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Acknowledgments

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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2- Books:

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(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.

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Contents :

Letter from the Editor:

Dear colleagues,

very interesting subjects are included in this edition. The vaginal misoprostol use before copper T380A IUD insertion during the bleeding-free days of the menstrual cycle is safe and reduces IUD insertion pain, increases easiness of insertion, and women's satisfaction. Despite the low level of awareness about HPV vaccine among our population, we reported the potential acceptability of the vaccine. Any patient with placenta accreta spectrum who have atypical presentation must be put under observation with close monitoring of the general condition for signs of hypovolemia, and ultrasonography should be performed by expert sonographer for early detection of hemoperitoneum. Confirmation of the diagnosis indicates emergent laparotomy, better via longitudinal incision, considering cesarean hysterectomy as a first line treatment. Infertile women are more likely to be exposed to physical, sexual and psychological violence. Psychological violence was found to be the most common type of reported violence against infertile women followed by physical and sexual violence. Moreover, the infertile women had a significantly higher prevalence of sexual dysfunctions than their fertile counterparts. Fetal trans cerebellar is a more reliable method in the 3rd trimester of gestation to determine gestational age than biparietal diameter and other biometric measures, especially in IUGR pregnancies. Oral NSAIDs is an effective method in reducing pain during hysteroscopy. Paracervical block reduce pain significantly only during introduction of hysteroscopy through the cervix, hindered by the time it takes, bleeding, lack of effectiveness through other stages of the procedure, while application of anesthetic gel though is proved to be an ineffective way to control pain during the procedures. Routine administration of prophylactic antenatal corticosteroids before elective caesarean sections at term does not reduce the risk of admission to the NICU compared to non- administration. Vitamin D deficiency was noted significantly among women with irregular cycles. Age was a significant predictor for irregular cycles rather than vitamin D levels. Khalaf maneuver is a safe effective and not time-consuming maneuver that can be used for cases of unresolved shoulder dystocia.

Best regards.

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Use of vaginal misoprostol in women demanded copper intrauterine device insertion after the end of bleeding days of their menses: a randomized clinical trial

Running title: Misoprostol before IUD insertion in non-menstruating women

Disclosure statement: The authors declare no conflicts of interest

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Abstract

Objective: To assess the effectiveness and safety of misoprostol before IUD insertion in women after the end of bleeding days of their menses.

Materials and methods: The study was a randomized clinical trial conducted at Assiut Woman's Health Hospital; Egypt from October 2021 to March 2023 including women who requested copper T380A IUD insertion after the stoppage of bleeding days of the menses. The women were randomized to either group I: misoprostol (400 μg misoprostol tablets vaginally 3 hours before IUD insertion) and group II: no intervention group. The primary outcome was the degree of pain during IUD insertion measured using the visual analogue scale (VAS). The data was analyzed by an unpaired t-test, Mann-Whitney test, and chi-square test.

Results: Sixty women consented to participate and were divided into two equal groups. There was a significantly lower VAS score for pain during and 5 minutes after IUD insertion. Also; a significantly lower easiness and higher woman's satisfaction was noted in the misoprostol group. However; the successful device placement, duration of insertion, and complications were comparable in both groups.

Conclusion: The vaginal misoprostol use before copper T380A IUD insertion during the bleeding-free days of the menstrual cycle is safe and reduces IUD insertion pain, increases easiness of insertion, and women's satisfaction.

Key words: Intrauterine device; insertion pain; satisfaction; misoprostol.

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Implications

Most of care providers as well as clients will be reluctant to insert IUD in non-bleeding days. The easiness and less pain associated with misoprostol use before insertion will increase acceptance of IUD use in non-bleeding days.

Introduction

The intrauterine device (IUD) is a reliable, safe, long-acting reversible, and effective contraceptive method [1]. Despite that, the associated pain with IUD insertion can be a cause of client's refusal of use [2]. Many researches have been done directing to decrease the pain during IUD insertion [3, 4].

The physicians usually prefer the insertion of the IUD during women's menses as the women are mostly not pregnant, the insertion is easier (opened cervix) and the pain is much lower [5, 6]. The easiness of IUD insertion is a very important issue that can increase both women's and physician's satisfaction [7, 8].

However; in practice; some women ask for IUD insertion on bleeding-free days of their menses. Those women may have lactational amenorrhea, want to switch from any birth control method to an IUD, or refuse to introduce an IUD into the uterus at a time of menses. Finally; some women want a rabid and reliable contraception because their husbands will come unscheduled within a few days. So; we think that those women may face some difficulty during insertion and subsequent more pain.

Misoprostol is a prostaglandin E1 analog that used successfully for cervical priming before IUD insertion [9]. It also was used in women with previous failed trials of IUD insertion with promising results [10].

A systematic review suggested that the timing of Cu-IUD insertion has little effect on pain at insertion but it recommended further randomized trials look at the IUD insertion effect during later days of the menstrual cycle [11].

So, this work aimed to evaluate the effectiveness and safety of misoprostol before IUD insertion in women not during the bleeding days of their menses. To our knowledge, this is the first trial that addressed this subject.

Material and methods

At Assiut Woman's Health Hospital; an open randomized registered clinical trial (Clinical trial.gov- NCT04932382) was conducted from 1st of October 2021 to March 2023. Women who came after the end of their menses and requested copper IUD insertion were invited to participate. The study protocol was approved by Assiut University Medical Ethical Review Board (IRB17101568).

Eligible participants

Non-pregnant women aged 18-45 years who want to use an IUD after the end of bleeding days of their menses were included. The exclusion criteria included women who received any analgesics or misoprostol in the 24 hours before insertion, any contraindications to IUD insertion [12] or misoprostol [13]. Women who refused to participate were also excluded.

Randomization

Blocked randomization was done using https://www.sealedenvelope.com. A table of random numbers and codes was generated. Eligible women were randomly assigned to either group I: misoprostol and group II: no intervention group. Allocation concealment was done using serially-numbered closed opaque envelopes. Once allocation has been done, it can't be changed.

Study intervention

All participant women signed a written consent before participation after discussing the details of the study. The participants received pre-insertion instructions, and then demographic and obstetrics-gynecology data were collected. BMI was measured. Transvaginal ultrasound (TVS) was done

using Medison X8, Digital Ultrasonic Diagnostic, Imaging System, USA machine to assess the uterine position and size before insertion.

Following that; women in group I received 400 µg misoprostol tablets vaginally (Misotac®; Sigma Pharma, SAE, Egypt); these tablets were introduced by the principal investigator 3 hours before IUD insertion into the posterior vaginal fornix in the lithotomy position [14]. While women in group II did not receive any pre-insertion medications.

The consistency of the cervix was assessed immediately before IUD insertion. It was divided into soft (like mouth lips), firm (tip of the nose), or hard. Then; women in the 2 study groups received a copper T380A IUD (PREGNA T380A; Pregna International Ltd, Chakan, India).

The principal investigator inserted the IUD in all participants. A Cusco speculum and single-toothed tenaculum were used, while uterine sound was not used [2, 3]. After insertion; the accurate place of the IUD was evaluated by TVS.

Study outcomes

The primary outcome was the degree of pain during IUD insertion measured by VAS from 0-10 (0 means no pain and 10 means maximum pain) [15]. While secondary outcomes included the degree of pain 5 minutes after IUD insertion, need for analgesics, easeness of IUD insertion as measured by VAS (0 means very difficult and 10 means very easy), the women's satisfaction (0 means maximum dissatisfaction and 10 means maximum satisfaction.) [3].The successful IUD placement, the duration of insertion, the rate of complications and side effects of misoprostol as well as the ideal device placement after 1 month were also assessed.

Sample size

To calculate the required sample size; the principal investigator recorded the degree of pain during IUD insertion in 15 non-menstruating women, after obtaining written consent; we did not include them in the study. The mean degree of pain during IUD insertion in those women by VAS was about 6.5 ±1.5. So, using 95% power with an error of 0.05, a sample size of about 60 women (30 in each group) to detect a 1.5 difference in the pain score between both groups assuming the rate of lost follow-up 10% (OpenEpi, Version 3, open source calculator-SS Mean).

Statistical Analysis

The data was collected and entered into the Microsoft access database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Comparisons between means of the groups were done using an unpaired t- in the scale variables. Non- parametric variables were shown as median and range and analyzed by Mann-Whitney test. Categorical data were shown by number or percentage. For dichotomous variables, chi-square was used to estimate the significance value. For analysis, $p<0.05$ considered to be significant.

Results

Seventy-four women were counseled for participation, however; 14 women were not included in the study. The remaining sixty women were allocated into two equal groups; group I (misoprostol group) and group II (no-intervention group). Forty-eight participant women were finally analyzed while 12 women were lost from follow-up (Fig.1 the study flow chart).

Both groups were comparable in baseline socio-demographic data without statistically significant differences (Table 1). The consistency of the cervix was softer in group I (Misoprostol group) (70%) than in group II (No- intervention group) (33.3%) with a statistically significant difference (P=0.006) (Table 2).The study outcomes were presented in table 3. The median of pain during IUD insertion (4.5 vs. 7) and 5 minutes after insertion (2.5 vs. 5) was lower in group I than

group II with statistically significant difference (P=0.000).

The insertion is easier in group I than in group II with a statistically significant difference (7.77 ± 0.68 vs. 5.57 ± 0.90; P=0.000). Also, the mean of women's satisfaction is higher in group I (8.30 ± 0.53) than in group II (7.33 ± 0.96) with a statistically significant difference (P=0.003). The need for analgesics was more in group II (51.7%) than in group I (20.0%) with a statistically significant difference (P=0.011). Duration for application, successful IUD placement, and ideal placement after 1 month were comparable in both groups (p>0.05) (Table 3).

No statistically significant difference was noted between groups regards the rate of early and late complications. Most of the women (76.7%) had no side effects from misoprostol. Other side effects included headache (3 cases), nausea/vomiting (2 cases), and shivering (2 cases) (Table 4).

Discussion

To our knowledge; this is the first randomized study compassing the efficacy and safety of using misoprostol before copper IUD device insertion in in women after the end of bleeding days of their menses. Our results showed that misoprostol was associated with lower pain and easier IUD insertion with higher women's satisfaction with a little bit of side effects and complications.

In practice; many providers recommend the IUD be inserted during the last few days of menstruation when the cervical opening is wide, the insertion's bleeding mixes with menstrual bleeding, and the woman is not pregnant. Although these advantages; there is no strong reason to delay insertion if the woman requests an IUD at any other time during her menstrual cycle [16].

