previous history of depression. The depression score was significantly increased among hospitalized women (13.24 ± 5.01) than the control group (10.32 ± 5.65) (p value 0.0001). High scores denoting depression was evident in a great proportion of the study group (52.8%) than the control group (29.3%). Suicidal thoughts were more prominent in the study group (52.8%) compared to the control group (28.5%) (p value 0.0001). None of the patients' related factors was associated with depression scores (P value > 0.05).

Conclusions: Maternal depression occurred in a great proportion among hospitalized women.

Key words: depression; pregnancy; hospital admission.

Introduction

Antepartum depression is a serious health problem affecting mothers with an incidence of 7-13% (1). Multiple risk factors were encountered including family history of depression, young maternal age < 20, multiparity (more than

3 children), smoking, intimate partner violence, low socioeconomic state, and low educational level (2). It is also associated with adverse maternal and neonatal outcomes as preterm birth, low birth weight, altered neonatal development, and altered childhood growth (3). It leads to impaired maternal-fetal bond which affects proper parenting (4) as well as increased future risk of depressive attacks (5). There is also increased risk for instrumental delivery, emergency cesarean delivery (6), low birth weight (7), and preterm delivery (8).

High risk pregnancies and hospital admission increased the risk of depression (9, 10) with an incidence of 32% among hospitalized patients (11) and the risk increased to 44% among pregnant women hospitalized in high-risk units (12). It has been reported that antepartum depression is commonly undiagnosed without intended screening, with recommendations for screening at least once during the peripartum period (13, 14). However; this is not applied universally which leads to misdiagnosed cases (15). Additionally, psychiatric consultation for inpatient obstetric cases was available for only 1.6% of cases (16). Few studies reported on the prevalence of depressive symptoms among hospitalized women with high- risk pregnancies. This study aimed to determining the association between hospital admission and maternal depression among hospitalized pregnant women.

Methods

This cross- sectional study was conducted at the obstetrics and gynecology department, at Suez Canal University hospital. The study recruited pregnant women admitted in the ward fulfilling the following inclusion and exclusion criteria. Inclusion criteria: a) patients' age 18-45 years, b) pregnant women of any gestational age, and c) singleton pregnancy. Exclusion criteria: a) any patient refusing to participate in the study, and b) women admitted because of fetal demise. A control group was recruited from the outpatient clinic including women attending for routine antenatal care.

After obtaining consent for participation in the study, eligible women were asked to fill in a self-administered questionnaire to determine depression. A researcher was available for help with illiterate women. Depression was evaluated using Arabic validated form of the Edinburgh Postnatal Depression Scale (EPDS). The scale comprises 10 questions that represent patients' feelings in the last seven days. Each question has multiple choices for answering it. Questions 1, 2, and 4 are scored 0, 1, 2, or 3 with the top choice scored as 0 while the last one as 3. Questions 3, 5- 10 are reverse scored with the top choice scored as 3 while the last one as 0. The maximum score is 30. Scores are interpreted as follows: a score less than 8 as depression is not likely, a score of 9- 11 as depression is possible, a score of 12- 13 as fairly high possibility of depression, and a score $\geq$ 14 as possible depression. Each situation was dealt with according to the recommendations of the reproductive health program (17, 18).

The sample size was calculated at a significance level of 99% and an error level of 20%, with a prevalence of probable depression among non-hospitalized pregnant women as 49% (19) and high possibility of depression in hospitalized women as 24% (20). After adding 10% drop out, the sample was 99 pregnant women per group.

Ethical approval: This study was conducted after approval of the research ethics committee at Faculty of Medicine, Suez Canal University on 29/11/2021 with a number of 4735.

Statistical Analysis

Data were statistically described in terms of mean and standard deviation, frequencies (number of cases) and percentages when appropriate. P values less than 0.05 was considered statistically significant. All statistical

calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 23 for Microsoft Windows. Chi-square test was used for categorical variables and (t) test for continuous variables with normally distributed data. Regression analysis was done for the variables predicting increased depression scores.

Results

One hundred eleven and 125 women were eligible for the study and control groups. Three and 2 women declined to participate in each group respectively. This resulted in 108 and 123 women included in the final analysis in the study and control groups respectively.

There was no difference between both groups but for employment, BMI, and parity. A great proportion of the control group was employed (30.1%) rather than the study group (21.3%). They have lower BMI (27.5 ± 3.9) than the study group (28.9 ± 5.7) (p value 0.028). the study group had a significantly increased parity (1.9 ± 1.5) than the control group (0.7 ± 0.4) (p value 0.0001) (Table 1). None of the recruited patients had history of alcohol intake or smoking.

The study group was admitted for a mean duration of 7.3 ± 3.3 days. The most prevalent cause for admission was preeclampsia (25.9%) followed by hyperemesis gravidarum (17.6%). 52.8% of the study group delivered during their admission. The most prevalent postpartum complication was meconium aspiration syndrome (19.3%) followed by established preterm birth (14%) (Table 2).

Only 1 patient (0.9%) in the study group had previous history of depression. The depression score was significantly increased among hospitalized women (13.24 ± 5.01) than the control group (10.32 ± 5.65) (p value 0.0001). high scores denoting depression was evident in a great proportion of the study group (52.8%) than the control group (29.3%). Suicidal thoughts were more prominent in the study group (52.8%) compared to the control group (28.5%) (p value 0.0001) (Table 3).

Using multivariate regression analysis, none of the patients' related factors was associated with depression score (Table 4).

Discussion

A great proportion of the control group was employed rather than the study group. An earlier study reported that almost half (55%) of the hospitalized women were unemployed at admission (20). About two-thirds of both groups reported middle education or less. This agreed with previous results where 56% of the participants had high school education or less (20). One patient in the study group had previous history of depression. This contradicted previous results where 47% of the studied population had previous history of depression or anxiety (20). This discrepancy would be rendered to different ethnic groups as they recruited African American (51%), while the current study recruited women of the same ethnicity. Also, a proportion (21%) of them reported history of intimate partner violence, while this was not evaluated in the current study. Additionally, 31% of their studied population were married, while all of our studied population were married.

The study group was admitted for a mean duration of 7.3 ± 3.3 days. Another study reported a mean hospital stay of 10 days (20). The most common cause of admission was prematurity issues (46%) (20), while preeclampsia was evident in the current study. It has been reported by a meta-analysis that 18% of the included population were evaluated immediately upon admission, while 34% were evaluated after 3 days. While more than half of the studies did not mention the timing of screening relative to hospital admission. This would reflect the nature of prehospitalization mental illness, rather than relation to hospitalization (21).

In the study group, 72.2% scored ≥ 12. This

was markedly elevated than the results reported earlier as 24% of the participants scored ≥ 12 (20). Other studies reported scores ≥ 13 in 32.9% (22) and ≥ 10 in 28.3% of their participants (23). One patient in the study group reported to have previous history of depression, while another study reported no history of depression in their studied population (24). This would be related to social fears from reporting having mental illness (22). The depression score was significantly increased among hospitalized women than the control group. High scores denoting depression were evident in a great proportion of the study group than the control group. This would be explained by the effect of frustration due to having a high- risk pregnancy (22). This striking increase in rate of depression among hospitalized women would be explained by the different races, as it has been mentioned that Muslim Bedouin women were more liable to depression than Jewish (23). This was rendered to their suffering from domestic violence due to increased parity and other additional factors (24). Although, the current study recruited Arab Muslim women, they were of the same ethnic group without recruitment of Bedouin. Additionally, domestic violence was not evaluated. Other contributing factors might include poverty, lack of social support, and neglect (23). Additionally, lack of privacy would result in underreporting which contributed to the great difference in depression rates (23).

Also, insufficient evaluation of pre-pregnancy mood disorders in previous studies would affect the cumulative rate of depression reported by different studies. Additionally, different cultural believes would affect symptom reporting because of fear of mental illness stigma. Different cut off values was noted between studies which relatively affects the rates of depression. The use of EPDS which is considered as a screening tool would result in overestimation of depression rates (21).

Suicidal thoughts were more prominent in the study group (52.8%) compared to the control group (28.5%). An earlier study reported that only 2 women (2.7%) of their participants had suicidal thought (21). These variable results would be rendered to different tools used to evaluate depression among studies, different sample size, recruitment of women with certain adverse pregnancy disorder only (FGR) (21), exposure to other factors as low income, unemployment, unstable marital status (25), and increased alcohol intake and smoking (26).

None of the patients' related factors was associated with depression scores. This contradicted previous results where depression was associated with maternal smoking and the gestational age on admission. However; this study recruited pregnant women with FGR only (22). Another study reported that maternal depression was associated with preterm delivery (23), however; the association between pregnancy outcomes and depression was not evaluated in the current study.

Strength and limitations: This was the first study in Egypt to evaluate the association between hospital admission and maternal depression. The sample size was relatively small. The association between maternal depression and adverse pregnancy outcome was not evaluated. The questionnaire was administered to women privately in the absence of her relatives to give her the chance to express her feelings. The duration of hospitalization was mentioned to avoid bias from possible preadmission mental illness. We used EPDS which is a screening tool and definitive diagnosis was not mentioned.