The idea of this study came from that some women, not during the menses; choose an IUD as contraception during their first visit to the family planning clinic. Some women are very anxious and refuse, at all, to be touched during their menses and it is easier to examine for signs of genital tract infections when a woman is not menstruating.

Assuming the challenges presented by unprepared cervix in those women, it might seem that misoprostol may be helpful in the IUD insertion process. Multiple studies have elucidated that prophylactic misoprostol increased the ease of IUD insertion and decreased the insertion pain [1, 17-19]. The misoprostol is also beneficial in patients who have already experienced failure of IUD insertion [6].

In this study; we found that the VAS for IUD insertion pain and 5 minutes after insertion were significantly lower and the easiness score was significantly higher in the misoprostol group. Also, the need for analgesia after IUD insertion was also few in his group. Reduced cervical tone and improved cervical consistency after using misoprostol may be behind these results. So; we are on the same track as all studies that proved the beneficial use of misoprostol before insertion of IUD [1, 17-19].

Although, many studies reported no significant differences among women receiving misoprostol to ease IUD insertion [20-25]; we think there is still a non-negligible role for misoprostol with IUD insertion. Priming with misoprostol before hysteroscopy, dilatation and curettage, and the sounding of the uterus in premenopausal women yielded an increased cervical dilatation and a lower rate of laceration of the cervix[7].

Increasing women's satisfaction during IUD insertion may improve IUD acceptance [3]. It is unsurprisingly, in this study, the women with misoprostol were more satisfied than women in no intervention group because they had little pain. Evaluation of women's satisfaction with the IUD is a very important issue because it increases the desire toward using this method [27].

Finally, both groups in this study had comparable either early or late side effects. Expulsion or displacement was reported in one woman in the no-intervention group (4.34%). Also, about 22% of women developed misoprostol side effects in the form of headache, nausea/vomiting, and shivering.

Nausea and abdominal cramps most common side effects reported as side effects for misoprostol [13, 27]. However; these side effects are dose and route dependent [27].

A major strength of this work was the novelty of the idea and the randomized type of this study. In spite of small sample size (60 women); we used 95% power to calculate the sample size was another good point in this research. Additionally, we standardized the insertion protocol for all participants by only one provider. However, the present work had some limitations. The study did not include other types of IUDs like multiload or LNG-IUS. The heterogenous characteristics of the studied women (some delivered vaginally and another women delivered by CS). The long-term outcomes were not studied. The subjective evaluation of the pain, easiness, and satisfaction is another limitation of this study.

Conclusion

The vaginal misoprostol's use before IUD insertion in women in the bleeding-free days of their menses is relatively safe and reduces IUD insertion pain and need for analgesics as well as increases women's satisfaction. In addition, clinicians will find the insertion procedure easier with misoprostol use.

Disclosure statement: The authors report no conflicts of interest

Authors' contributions

MA and MY designed the study and prepared the proposal. NM and AA did the intervention and collected data. AN and II did the analysis of data and prepared first manuscript. All authors contributed in the preparation and revision of the final manuscript.

Table 1: Socio-demographic and obstetrics data of the women sharing in the study
BMI body mass index, **CS** cesarean section, **IUD** intrauterine device, **kg/m²** kilogram

Personal data	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Residence, n (%)			
Rural	15(50.0)	14(46.7)	0.796
Urban	15(50.0)	16(53.3)	
Level of education, n (%)			
Illiterate	5(16.7)	4(13.3)	0.714
Basic education	16(53.3)	14(46.7)	
Secondary or more	9(30.0)	12(40.0)	
BMI (kg/m²), mean ± SD	26.12 ± 3.30	25.77 ± 4.00	0.711
Parity, median (Range)	4.0 (1.0-6.0)	3.0 (1.0-7.0)	0.774
History of previous abortion, n (%)	8(26.7)	5(16.7)	0.347
Mode of previous delivery, n (%)			
Vaginal only	13(43.3)	14(46.7)	
Cesarean section only	14(46.7)	12(40.0)	0.846
Vaginal and Cesarean section	3(10.0)	4(13.3)	
Number of living children, median (Range)	3.0 (1.0-6.0)	3.0 (1.0-7.0)	0.970

Duration from last pregnancy (years), median (Range)	4.0 (1.0-120.0)	6.0 (1.0-168.0)	0.519
Previous IUD insertion, n (%)	12(40.0)	14(46.7)	0.286
Indications of IUD insertion, n (%)			
Switch from birth control method	16(53.3)	11(36.7)	0.291
LAM	11(36.7)	15(50.0)	
Refused IUD insertion during menses	0(0.0)	2(6.7)	
Unscheduled coming of the husband	3(10.0)	2(6.7)	

per square meter, **n (%)** number and percentage, **LAM** lactational amenorrhea, **SD** standard deviation, **VD** vaginal delivery

Table 2: Ultrasonographic and per-vaginal examinations in the studied women

	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Uterine length (mm), mean ± SD	76.10 ± 5.79	75.47 ± 5.72	0.672
Uterine position, n (%)			
Anteverted	20 (66.7)	24 (80.0)	0.501
Midway	7 (23.3)	4 (13.3)	
Retroverted	3 (10.0)	2 (6.7)	
Consistency of cervix, n (%)			
Soft	21(70.0)	10(33.3)	0.006*
Firm	9(30.0)	15(50.0)	
Hard	0(0.0)	5(16.7)	

***** Statistical significant difference (P < 0.05)

mm millimeter, **n (%)** number and percentage, **SD** standard deviation

Table 3: The study outcomes

Study outcome	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Pain during IUD insertion, median (Range)	4.5 (3.0-6.0)	7 (4.0-8.0)	0.000*
Pain 5 minutes after IUD insertion, median (Range)	2.5 (1.0-5.0)	5 (2.0-7.0)	0.000*
Easiness of the insertion, mean ± SD	7.77 ± 0.68	5.57 ± 0.90	0.000*
Woman's satisfaction, mean ± SD	8.30 ± 0.53	7.33 ± 0.96	0.003*
Need of analgesia, n (%)	6 (20.0%)	15 (50.0%)	0.011*
Duration of insertion (minutes), mean ± SD	6.53 ± 1.20	6.76 ± 1.43	0.514
Successful IUD insertion, n (%)	30 (100%)	29 (96.7%)	1.000
Ideal IUD placement after 1 month, n (%)	1(4.0)	2(8.7)	0.601

***** Statistical significant difference (P < 0.05)

IUD intrauterine device, **n (%)** number and percentage, **SD** standard deviation

Table 4: The reported complications and side effects in women shared in this RCT

	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Early complications, n (%)			
Cramps	2 (6.7)	5 (16.7)	
Vaginal bleeding	3(10.0)	1 (3.3)	
Failure of insertion	0 (0.0)	0 (0.0)	0.316
Vasovagal	0 (0.0)	0 (0.0)	
No	25 (83.3)	24 (80.0)	
Side effects of misoprostol, n (%)			
Headache	3 (10.0)	0(0.0)	
Nausea/ vomiting	2 (6.7)	0(0.0)	0.053
Shivering	2 (6.7)	0(0.0)	
No	23 (76.7)	0(0.0)	
Late complications at 1 month, n (%)			
Perforation	0 (0.0)	0 (0.0)	
Expulsion/ displacement	0 (0.0)	1 (4.34)	0.132
PID	0 (0.0)	0 (0.0)	
No	25 (100.0)	22 (95.66)	

IUD intrauterine device, **n (%)** number and percentage, **PID** pelvic inflammatory disease

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Assessment of Galectins -1, -2, -3, and -8 Expression in Endometrial Carcinoma and Its Clinical Implications

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Abstract

Background and aim: Galectins are a type of animal lectins that play a crucial role in regulating various cellular functions that can promote cancer progression including endometrial carcinoma. The aim of this study is to explore the expression of m RNA of galectins 1, 2, 3, and 8 in endometrial cancer and determine their relation to the extent of the disease.

Methods: This case-control study was carried out at the Ain Shams University Maternity Hospital, as well as in the molecular biology laboratory located in the Zoology Department of the Faculty of Science at Ain Shams University. The study was conducted between October 2019 and January 2022. A total of 72 patients were scheduled for hysterectomy due to endometrial diseases. The study involved two groups. Group 1 comprised 60 women with endometrial malignancy, which includes atypical endometrial hyperplasia and/or endometrioid adenocarcinoma. Group 2 was the control group, which had 12 women with normal endometrial tissues. 58 tumor samples of endometrial pre-cancer and cancer lesions for mRNA expression using qRT-PCR.

Results: The present study included 58 women with endometrial carcinoma, out of which almost 57% had endometrioid adenocarcinoma. Among them, 37 women were in FIGO stage I and II. The study found that LGALS1, LGALS2, LGALS3, and LGALS8 were significantly over-expressed in endometrial carcinoma patients as compared to the control group. However, the expression of these genes did not differ significantly when compared in different FIGO staging or based on the presence or absence of lymph node metastasis. There was also no significant difference in their expression when comparing patients with either endometrioid or non-endometrioid adenocarcinoma of the uterus.

Conclusion: Our findings support the role of galectins in endometrial carcinogenesis, disease progression, and lymph node metastasis.

Running title: Galectins in Endometrial Carcinoma

Keywords: Endometrial carcinoma; galectins; mRNA; qRT-PCR; biomarkers; lymph node metastasis.

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Introduction

Endometrial cancer is the second most common gynecologic cancer in Egypt after ovarian cancer (1).It is the fourth leading cause of death in women due to gynecologic cancers globally, with 382,069 new cases and 89,929 deaths in 2018 (2) . The incidence rate of EC is increasing rapidly and projected to increase by more than 50% worldwide by 2040 (3).

Endometrial cancer is classified into endometrioid and non-endometrioid types. Molecular-based classification is now used for improved diagnosis and prognosis.

Galectins are a type of animal lectins that possess one or more carbohydrate recognition domains.. (4-8) Galectins are proteins that can specifically bind to sugar molecules and exert their effects either inside or outside cells. Numerous studies have strongly linked galectins to tumor progression, due to their impact on immune surveillance, angiogenesis, cell migration, tumor cell adhesion, and cellular response to chemotherapy (9). Galectins have been studied in various types of cancer including hematologic, gastrointestinal, breast, prostatic, and gynecologic cancers, such as ovarian, cervical, and endometrial cancer (10-15).

In this study, we investigated galectins mRNA expression in endometrial carcinoma patients to evaluate their potential as biomarkers to disease stage and prognosis.

Patients and Methods

This case-control study was carried out at the Ain Shams University Maternity Hospital, as well as in the molecular biology laboratory located in the Zoology Department of the Faculty of Science at Ain Shams University. The study was conducted between October 2019 and January 2022. A total of 72 patients were scheduled for hysterectomy due to endometrial diseases. The study was approved by the Department of Obstetrics and Gynecology and gained the approval of the Faculty of Medicine (FMASU 258/2021).

Sample size Justification: To determine the sample size, we used the STATA program. The type of error (alpha) was set to 0.05 and the power (1-p) to 0.9. A previous study by Sun and Dai in 2019 (17) found that the expression of galactin 9 among normal cases was 20%, compared to 10.8% among cases group. Based on these values, the sample size was calculated to be 20 cases and 20 controls. However, we increased the sample size to strengthen the study.

The study involved two groups. Group 1 comprised 60 women with endometrial malignancy, which includes atypical endometrial hyperplasia and/or endometrioid adenocarcinoma. Group 2 was the control group, which had 12 women with normal endometrial tissues.

The population sample under study were informed about research protocol and were asked to participate and informed consent was taken from each participant.

- All data from participating women were confidentially protected.

The inclusion criteria were the women eligible for hysterectomy due to endometrial cancer or benign causes, willing to participate, and consent.

Exclusion criteria: were women who received hormone therapy, radiotherapy, or chemotherapy before surgery. (unlikely with endometrial cancer) Or women refused to participate in our study.

The personal and demographic data were collected, including age, parity, body mass index (BMI), menopausal status, medical and surgical co-morbidities.

Operative data:

All intraoperative details were collected from eligible women. During the surgical procedure, all intraoperative findings and

extent of surgery were documented, followed by the immediate removal of the uterus. A 2*2 cm sample of the endometrial tissue was collected and preserved in TRIzol reagent, then stored at -80 C until the beginning of the RNA extraction process. The remaining excised tissues were sent for histopathology, where the final FIGO staging and grade of endometrial carcinoma and histological subtype were recorded.

The tissues were preserved in RNA Later (Qiagen, Germany) and stored at -80°C until the RNA purification step takes place.

RNA isolation, cDNA synthesis, and qRT-PCR

To extract the total RNA from the freshly collected tumours, TRIZOL reagent (Bioflux, China) was used according to the manufacturer's instructions. Subsequently, cDNAs were synthesized with Genedirex's MMLV reverse transcriptase. PCR was carried out using specific primers for five Galectins (1, 2, 3, and 8) and GAPDH genes, with the same primer sequences as previously published data (16) . The Cycle threshold (CT) data was extracted onto Excel sheets and normalized to GAPDH. The fold change analysis was conducted using the 2-ΔΔ Cycle threshold formula.

Determination and purification of RNA concentration

The concentration of isolated RNA from endometrial tissue sample was measured using Nano Drop by calculating the absorbance ratio at 260nm to 280nm. Pure RNA has a ratio of 2.0 and isolated RNA has a ratio of 1.6-2.0.

Reverse Transcription

The purified RNA from endometrial tissue sample was reversely transcriped to cDNA using MMLV reverse transcriptase (Genedirex Taiwan) method.

Real- Time PCR Analysis

The qRT-PCR was performed using SYBR Green Real-Time Master Mix (Genedirex, Taiwan). The forward and reverse primers for the studied genes LGALS1, LGALS2, LGALS3 and LGALS8 were utilized. The fold changes of the Galactin family members, namely LGALS1, LGALS2, LGALS3, and LGALS8 were calculated and compared with the control group.

Statistical analysis

The data analysis was performed using IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

For non-normally distributed continuous variables, the median and interquartile range were used, and differences were compared using the Mann-Whitney test for two-group comparison or the Jonckheere-Terpestra trend test for multiple-group comparison. Normally distributed continuous variables were presented as mean and standard deviation and categorical variables as counts and percentages.

The Spearman rank correlation was used to test correlations between numerical variables. The correlation coefficient (Spearman's rho) was interpreted as follows: <0.2 = very weak, 0.2 to 0.39 = weak, 0.4 to 0.59 = moderate, 0.6 to 0.79 = strong, and ≥0.8 = very strong.

To evaluate the predictive value of galectins expression, a Receiver-operating characteristic (ROC) curve analysis was conducted. The area under the ROC curve (AUC) was interpreted as follows: AUC < 0.6 = fail, 0.6 to 0.69 = poor, 0.7 to 0.79 = fair, 0.8 to 0.89 = good, and ≥ 0.9 = excellent.

Finally, multivariable binary logistic regression analysis was used to calculate the adjusted odds ratio for relevant outcome measures. P-values less than 0.05 were considered statistically significant.

Results

In this study, 80 patients were assessed for eligibility, of which 72 were included. Eight patients were excluded due to issues with RNA extraction caused by storage or processing problems. The analysis was based on data collected from 72 women diagnosed with endometrial diseases planned for endometrial sampling or hysterectomy. These women were divided into two groups: the study group, consisting of 60 women with endometrial malignancy (endometrioid adenocarcinoma), and the control group, composed of 12 women with normal endometrial tissues at the proliferative stage removed for benign causes.

Table 1. shows the different demographic, clinical, FIGO staging, histopathological diagnosis, and the fold change in galectin expression in studied cases.

Fifty-eight endometrial cancer samples were included in the final statistical analysis. The histopathology examination of the removed specimens proved endometrioid adenocarcinoma in 56.9% of the samples (33 patients) while the rest were of non-endometrioid type (43.1%).

Fifty-eight samples of endometrial carcinomas were analyzed using qRT-PCR to evaluate the mRNA expression of four galectins. The obtained Cycle threshold values were normalized to GAPDH. Then, the fold change was calculated by comparing samples to twelve samples of normal endometrial tissue.

Even though endometrioid adenocarcinoma is the most common clinicopathological findings of endometrial carcinoma (20), the current study revealed that endometrioid adenocarcinoma was found in 56.9% of cases followed by the non-endometrioid type in 43.1% of cases with LN metastasis in 62.1%.

Accordingly, the four galectins -1, -2, -3, and -8 showed no statistically significant difference in expression between cases with lymph nodes metastasis and those with no metastasis (p values = 0.791, 0.501, 0.370, 0.501) respectively (table 2,3).

The expression of galectins was also checked in relation to FIGO staging. that there were no statistically significant differences between the studied groups regarding Galectin-1, 2, 3 and 8 expressions in patients with various FIGO stages of stage IC, IIB, IIC, IIIB, IIIC and IV (p values = 0.890, 0.441, 0.961, 0.750) respectively (Table 4).

There was no significant statistical difference in the expression of the four tested galectins in endometrioid and non- endometrioid endometrial cancer.

The prediction value of the tested galectins was assessed by ROC curve either for lymph node metastasis , or high FIGO staging (stages III and IV) and they showed poor prediction value (figure 1and 2). Similarly, they were examined for the predictive value for the presence of organ metastasis. All four galectins had poor predictive value (AUC = 0.513, 0.558, 0.526 or 0.554 for galectin-1, galectin-2, galectin-3 or galectin-8, respectively) [Tables 5-7, Figures 1-3] .

DISCUSSION

Endometrial cancer is an epithelial malignant tumor that originates in the endometrium. It is one of the most common malignant tumors of the female reproductive tract (17). Its incidence rate is still rising, and the number of new deaths is expected to increase by 17.4% by 2025 [18]

Galectins regulate numerous cell functions critical for cancer progression, including elevated cell proliferation, cell adhesion and migration, apoptosis and immune suppression. Furthermore, the cell-cell and cell-matrix interactions exhibited by galectins and their high affinity for specific oligosaccharides make galectins promising markers and/or therapeutic targets for cancer. The expression and function of galectins in

EC prognosis and progression have not been well investigated to date [19].

Interest in the galectin family and its role as a diagnostic and prognostic marker for endometrial cancer has been addressed in many studies [20].

This study aimed to explore the galectins family expression in endometrial carcinoma and its relation to the stage of the disease.

As part of this study, seventy-two endometrial samples were analyzed, including twelve benign endometrium samples which were used as controls. The study focused on sixty women who had either endometrial malignancy or endometrial hyperplasia with atypia and investigated the expression of galectins 1, 2, 3, and 8 in these patients. The results showed that LGALS1, LGALS2, LGALS3, and LGALS8 were significantly overexpressed in patients with endometrial carcinoma, as compared to the control group. However, there was no significant difference in the expression of these genes when comparing different FIGO staging or based on the presence or absence of lymph node metastasis. Additionally, there was no significant difference in their expression when comparing patients with either endometrioid or non-endometrioid adenocarcinoma of the uterus.

Comparison of our results to similar studies

Different studies were done exploring the expression of Galectins family and clinicopathological features in endometrial carcinoma, some of them agree and others differ from these current results.

Galectin-1 expression by tumours is associated with poor prognosis and the formation of metastasis through modulation of among others cell migration, adhesion and angiogenesis [21].

Another team, Sun et al. [17] conducted a prospective study to explore the expression of Galectin-1 and clinicopathological features in endometrial carcinoma. The study involved the collection of endometrial tissues from a total of 91 patients who were admitted and treated surgically for endometrial diseases and revealed that the rates of positive expression of Galectin-1 in normal endometrial tissue (NE), atypical endometrial hyperplasia (AH), and endometrial adenocarcinoma (EC) were 30, 70, and 90.2%, respectively which was significantly higher in EC and AH than that in NE ($p < 0.05$) indicating that Galectin-1 is involved in the occurrence and development of tumor cells, while high expression of Galectin-1 suggested a poor prognosis.

Other several studies have been published on galectins in endometrial cancer, with contradictory results. Galectin-1, but not galectin-3, has been shown to increase in EC compared with normal endometrium (22). Similarly, galectin-1 was found to be increased in endometrioid EC from well differentiated to undifferentiated carcinoma [23-24]

Regarding galectin-2 expression in cancerous vs. normal tissue, few reports are published which are scarce and unpredictable. Cada et al. (2009) (25) reported on reduced expression in basal cell carcinoma of the skin as compared to normal skin. Another large study on galectin-2 expression in numerous cancerous tissues and their normal counterparts was performed by Saal et al. (2005) (26). They observed a reduction in colon cancer and an increase in thyroid cancer. No changes were observed in stomach, lung, kidney or bladder cancer (26).. Subsequently a systematic review showed no changes in pancreatic, colon, skin or kidney cancer while galectin-2 levels were elevated in ovarian cancer as well as in the stroma of lung and bladder cancer but decreased in liver and breast cancer [27].