Conclusion: Maternal depression occurred in a great proportion among hospitalized women.

Conflict of interest: None

References

1. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstetrics & Gynecology. 2005;106(5 Part 1):1071-83.
2. Wisner KL, Sit DK, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, Eng HF, Luther JF, Wisniewski SR, Costantino ML, Confer AL. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA psychiatry. 2013;70(5):490-8.
3. Pearlstein T. Depression during pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology. 2015;29(5):754-64.
4. Alhusen JL, Gross D, Hayat MJ, Rose L, Sharps P. The role of mental health on maternal-fetal attachment in low-income women. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2012;41(6):E71-81.
5. Stevens AW, Daggenvoorde TH, van der Klis SM, Kupka RW, Goossens PJ. Thoughts and considerations of women with bipolar disorder about family planning and pregnancy: a qualitative study. Journal of the American Psychiatric Nurses Association. 2018;24(2):118-26.
6. Bayrampour H, Salmon C, Vinturache A, Tough S. Effect of depressive and anxiety symptoms during pregnancy on risk of obstetric interventions. Journal of Obstetrics and Gynaecology Research. 2015;41(7):1040-8.
7. Henrichs J, Schenk JJ, Roza SJ, Van den Berg MP, Schmidt HG, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC, Tiemeier H. Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychological medicine. 2010;40(4):633-43.
8. Mitchell AR, Gordon H, Lindquist A, Walker SP, Homer CS, Middleton A, Cluver CA, Tong S, Hastie R. Prevalence of perinatal depression in low-and middle-income countries: a systematic review and meta-analysis. JAMA psychiatry. 2023;80(5):425-31.
9. Littleton HL, Breitkopf CR, Berenson AB. Correlates of anxiety symptoms during pregnancy and association with perinatal outcomes: a meta-analysis. American journal of obstetrics and gynecology. 2007;196(5):424-32.
10. Brandon AR, Trivedi MH, Hynan LS, Miltenberger PD, Labat DB, Rifkin JB, Stringer CA. Prenatal depression in women hospitalized for obstetric risk. Journal of Clinical Psychiatry. 2008;69(4):635.
11. Sharma P, Avasthi A, Chakrabarti S, Varma S. Depression among hospitalised medically ill patients: a two-stage screening study. Journal of affective disorders. 2002;70(2):205-9.
12. Byatt N, Hicks-Courant K, Davidson A, Levesque R, Mick E, Allison J, Simas TA. Depression and anxiety among high-risk obstetric inpatients. General Hospital Psychiatry. 2014;36(6):644-9.
13. Goodman JH, Tyer-Viola L. Detection, treatment, and referral of perinatal depression and anxiety by obstetrical providers. Journal of women's health. 2010;19(3):477-90.
14. Committee on Obstetric Practice. The American College of Obstetricians and Gynecologists Committee opinion no. 630. Screening for perinatal depression. Obstet Gynecol. 2015;125(5):1268-71.
15. Andersson L, Sundström-Poromaa I, Bixo M, Wulff M, Bondestam K, Åström M. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. American journal of obstetrics and gynecology. 2003;189(1):148-54.

16. Sloan EP, Kirsh S. Characteristics of obstetrical inpatients referred to a consultation-liaison psychiatry service in a tertiary-level university hospital. Archives of women's mental health. 2008; 11:327-33.

17. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. The British journal of psychiatry. 1987;150(6):782-6.

18. Friedman SH, Reed E, Ross NE. Postpartum psychosis. Current psychiatry reports. 2023;25(2):65-72.

19. Ghoneim HM, Elprince M, Ali TY, Gharieb WF, Ahmed AA. Violence and depression among pregnant women in Egypt. BMC pregnancy and childbirth. 2021;21(1):1-7.

20. Nagle-Yang S, Phillips M, Albaugh A, Zhao L, Amin J, Ahmad E, Hatters Friedman S. Depression, anxiety, and attachment among women hospitalized on an antepartum unit. The International Journal of Psychiatry in Medicine. 2019;54(6):395-407.

21. Toscano M, Royzer R, Castillo D, Li D, Poleshuck E. Prevalence of depression or anxiety during antepartum hospitalizations for obstetric complications: A systematic review and meta-analysis. Obstetrics and gynecology. 2021;137(5):881.

22. Tsakiridis I, Dagklis T, Zerva C, Mamopoulos A, Athanasiadis A, Papazisis G. Depression in pregnant women hospitalized due to intrauterine growth restriction: prevalence and associated factors. Midwifery. 2019;70:71-5.