As regard Galectin-3, Boutas et al. (2021) (20) conducted a systematic review to describe the outcomes of some studies which examined the levels of Galectin-3 expression in endometrial carcinomas, the outcomes, and the prognosis of these carcinomas. Two of the studies concluded that high expression

of Galectin-3 is associated with a tumor's histological grade, type and depth. This enhanced nuclear Galectin-3 expression might assist in progression to atypia and neoplasia (28-29). The other three on the contrary concluded that malignant tumors had a decreased expression of Galectin-3 and that Galectin-3 played a suppressive role in tumor growth [23-30-31]. Moreover, Labropoulou et al. (2016) (28) observed that the Galectin-3 expression level increased from low to high-grade endometrial tumors. Thus, demonstrated a strong correlation between protein expression levels, poor prognosis and survival in patients with EC.

Also, Ege et al. (2010) [30] examined 64 individuals diagnosed with endometrial cancer who underwent hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy and evaluated the relationship of Galectin-3 expression to clinicopathological findings. They reported decreased expression of epithelial and stromal Galectin-3 in endometrial carcinogenesis and demonstrated the possible interaction of Galectin-3 with ER, PR, c-erbB2, and Ki-67 indicating a down-regulation of Galectin-3 in the endometrial cancer group compared to healthy individuals which was in concordance with Van de Brule et al. (1996) [23] who observed a significant down-regulation of Galectin-3 expression in endometrial cancer cells compared with normal mucosa.

Brustmann et al. (2003) [29] evaluated the expression of Galectin-3 in 101 curettage specimens from normal, hyperplastic, and neoplastic endometrial tissues by performing immunostaining and suggested that Galectin-3 expression may reflect the progression to atypia and neoplasia in endometrial tissues and Galectin-3 expression increased from normal to hyperplastic, atypical, and cancerous states of endometrial tissues, reflecting the classification of non-atypical hyperplasia, atypical hyperplasia with relation to endometrioid adenocarcinoma, and high grade endometrial serous papillary and clear cell carcinomas.

As regard Galectin-8, to our knowledge, Galectin-8 expression was not examined in women with endometrial carcinoma although Nikzad et al. (2013) [32] reported expression of Galectin-8 on normal human endometrium. They used immunohistochemistry staining to demonstrate that galectin-8 was expressed at a very low concentration during the proliferative phase but showed a high expression throughout the luteal phase. The expression of galectin-8 was observed in luminal surface epithelium, glandular epithelium and stroma. The up-regulation of the expression of galectin-8 during luteal phase may suggest galectin-8 as one of the potential molecular markers of the endometrial receptivity. [32]

Consequently, the current study is the first study that explores galectin-8 immuno- expression status in endometrial carcinomas and its association with other clinicopathological findings.

Other studies investigated Galectin-8 expression in other cancer types. Nagy et al. [33] reported a marked decrease in immunohistochemical expression of galectin-8 occurred with malignancy development in human colon tissue. Compared to normal tissues, galectin-8 expression appears to be increased in breast cancer, larynx cancer [34] and a subset of cutaneous T cell lymphomas, and decreased in skin cancer [25] as well as in several cancers of the digestive tract including pancreas and liver and.

Other Galectins family (Galectin-7, Galectin-9) may have role in EC and associations between galectin immuno- expression and grade, stage and poor differentiation of endometrial carcinomas but, unfortunately, their expressions in our study was not done due to limited resources and unavailability of kits.

Strengths and Limitations of Study

This study has several strengths, including its prospective study design, its location at a single tertiary care center, and having no

patients lost to follow-up during the study period. It is the first study to investigate the expression of galectin-2 and galectin-8 in endometrial carcinomas and its relation to the disease's stage.

However, there are also some limitations worth mentioning. Firstly, the study had a relatively small sample size compared to previous studies, and it was not a multicentric study. This represents a significant risk of publication bias. Secondly, the follow-up period for patients after surgery was relatively short, and there were no observations on patient survival and recurrence. Thirdly, the study was conducted during the pandemic covid-19, which limited the availability of patients.

Recommendation for Further studies: While informative, the number of samples per group was too small for conclusive observations and additional studies are required using larger patient groups. However, greater inclusive studies are undoubtedly of great value for estimating the diagnostic and prognostic values of this galectins in endometrial tumors.

CONCLUSION

Based on current evidence, Galectin-1, 2, 3 and 8 expressions in patients with endometrial carcinomas had no role for prediction of EC prognosis, LN metastasis and FIGO Stage.

Availability of data and materials

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

Ethical statements

The study was approved by the clinical research ethical committee. A written consent was taken from each patient or their legal guardian.

Consent for publication

Not applicable.

Competing interest

Authors declare no competing interest.

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Authors' contribution

Mahmoud M. Abdelfattah, Amira A Ghonim and Hany Naeem performed the experiments. Radwa Mansour Mohamed, Ahmed Sherif Abdelhamid, and Mohamed A M F Kortam supervised samples collection and data collection. Reham Helwa was involved in experimental design, data interpretation, and writing. All Authors revised and approved this manuscript.

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Table 1. Characteristics of the study population

Variable	Value
Age (years), mean ± SD (range)	50.2 ± 8.4 (30.0 to 76.0)
Age at menarche (years), mean ± SD (range)	11.7 ± 0.8 (10.0 to 13.0)
BMI (kg/m^2), mean ± SD (range)	28.4 ± 3.8 (21.0 to 36.0)
Parity, N (%)	
Nullipara	3 (5.2%)
Multipara	55 (94.8%)
Menopausal status, N (%)	
Premenopausal	43 (74.1%)
Postmenopausal	15 (25.9%)
Comorbidities, N (%)	
Medical	53 (91.4%)
Surgical	44 (75.9%)
Histopathology of D & C biopsy, N (%)	
Normal	5 (8.6%)
Endometrial hyperplasia	8 (13.8%)
Endometrial Carcinoma	45 (77.6%)
Optimal debulking, N (%)	58 (100.0%)
Metastasis, N (%)	
LN metastasis	36 (62.1%)
Organ metastasis	52 (89.7%)
FIGO classification, N (%)	
Stage IC	21 (36.2%)
Stage IIB	10 (17.2%)
Stage IIC	6 (10.3%)
Stage IIIB	10 (17.2%)
Stage IIIC	7 (12.1%)
Stage IV	4 (6.9%)
Histopathology, N (%)	
Non-Endometrioid	25 (43.1%)
Endometrioid	33 (56.9%)
Galectins expression (fold change), median (IQR) (min, max)	
Galectin-1	15.66 (0.95, 113.38) (0.01, 3136.63)
Galectin-2	1.21 (0.28, 4.59) (0.01, 140.07)
Galectin-3	1.26 (0.31, 4.53) (0.01, 168.90)
Galectin-8	7.41 (1.09, 32.22) (0.06, 3848.29)

IQR = interquartile range, max = maximum, min = minimum, N = number, SD = standard deviation

Table 2. Galectins expression in patients with or without LN metastasis

	No LN metastasis (N=22)		LN metastasis (N=36)		Mann-Whitney U test		
Variable	**Median**	**IQR**	**Median**	**IQR**	**U**	**Z**	**P-value**
Galectin-1 (fold change)	17.51	0.95 to 113.38	13.74	0.96 to 133.75	379.500	-0.264	0.791
Galectin-2 (fold change)	1.77	0.28 to 4.76	1.01	0.28 to 4.43	354.000	-0.673	0.501
Galectin-3 (fold change)	2.08	0.50 to 4.53	1.14	0.29 to 4.53	340.000	-0.897	0.370
Galectin-8 (fold change)	8.39	1.26 to 32.00	6.63	0.99 to 33.26	354.000	-0.673	0.501

IQR = interquartile range, U = Mann-Whitney U statistic, Z = Z-statistic

Table 3. Galectins expression in patients with or without organ metastasis

	No organ metastasis (N=6)		Organ metastasis (N=52)		Mann-Whitney U test		
Variable	**Median**	**IQR**	**Median**	**IQR**	**U**	**Z**	**P-value**
Galectin-1 (fold change)	14.13	0.95 to 223.63	15.66	0.96 to 105.70	152.000	-0.102	0.919
Galectin-2 (fold change)	1.77	0.65 to 2.66	1.15	0.28 to 4.68	138.000	-0.460	0.646
Galectin-3 (fold change)	1.07	0.63 to 4.38	1.26	0.29 to 5.28	148.000	-0.204	0.838
Galectin-8 (fold change)	3.43	1.26 to 7.26	8.62	1.06 to 33.26	139.000	-0.434	0.664

IQR = interquartile range, U = Mann-Whitney U statistic, Z = Z-statistic

Table (4): Galectins expression in patients with various FIGO stages

	Stage IC (N=21)		Stage IIB (N=10)		Stage IIC (N=6)		Stage IIIB (N=10)		Stage IIIC (N=7)		Stage IV (N=4)		Jonckheere-Terpstra trend test		
Variable	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	J-T	Z	P-value
Galectin-1 (fold change)	39.26	0.43 to 169.48	4.70	3.62 to 27.19	14.86	0.67 to 34.42	9.66	0.59 to 223.63	13.88	0.19 to 985.70	36.76	10.06 to 77.63	645.500	-0.139	0.890
Galectin-2 (fold change)	1.21	0.22 to 2.38	3.46	0.28 to 48.50	0.32	0.14 to 2.45	1.33	0.66 to 2.07	0.70	0.27 to 19.03	2.81	1.07 to 8.81	711.000	0.770	0.441
Galectin-3 (fold change)	1.27	0.42 to 2.87	5.20	0.57 to 62.25	0.23	0.15 to 3.86	0.77	0.34 to 3.03	0.50	0.08 to 32.67	2.35	1.32 to 6.01	652.000	-0.049	0.961
Galectin-8 (fold change)	5.70	1.25 to 13.74	12.69	2.89 to 212.31	26.27	0.76 to 34.30	7.24	1.91 to 38.85	1.05	0.46 to 136.24	13.98	5.59 to 26.31	678.500	0.319	0.750

IQR = interquartile range, J-T = Jonckheere-Terpstra statistic, Z = Z-statistic

Table 5. Receiver-operating characteristic (ROC) curve analysis for prediction of LN metastasis using galectins expression

	Marker			
ROC metric	**Galectin-1**	**Galectin-2**	**Galectin-3**	**Galectin-8**
Area under ROC curve (AUC)	0.521	0.553	0.571	0.552
Standard Error (SE)	0.081	0.080	0.079	0.078
95% Confidence interval	0.386 to 0.654	0.417 to 0.684	0.434 to 0.700	0.416 to 0.683
z statistic	0.259	0.659	0.892	0.672
Significance level P (AUC=0.5)	0.796	0.510	0.373	0.501
Youden (J) index†	0.104	0.230	0.205	0.139
Associated criterion	>1.952	≤1.414	≤3.031	≤0.323
Sensitivity (%)	69.4	63.9	75.0	13.9
Specificity (%)	40.9	59.1	45.5	100.0

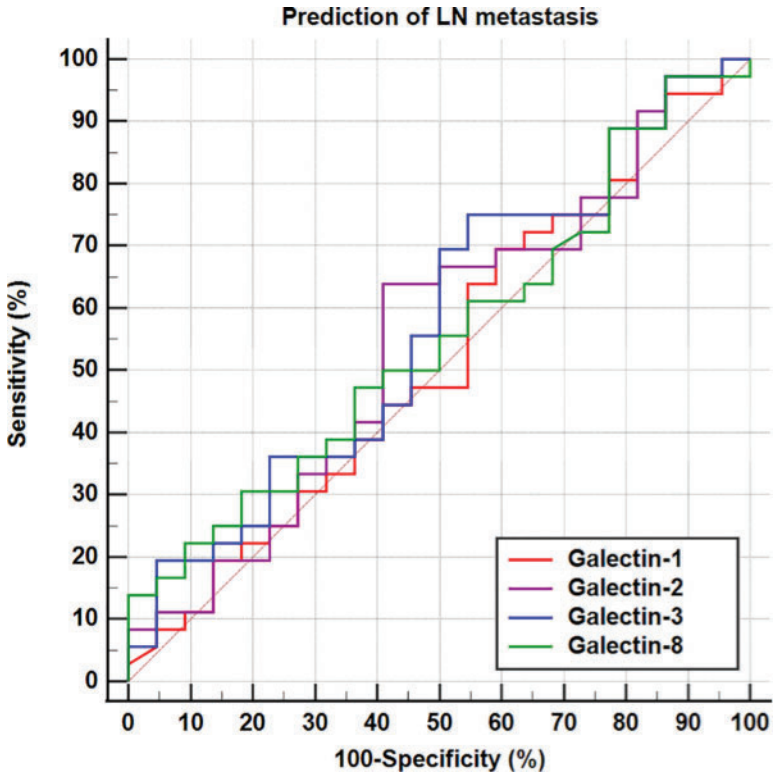

Figure 1. Receiver-operating characteristic (ROC) curves for prediction of LN metastasis using galectins expression. All four galectins had poor predictive value (AUC = 0.521, 0.553, 0.571 or 0.552 for galectin-1, galectin-2, galectin-3 or galectin-8, respectively).

Table 6. Receiver-operating characteristic (ROC) curve analysis for prediction of organ metastasis using galectins expression

	Marker			
ROC metric	**Galectin-1**	**Galectin-2**	**Galectin-3**	**Galectin-8**
Area under ROC curve (AUC)	0.513	0.558	0.526	0.554
Standard Error (SE)	0.140	0.117	0.119	0.107
95% Confidence interval	0.378 to 0.646	0.421 to 0.688	0.390 to 0.658	0.418 to 0.685
z statistic	0.092	0.493	0.216	0.509
Significance level P (AUC=0.5)	0.927	0.622	0.829	0.611
Youden (J) index†	0.250	0.263	0.199	0.372
Associated criterion	>1.075	≤1.682	≤0.574	>7.260
Sensitivity (%)	75.0	59.6	36.5	53.9
Specificity (%)	50.0	66.7	83.3	83.3

†. Youden (J) index = (Sensitivity + Specificity) - 1

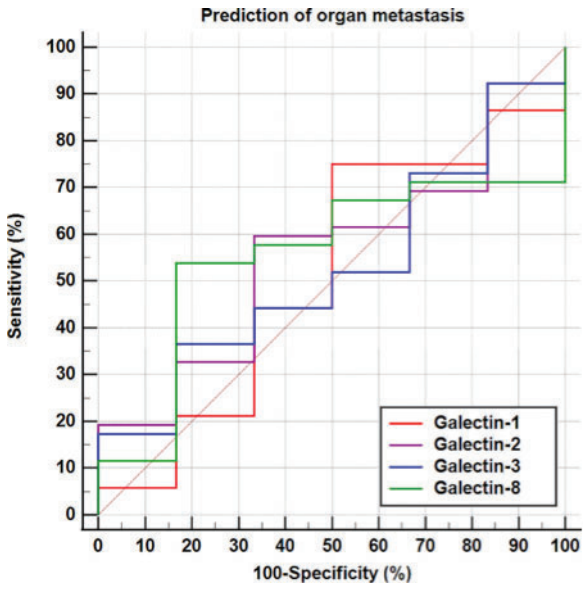

Figure 2. Receiver-operating characteristic (ROC) curves for prediction of organ metastasis using galectins expression. All four galectins had poor predictive value (AUC = 0.513, 0.558, 0.526 or 0.554 for galectin-1, galectin-2, galectin-3 or galectin-8, respectively).

Table 7. Receiver-operating characteristic (ROC) curve analysis for prediction of FIGO stage III/IV using galectins expression

	Marker			
ROC metric	**Galectin-1**	**Galectin-2**	**Galectin-3**	**Galectin-8**
Area under ROC curve (AUC)	0.501	0.560	0.515	0.526
Standard Error (SE)	0.082	0.077	0.080	0.080
95% Confidence interval	0.367 to 0.635	0.423 to 0.690	0.380 to 0.648	0.391 to 0.659
z statistic	0.016	0.776	0.184	0.329
Significance level P (AUC=0.5)	0.988	0.438	0.854	0.742
Youden (J) index†	0.109	0.263	0.109	0.115
Associated criterion	>0.190	>0.409	≤0.090	≤152.219
Sensitivity (%)	81.0	85.7	19.1	95.2
Specificity (%)	8.1	40.5	91.9	16.2

†. Youden (J) index = (Sensitivity + Specificity) - 1

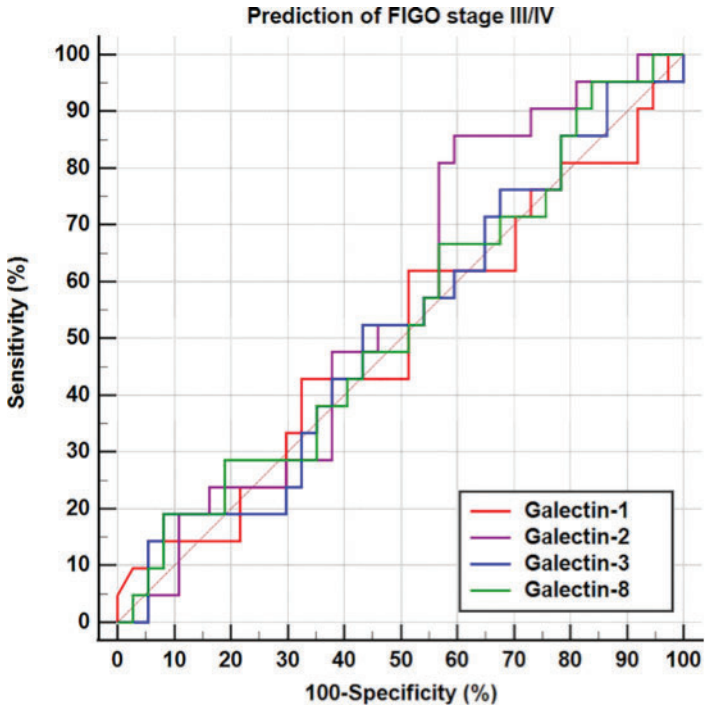

Figure 3. Receiver-operating characteristic (ROC) curves for prediction of FIGO stage III/IV using galectins expression. All four galectins had poor predictive value (AUC = 0.501, 0.560, 0.515 or 0.526 for galectin-1, galectin-2, galectin-3 or galectin-8, respectively).

Diagnostic Accuracy of Nuchal and Intracranial Translucency by Two-dimensional versus Three- dimensional Ultrasonography in Low-Risk Pregnancy

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Abstract

Background: First-trimester ultrasound was initially done for confirming pregnancy, counting fetuses, and dating. Later, combined trisomy 21 screening became crucial, Nuchal Translucency (NT), measured at 11-13 weeks + 6 days, indicates chromosomal defects with increased thickness. It's an effective marker for trisomies, triploidy, Turner syndrome, and congenital heart defects. More over, intracranial translucency (IT) assessment is a useful tool for prediction NTDs.

Aim of study: The aim was to evaluate the diagnostic accuracy of nuchal and intracranial translucency assessment by two-dimensional (2D) versus three-dimensional (3D) ultrasonography in low-risk pregnancy at the first trimester.

Patients and methods: This study was a Cross sectional study conducted at Outpatient clinic at obstetrics and gynecology department at Mansoura University Hospital from May 2021 to May 2022. Study population included 30 Low risk pregnant women with their gestational ages ranging from 11–13 weeks and six days.

Results : there was no statistically significant difference in assessment the NT and IT by 2D ultrasound and 3D ultrasound.

Conclusion: There was a complete matching between 2D and 3D ultrasound in detection of IT and NT in low-risk pregnancy at the first trimester.

Keywords: Nuchal Translucency; 3D ultrasonography; pregnancy.

INTRODUCTION

In the introduction of routine first trimester ultrasound for prenatal care, the focus was primarily on confirming pregnancy, viability, fetus count, and accurate dating. However, as prenatal care evolved in the late 1990s to include combined screening for trisomy 21, using nuchal translucency (NT) measurements and assessment of early fetal anatomy became a crucial part of first trimester

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imaging. This detailed examination now has the potential to detect around 50% of major structural anomalies.[1]

The NT is a measure of fluid accumulation behind the fetal neck during the first trimester between 11 and 13 weeks and 6 days gestation, with a minimum fetal crown-rump length (CRL) of 45 mm and a maximum of 84 mm. An increase in NT thickness during this period is associated with major chromosomal defects, Median and 95th centile NT values at CRL of 45 mm are 1.2 and 2.1 mm, while at CRL of 84 mm, they are 1.9 and 2.7 mm.[2]

Studies have highlighted the effectiveness of specific ultrasound markers, such as NT, nasal bone, long bone biometry, and ductus venosus Doppler assessment, for screening trisomies, triploidy, Turner syndrome, and congenital heart defects. An NT thickness exceeding 2.5 mm between 10 and 13 weeks and 6 days is linked to an increased risk of these conditions.[3]

Normal fetuses display an intracranial translucency (IT) parallel to the NT, while fetuses with open spina bifida may lack IT.[4]

The best time to measure fetal IT is between 11 and 13 weeks and 6 days.[5]

The anteroposterior diameter of IT increases with fetal CRL within the 11-13 week range, from 1.5 mm at a CRL of 45 mm to 2.5 mm at a CRL of 85 mm.[6]

Moreover, measuring IT has proven valuable for the early detection of neural tube defects (NTDs).[7]

Early identification of NTDs can aid in decision-making, as some cases may benefit from fetal surgery. Therefore, offering screening for NTDs as part of routine first-trimester scan is crucial.[8]

Overall, sonographic examination of NT and IT between 11 and 13+6 weeks of gestation is recommended as a screening method for chromosomal anomalies, and NTDs.[9]

Therefore, the present study was carried out to evaluate the diagnostic accuracy of (NT) and (IT) assessment by two-dimensional (2D) versus three- dimensional (3D) ultrasonography in low-risk pregnancy at first trimester.