23. Hermon N, Wainstock T, Sheiner E, Golan A, Walfisch A. Impact of maternal depression on perinatal outcomes in hospitalized women—a prospective study. Archives of women's mental health. 2019;22:85-91.

24. Cwikel J, Lev-Wiesel R, Al-Krenawi A. The physical and psychosocial health of Bedouin Arab women of the Negev area of Israel: The impact of high fertility and pervasive domestic violence. Violence Against Women. 2003;9(2):240-57.

25. Van Heyningen T, Myer L, Onah M, Tomlinson M, Field S, Honikman S. Antenatal depression and adversity in urban South Africa. Journal of affective Disorders. 2016;203:121-9.

26. Dagklis T, Tsakiridis I, Chouliara F, Mamopoulos A, Rousso D, Athanasiadis A, Papazisis G. Antenatal depression among women hospitalized due to threatened preterm labor in a high-risk pregnancy unit in Greece. The Journal of Maternal-Fetal & Neonatal Medicine. 2018;31(7):919-25.

Table 1: Basic demographic data of the studied population:

		Study group (N= 108)	Control group (N= 123)	P value
Age (years) (Mean ± SD)		29.4 ± 7.5	28.7 ± 5.7	0.452
Education N (%)	**None**	34 (31.5%)	25 (20.3%)	0.149
	Middle	48 (44.4%)	62 (50.4%)	
	High	26 (24.1%)	36 (29.3%)	
Job N (%)	**Housewife**	85 (78.7%)	86 (69.9%)	0.0001
	Employee	23 (21.3%)	37 (30.1%)	
BMI (kg/m^2) (Mean ± SD)		28.9 ± 5.7	27.5 ± 3.9	0.028
Parity (Mean ± SD)		1.9 ± 1.5	0.7 ± 0.4	0.0001
GA (weeks) (Mean ± SD)		28.7 ± 11.3*	30.2 ± 7.9	0.263

*Gestational age at admission, BMI: body mass index, GA: gestational age

Table 2: Admission data of the study group

Duration of admission (Days) (Mean ± SD)		7.3 ± 3.3
Cause of admission N (%)	**Antepartum hemorrhage**	11 (10.2%)
	Acute urinary tract infection	6 (5.6 %)
	Uncontrolled hypertension	2 (1.9%)
	Hyperemesis gravidarum	19 (17.6%)
	preeclampsia	28 (25.9%)
	Uncontrolled diabetes	17 (15.7%)
	Ectopic pregnancy	3 (2.8%)
	Premature rupture of membranes	14 (12.9%)
	Preterm labor	9 (8.3%)
	Placenta previa	1 (0.9%)
	Placenta accreta	3 (2.8%)
	Eclampsia	1 (0.9%)
	Diabetic ketoacidosis	1 (0.9%)
Delivered N (%)	**Yes**	57 (52.8%)
	No	51 (47.2%)
Postpartum complications N (%)	**Postpartum hemorrhage**	5 (8.8%)
	Blood transfusion	6 (10.5%)
	Superimposed preeclampsia	2 (3.5%)
	Preterm birth	8 (14%)
	Septic wound	2 (3.5%)
	Meconium aspiration syndrome	11 (19.3%)
	Neonatal hypoglycemia	4 (7%)
	Bladder injury	3 (5.3%)
	Neonatal tachypnea	1 (1.8%)

Mode of delivery N (%)	**Vaginal delivery**	12 (21.1%)
	Cesarean delivery	45 (78.9%)
Fetal weight (grams) (Mean ± SD)		2926.6 ± 659

Table 3: Depression scores between both groups

		Study group (N= 108)	Control group (N= 123)	P value
Depression score (Mean ± SD)		13.24 ± 5.01	10.32 ± 5.65	0.0001
Depression category N (%)	**No depression**	20 (18.5%)	47 (38.2%)	0.0001
	Possible depression	10 (9.3%)	19 (15.4%)	
	High possibility of depression	21 (19.4%)	21 (17.1%)	
	Depression	57 (52.8%)	36 (29.3%)	
Suicidal thoughts N (%)	**No**	51 (47.2%)	88 (71.5%)	0.0001
	Yes	57 (52.8%)	35 (28.5%)	

Table 4: Multivariate regression analysis for the factors associated with depression score

	β	95% confidence interval	P value
Age	0.077	-0.114- 0.268	0.424
Education	-0.496	-1.999- 1.006	0.514
Job	1.463	-1.275- 4.201	0.292
BMI	-0.040	-0.241- 0.161	0.693
Parity	0.521	-0.369- 1.410	0.248
GA	0.074	-0.020- 0.168	0.122
Duration of admission	-0.100	-0.382- 0.181	0.481