Patients and Methods

This study was a Cross sectional study conducted at Outpatient clinic at obstetrics and gynecology department at Mansoura University Hospital from May 2021 to May 2022.

Study population: Low risk 30 pregnant women with gestational ages ranging from 11–13 weeks and six days.

Inclusion criteria: young age below 35 years old with No history of chronic disease.

Exclusion criteria: Multiple pregnancies, history of recurrent miscarriage, family history of fetal anomalies, past history of previous sibling with congenital anomaly, history of consanguinity. As well as Patient refusal

All patients enrolled in this study had the following:

- Verbal consent was obtained from the pregnant women participate of the study
- Every participated was subjected to a full history taking and General examination was carried out for pulse, blood pressure, temperature, BMI (height and weight), abdominal examination, Obstetric examination were also carried out if needed Relevant investigations were done such as Complete blood count (CBC), prothrombin time (PT) and blood sugar and urine analysis.
- Method of Ultrasound examination: Women at 7 to 10 weeks' gestation initially had an abdominal ultrasound to confirm pregnancy viability, gestational age, and singleton pregnancy. For abdominal scans, patients lay supine with a full bladder, The Samsung-H60 ultrasound

system was employed, Transvaginal scans were used when needed for better fetal structure imaging or when structural anomalies were suspected.

- Detailed ultrasound was performed at 11-13 weeks + 6 days for fetal viability, CRL, fetal position, NT and IT
- Fetal medicine foundation (FMF) protocol for measurement of NT. The gestational age of examination was must be 11-13 weeks and six days. The fetal (CRL) ranged from 45 to 84 mm. image magnified covers the fetal head and thorax entirely. mid-sagittal view was obtained the face, defined by specific facial features. With the fetus in neutral position and the head aligned with the spine. fetal skin and amnion was distinguished. the widest part of translucency was measured. NT measurements, IT presence, and IT antero-posterior diameter.
- measurement of the IT has been previously described as a useful US marker for the early detection of NTDs .10
- After 2D-NT measurement, 3D volume acquisition was performed. A 3D sweep encompassing the fetal head and upper thorax was stored for later use. Unsuccessful 3D volume acquisition, due to fetal position or movement issues within 15 minutes, led to exclusion from the study .11
- Data Management and Analysis The collected data were analyzed using the SPSS (Statistical Package for Social Sciences) version 27 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The comparison between two groups was done by using Chi-square test. The comparison between two independent groups was done by using independent t-test.

RESULTS

There was no statistically significant difference among the participant of the study regarding their age , BMI, Parity and gravidity with mean age of the studied cases of about 27.10 ± 3.49 years, and mean body mass index of about 27.91 ± 2.74 kg/m2. There was a statistically significant positive correlation between NT measured by 2D (mm) with CRL (rs= 0.559, p= 0.001). Moreover, there was a statistically significant positive correlation between NT by 2D (mm) with GA (rs= 0.495, p= 0.005) (As showed by Table 1).

Table (1): Correlation of NT by 2D with other variables.

		NT by 2D (mm)
	rs	P
Age (years)	**0.342**	**0.065**
Weight (Years)	**- 0.154**	**0.416**
Height (Cm)	**0.118**	**0.534**
BMI (Kg/m^2)	**-0.100**	**0.597**
Gravidity	**0.175**	**0.354**
Parity	**0.376**	**0.041***
GA (Days)	**0.495**	**0.005***
CRL (mm)	**0.559**	**0.001***

rs: Spearman's correlation; P: Probability; *: statistically significant (P ≤ 0.05); CRL: Crown-rump length; GA: Gestational age.

There was a statistically significant positive correlation between NT measured by 3D with CRL (rs= 0.559, p= 0.001) as well as GA (rs= 0.509, p= 0.004) **(As showed by Table 2)**.

Table2: Correlation of NT by 3D with other variables.

		NT by 3D (mm)
	r s	**P**
Age (years)	0.319	**0.085**
Weight (Years)	- 0.144	**0.448**
Height (Cm)	0.086	**0.651**
BMI (Kg/m^2)	-0.074	**0.696**
Gravidity	0.182	**0.336**
Parity	**0.351**	**0.057**
GA (Days)	**0.509**	**0.004***
CRL (mm)	**0.559**	**0.001***

BMI: Body mass index; CRL: Crown-rump length; GA: Gestational age; NT: Nuchal translucency; P: Probability; rs: Spearman's correlation; *: statistically significant (P ≤ 0.05).

interclass agreement coefficient between NT by 2D (mm) and NT by 3D (mm) was 0.991 (CI: 0.995) and this agreement showed high statistically significant value (p< 0.001) (As showed by Table 3).

Table (3): Agreement analysis (Interclass correlation) in detection

	Agreement coefficient (Interclass correlation)	95% CI	P
NT by 2D (mm) and NT by 3D (mm)	**0.991**	**0.995**	**< 0.001***

of NT by 2D and 3D ultrasound.

CI: Confidence interval; *: Statistically significant (p< 0.05).

There was a complete matching between the 2D and 3D ultrasound in detection of IT **(Table 4)**.

Table (4) Agreement between 2D and 3D ultrasound in detection of IT.

Variables	IT by 2D N = 30		IT by 3D N = 30		Test of significance
	No.	%	No.	%	
IT					
Absent	2	6.7%	2	6.7%	**k = 1 P < 0.001***
Present	**28**	**93.3%**	**28**	**93.3%**	

Demographic data expressed as Number (%); k: Kappa agreement coefficient; *: Statistically significant

at 11-13 + 6d was 1.56 ± 0.37 mm that was statistically significantly lower as compared to the cases with abnormal scan (5.39 ± 0.30 mm) (P < 0.001). The mean NT by 3D in the cases with normal results of scan at 11-13+ 6d was 1.68 ± 0.35 mm that was statistically significantly lower as compared to the cases with abnormal scan (5.39 ± 0.30 mm) (P < 0.001), **Fig (2 & 3) (As showed by Table 5)** .

Table (5): Relation between scan at 11-13 + 6d and NT by 2D & NT by 3D.

Scan at 11-13 + 6d	Normal (N=28)	Abnormal (N=2)	Test of significance
NT by 2D (mm)	1.56 ± 0.37	5.39 ± 0.30	**t= -14.388 P < 0.001***
NT by 3D (mm)	1.68 ± 0.35	5.39 ± 0.30	**t= -14.509 P < 0.001***

NT: Nuchal translucency; t= independent samples t-test; $\chi 2$= Chi-square test

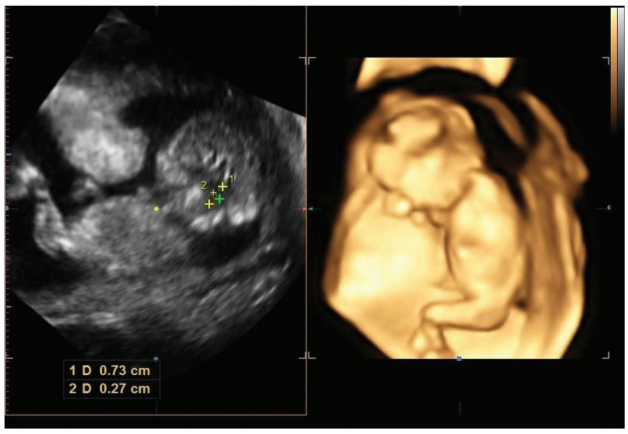
showed that the interclass agreement coefficient scan time by 2D (min) and scan time by 3D (min) is 0.555 (CI: 0.249-0.760) and this agreement showed statistically significant value (p= 0.002). (As showed by Table 6)

Table (6): Agreement analysis (Interclass correlation) between 2D and 3D regarding the time of scanning.

Scan time	Agreement coefficient (Interclass correlation)	95% CI	P
by 2D (min) and 3D (min)	**0.555**	**0.249-0.760**	**0.002***

CI: Confidence interval; *: statistically significant (P ≤ 0.05).

Transvaginal approach was carried out for assessment of NT in 5 cases of the study for technical difficulties.



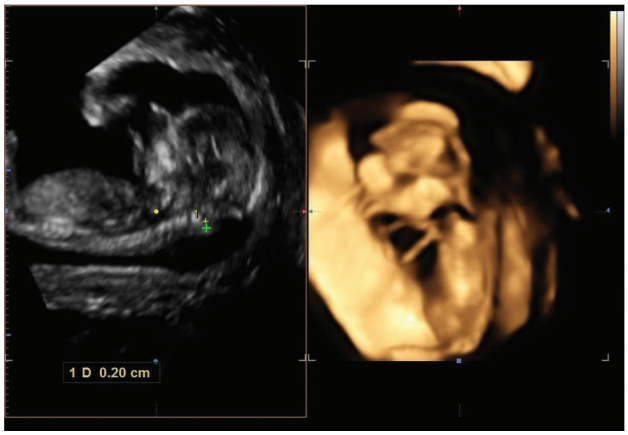


Figure (1): Normal NT and IT by 3D ultrasound.

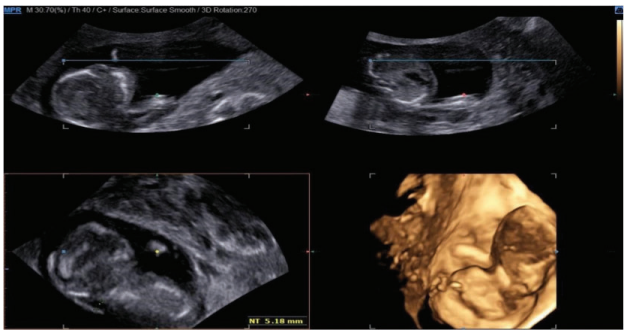


Figure (2): Case of cystic hygroma abnormal NT 5.18 mm and absent of IT.

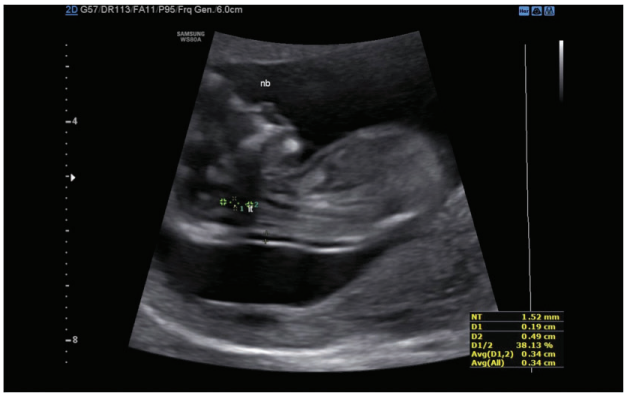


Figure (3): Normal NT and IT with 2D ultrasound.

DISCUSSION

The aim of this study was to detect the diagnostic accuracy of NT and IT by 2D versus 3D ultrasonography in low-risk pregnancy. In the current study, there were two women with Abnormal Scan and 28 were normal Scan (mean 6.66) and the CRL (mm) ranged from 46 to 91 mm (mean 64.43mm) and the G.A ranged from 11 weeks to 13 days. The mean NT by 2D was 1.82 ± 1.03 mm while the mean NT by 3D was 1.93 ± 1.00 mm.

This was in accordance with Khalifeh et al. .12 who included 366 patients with singleton pregnancies at a mean GA of 12.3 weeks) and a mean CRL of 58 mm. NT ranged from 0.8 to 2.9 mm. 2D NT was obtained in 359 (98%) patients, while 3D NT in sagittal planes was obtained for all 359 patients. 3D NT measurements in axial planes were obtained in 322 patients (88%). The mean maximal NT measurement for 2D, 3D sagittal, and 3D axial planes were 1.65 (± 0.34), 1.70 (± 0.42), and 1.66 mm (± 1.28), respectively.

This was in accordance with Dinç and Eyüboğlu .13 who showed that in the First trimester screen was done in 1640 singleton pregnancies. The measurements were performed on 1541 (%94) fetuses by the transabdominal route and on 99 cases (%4) by the transvaginal route. The mean NT measurements at 11– 11+6, 12-12+6, and 13–13+6 gestational weeks were 1.40 ± 79 mm, 1.58 ± 0.76 mm, and 1.68 ± 0.64 mm, respectively. NT thickness for the 95th, 97th, and 99th percentiles were

2.82 mm, 3.17 mm, and 4.75 mm, respectively.

Also, the current results agreed those of Lee et al. .14 who retrospectively analyzed the IT of 93 singleton fetuses. They showed that the median GA was 11.6 weeks, and the mean CRL was 54.0 ± 7.4 mm. All fetuses appeared normal on their secondtrimester scan.

The mean NT thicknesses in Caucasian, African, Asian, and Caribbean populations were 1.54 mm, 1.48 mm, 1.61 mm, and 1.51 mm respectively.[15]

In the current study, there was a complete matching between the 2D and 3D ultrasound in detection of IT that was detected in 28 cases (93.3%) by both techniques.

This disagreed with the study by Mein et al. .16 that included the analysis of data of four operators of 173 women who attended the Perinatal Ultrasound Department for their NT scan, at which time a 2D measurement of IT was recorded. A 3D sweep of the fetal brain was also performed on the same patient by a qualified sonographer. There is a low level of agreement, an inter-rater correlation coefficient (ICC) =of about 0.227, 95% CI (0.15, 0.313). The average 3D measurement correlated poorly with the 2D gold standard, ICC=of about 0.22, 95% CI (0.076, 0.355)

This variation could be attributed to the nature of data representation, as previous study used the numerical values which could affect the degree of agreement based on minor variations, especially with the increased sample size.

In the current study, the interclass agreement coefficient between NT by 2D (mm) and NT by 3D (mm) was 0.991 (CI: 0.980-0.995) and this agreement showed high statistically significant value ($p< 0.001$).

This was in accordance with Khalifeh et al. .12 who showed that the Spearman rank correlation (r) of 2D sagittal plane sonography with 3D sagittal and axial plane sonography was 0.73 and 0.68, respectively ($p <0.001$).

Similar results were shown by Wee et al. .3 who conducted a study on a total number of 23 patient. The results showed that there was a strong positive linear relationship between 3D and 2D-NT measurements within Pearson's correlation coefficient values, R = 0.861. as 2D-NT measurement increases, 3D-NT measurement increases as well. The computed linear regression line equation was 3D_NT = (0.945)2D-NT - 0.013.

Furthermore, the current study agreed with those of Cho et al. .16 who included 114 cases in their study. NT measurement was successful by the conventional 2D method in 95.6% (109/114) of cases and by 3D and Volume NTTM measurements in 103 and 93 cases, respectively. Success rate was not significantly different between methods. In 89 cases, NT values were available using all three methods. Among them, mean ± SD

2D-NT was 1.3 ± 0.4 mm, 3D-NT was 1.2 ± 0.4 mm and Volume NTTM was 1.3 ± 0.4 mm. The mean differences of the intra- and interobserver variability of each method were not significantly different from zero for each method.

In the study by Kurjak et al. .17 examinations were performed on 120 women undergoing ultrasound screening at 10 to 14 weeks' gestation. They were examined by two experienced ultra-sonographers using both methods two times consecutively. Statistical analysis for the assessment of intra-observer reproducibility was paired t-test. NT measurements were obtained in 100 % of cases with three-dimensional sonography compared to only 85 % with two-dimensional sonography. Better intra-observer reproducibility was obtained for three-dimensional than for two-dimensional ultrasound. Three-dimensional transvaginal ultrasound improves accuracy of NT measurement allowing appropriate mid-sagittal section of the fetus and clear distinction of the nuchal region from the amniotic membrane.

On the other hand, the study of Antsaklis et al. .18 upend 199 patients were included in that study suggests that the 3D ultrasound examination was insufficient to perform the fetal anatomy required in the 1st trimester of pregnancy. In a significant percentage of the cases, examination of the anatomical parameters could not be performed at all, or their assessment deviated from the clinically acceptable level. The mean NT measured by 2D was 1.65 ± 0.33 mm while the mean NT by 3D was 1.19 ± 0.63 mm.

In the current study, there was a statistically significant moderate positive correlation between NT by 2D (mm) with CRL (rs= 0.559, p= 0.001). Moreover, there was a statistically significant moderate positive correlation between NT by 2D (mm) with GA (rs= 0.495, p= 0.005). Also, there was a statistically significant moderate positive correlation between NT by 3D (mm) with CRL (rs= 0.559, p= 0.001). Moreover, there was a statistically significant moderate positive correlation between NT by 3D (mm) with GA (rs= 0.509, p= 0.004).

With the study conducted by Dinç and Eyüboğlu İL. .19 who showed that there was a significant and positive correlation between NT and CRL ($r = 0.131$ and $P < 0.001$)

In their study, Wee et al. .3 showed that the Pearson's correlation between GA and CRL with 3D-NT measurements, at values $R = 0.005$ and 0.017 respectively. Also, their Results showed that 3D-NT variables had positive relationship with GA and CRL.

Chen and et al. (2012) .20 reported similar conclusions, where they showed that at 11 to 13 + 6 weeks of gestation the IT anterior and posterior diameter at first trimester ranged from 1.35 to 2.6 mm as the CRL increased from 45 to 84 mm.

The main Drawbacks of current study was relative small sample size need large scale studies for fortification of results.

CONCLUSION

There was a complete matching between 2D and 3D ultrasound in detection of IT and NT in low-risk pregnancy at the first trimester. No difference in NT by 2D or 3D according to the scanning approach either transabdominal alone or both transabdominal and transvaginal together. We suggest that 3D ultrasound is an effective means of assessment of NT & IT and offers some potential advantages over 2D ultrasound.

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Human Papilloma Virus Vaccine Awareness Among Patients Attending Gynecology Outpatient Clinic At Mansoura University Hospitals

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Short Running Title: HPV Vaccine Awareness among Egyptian Females.

Abstract

Objective: To evaluate the patient acceptance, satisfaction, and possible side effects of the human papilloma virus (HPV) vaccine among Egyptian females.

Patients and Methods : This was a cross-sectional study conducted to evaluate women's HPV infection knowledge and HPV vaccine acceptance in Egypt using a face-to-face interviewing questionnaire. The study included 408 Egyptian females aged 15 to 40 years who attended the gynecology outpatient clinic at Mansoura University Hospitals.

Results: Most of Egyptian females did not know what is HPV, the cause of HPV, and how it spreads. Only 48 females (12%) know about HPV vaccination, however, the majority of females (278 females; 68.1%) accepted to be vaccinated while 130 females refused owing to cost in 104 females (80%) or harm in 26 females (20%) from females who refused. Among the participating females who answered about side effect (104 females) , 23 females (22.1%) confirmed that no side effects of the vaccine while erythema, pain, induration, and myalgia were reported in 39.4%, 36.5%, 0.9%, and 0.9%, respectively. There were statistically significant relations between accepting the vaccine and age ($p= 0.005$), residence ($p= 0.004$), marriage duration ($p= 0.01$), vaginal discharge ($p< 0.001$), and husband age ($p= 0.003$).

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Conclusion: Despite the low level of awareness about the vaccine among our population, we reported the potential acceptability of the vaccine.

Keywords: Human papilloma virus (HPV), Vaccine, Awareness, Cervical cancer.

Introduction

Worldwide, HPV infection has been considered a prevalent sexually transmitted disease (STD). A lifetime exposure to one or more HPV types happens in at least 50% of sexually active females (1). In recent years, at least two hundred of HPV types have been recognized. Certain HPV types mainly infect skin and induce warts, on the other hand other HPV types mainly target mucosal tissues of cervical canal and oral cavity(2, 3).

Most of genital HPV infections are self-limited and occur without manifestations. On the other hand, a lot of epidemiologic researches have demonstrated that persistent infections with particular forms of HPV are an essential predisposing factor in the context of invasive cervical cancer (CC) development(4, 5).

Vaccines are considered the most efficient interventions in terms of infectious diseases (6). The eventual goal of HPV vaccination is to prevent invasive CC by preventing infection with major oncogenic types of HPV (7, 8).

On the other hand, it is noteworthy that awareness of HPV and the general attitude towards vaccination were important factors for the acceptance of vaccination among the population. Additionally, an increasing number of researches addressing the debate to get vaccinated are conducted nowadays, depicting the challenging and dynamic period of indecisiveness as regards HPV vaccination (9, 10).

In spite of the numerous reported researches emphasizing on the topic of HPV and vaccination recently, there is no detailed data as regards the acceptance and obstacles accompanied by vaccination among the Egyptian people. To plan a practical vaccination program, it is of great importance to properly evaluate the degree of awareness and knowledge as regards HPV, and the general attitude towards HPV vaccination among the Egyptian people, as they are essential behavioral determinants which will actually interfere with the acceptance of vaccination among the Egyptian population. As a result, we conducted this study to gain a better understanding of this issue which might help generate novel ideas to make future generalizations of HPV vaccination possible in Egypt.

Patients and Methods

This was a cross-sectional descriptive pilot study performed to assess women's HPV infection knowledge and HPV vaccine acceptance in Egypt. The study included 408 Egyptian females aged 15 to 40 years who attended the gynecology outpatient clinic at Mansoura University Hospitals from 1st March 2022 to 1st September 2022 (six months) after obtaining approval from the institutional review board (IRB), Faculty of Medicine, Mansoura University.

An informed consent was obtained from entire subjects after a compressive explanation of the study and its consequences. The research approval of the study was acquired from the IRB of the Faculty of Medicine at Mansoura University before starting the study.

Methods

All cases were subjected to a face-to-face interviewing questionnaire focusing on personal history taking e.g., age, sex, and residency, history of HPV infection symptoms e.g., genital warts, around the genitals and anus, genital irritation, or pain, and history of CC symptoms of e.g., pain during sex, pain in the pelvic region, abnormal discharge from the vagina, or abnormal bleeding, which include

after sexual intercourse and so on.

After a detailed description of HPV infection and its severity, the HPV vaccine was offered to all participating females. The acceptance rate, of females who took the vaccine, was measured as a primary outcome in our study.

In the case of vaccine acceptance, all cases that agreed to take the vaccine continued the study and were subjected to assessing the secondary outcomes, including:

1. Vaccination satisfaction: Satisfaction of females as regards the HPV vaccine was evaluated at three and six months post-vaccination as to whether they were satisfied or not and if they recommended it to others.
2. Vaccination side effects : Also, side effects of the HPV vaccine were evaluated at the time of vaccine administration, as well as 3 and 6 months post-vaccination as to whether they have side effects or not.

Statistical analysis: Data were analysed by utilizing SPSS version 22. Qualitative data were presented as numbers and percentages. Quantitative data were tested for normal distribution by using the Shapiro-Wilk test, then described as mean and SD for normally distributed data and median and range for non-normal distribution of data. The proper statistical tests were applied based on the data type with the following recommended tests: Chi-Square for categorical variable. Student t-test and Mann Whitney U test for continuous variables.

Results

The females' age ranged from 15 to 40 years with a mean ± SD of 34.77±6.65 years. The majority of females were from urban areas (354 females; 86.8%). More than half of the females (56.6%) were housewives. (Table 1)

Concerning marital status, 407 females (99.8%) were married. The marriage duration ranged from 1 to 25 years with a median of 12 years. Only one female married twice (0.2%). (Table 1)

None of the females were smokers or exposed to an abnormal sexual offense. The majority of the females had no vaginal discharge (231 females; 56.6%). Pain during intercourse was reported in 175 females (43%).(Table 1)

The age of female husbands ranged from 25 to 52 years with a mean ± SD of 40.09 ± 6.98 years. The majority of husbands were employees (62.5%). Smoking was reported in 176 husbands (43.1%). Regarding marriage numbers, 402 husbands (98.5%) get married once, and 6 husbands (1.5%) get married twice. Two husbands (0.5%) practiced abnormal sexuality. Finally, 183 husbands (44.9%) had genital warts.

Table 2 shows the knowledge among participants about HPV and CC.On asking the participating females about HPV, most of them 341 females (83.5) did not know what is HPV, the cause of HPV, and how it spreads, 364 females (89,3%) did not know any information about HPV spread ,Only 44 females (10.4%) know about spread (sexual transmitted, skin or mucosal contact) .94 females; 23 % had genital warts.Among the participating females, 150 females (36.8%) did not know about cervical cancer ,258 females (63.2%) heard about cervical cancer, 371 females (90.9%) did not know any relation between HPV and cancer cervix , 37 females (9.1%) know about relation between HPV and cervical cancer from media , they discovered CIN with genital warts or family history of cervical cancer, 11 females(2.7%) think no relation between HPV and other cancer , 13 females (3.3%) think relation between HPV and other cancer , majority of females 384 (94%) did not know relation between HPV and other cancer. In addition, most of females did not know about HPV prevention, pap smear tests for cervical screening, or HPV vaccine.

The knowledge among participants about the HPV vaccine is demonstrated in Table 3. Only 48 females (12%) know about

HPV vaccination, however, the majority of females (278 females; 68.1%) accepted to be vaccinated while 130 females refused owing to cost in 104 females (80%) or harm in 26 females (12%) among females who refused . The knowledge vaccination types, in 106 females (26%), preferred Gardasil Regarding the vaccine schedule after awareness , 304 females (74.5%) did not know about types and all schedules. As regards the need for Pap smear screening after vaccination, 16 females (2.4%) answered yes ,96 females (23.52%) answered no and 304 females (74.5%) did not know. Concerning the disease (gential warts and cervical cancer) protected using vaccine after awareness ,246 females (60.3%) knew it while 162 females (39.7%) did not know. More than half of the participating females (60.3%) confirmed that they would permit their daughter to get the vaccine while 39.7% refused, suggesting vaccine unsafely in 70 females (43.2%) or because they are against vaccine in 92 females (22.54%). Concerning the effect of vaccines, 68 females (16.6%) believed that vaccines have no impact on daily activity, 340 females (83.3%) did not know any information about effect of vaccine impact on daily activity as majority of females did not know about vaccine.

Among the participating females answered about side effects , 23 females (22.1%) confirmed that no side effects of the vaccine while 38 females (36.4%), 38 females (36.5%), one female (0.9%) and one female (0.9%) reported that vaccine causes erythema, pain, induration, and myalgia, respectively. Nearly three-quarters of females (302 females; 74%) did not know about the effect of the vaccine on fertility, while 87 females (21.3%) believed that the vaccine impacts fertility, and 19 females (4.7%) answered no effect of the vaccine on fertility. The impaction of vaccine on early menopause knowledge 322 females (78.9%) reported who did not know, sixty females (14.7%) answered no impaction of vaccine on early menopause, while 26 females(6.3%) believed that HPV vaccine has impact on early menopause , in addition, 108 females (26.4%) thought that the vaccine affected promiscuity. However, 278 females (68.1%) believe that our community is appropriate for vaccines after awareness . (Table 4)

There were statistically significant relations between accepting the vaccine and age (p= 0.005), residence (p= 0.004), marriage duration (p= 0.01), vaginal discharge (p< 0.001), and husband age (p= 0.003).(Table 5)

Whereas, no statistically significant relations were observed between accepting the vaccine and occupation (p= 0.06), marital status (p= 1.0), marriage number (p= 1.0), pain during intercourse (p= 0.242), the husband's occupation (p= 0.112), husband's marriage number (p= 0.09), husband's abnormal sexuality (p= 1.0), and husband's genital warts (p= 0.357).(Table 5)

Discussion

HPV infection is common among young females. On the other hand, the majority of the infections are managed with six to twelve months and only a small percentage develop a persistent infection (11). In the current study, most of the females were asymptomatic, two females complained (0.5%) of vaginal bleeding, 81 females (19.9%) had offensive yellowish discharge and 94 females (23%) suffered from whitish creamy discharge. Pain during intercourse was reported in 175 females (43%).Nearly a quarter of females (96 females; 24%) had history of genital warts. All of these symptoms may suggest HPV infection or early CC. This was proved in our work as Pap smears revealed that 166 females (40.7%) were infected with HPV and 242 females (59.3%) had no HPV. History of histopathological examination confirmed carcinoma in situ (CIN) in one case. However, confirming the diagnosis and following up on the diagnosed disease was beyond the aim of our work.

Accordingly, HPV infection among Egyptian women who had cervical cytology or clinical

genital warts , older than 17 years old who were who attended the gynecology outpatient clinic at Mansoura University Hospitals was 24%. However, previous Egyptian studies showed a much lower prevalence rate of HPV infection, representing 10.3% (12), 15.06% (13), and 23.3% (14).

The variation in the prevalence rates of HPV reported by various researchers could be explained by first, the nature of HPV infections being transient and resolving on their own, so the prevalence of HPV may change over time. Second, different inclusion criteria for participant women may lead to variation in HPV prevalence. Third, the difference in sensitivity of the tests used to measure the prevalence might be a contributing factor. Fourth, the different socioeconomic status of participants , different behavior changes, different risk factors as immunocompromised females who had HIV infection , diabetes mellitus or autoimmune diseases .

Concerning the knowledge of HPV infection, 88% of females did not know what is HPV, the cause of HPV and how it spreads which was higher than that reported by a previous Egyptian study by Shaltout et al. who mentioned that few women (33.2%) in their study had formerly heard of HPV (12).

Generally, this may imply conservative sexual behaviour in Egypt. In addition, discussing such issues is comparatively very low among subjects in society with no formal sexual education (15).

Among the participating females, the majority of females (90.9%) didn't know about the relation between HPV and cancer cervix. Furthermore, most of them didn't know about HPV prevention, pap smear tests for cervical screening, or HPV vaccine.

The current results demonstrate that there exist gaps in the knowledge of women on this topic, in particular with regard to the latest data on cancer cervix prevention through HPV testing and vaccination, indicating improper knowledge as regards cervical cancer epidemiology in comparison with different researches performed all nations(16-18). Therefore, Egyptian females may be facing a threatening health trouble of increased cervical cancer. This is most lyowing to the absence of efficient cervical cancer screening plans and vaccination programs too. Additionally, there is low knowledge and attitude among overall populations as regards the HPV vaccine in certain communities(16, 19).

Our findings were in accordance with the results by Alsous et al. who studied the knowledge and awareness as regards HPV infection and its vaccination among females in Arab communities. They found a relatively low knowledge of the strong correlation between HPV and cervical cancer among Arab women (20).

In a Greek study, Farazi et al. proposed that further data requires to be transmitted to Greek females and males on HPV testing and vaccination (21).

In our study, only 48 females (12%) knew about HPV vaccination .The awareness about the vaccine was lower than that reported in preceding researches conducted by Yu et al. and Zhang et al. who recorded that only 19.33% and 25.1%, respectively of all females in their works were aware of HPV before the study (22, 23) Also, it was lower than that mentioned by Marek et al. study which found that 35% of female subjects recorded they had heard about the HPV vaccine before the survey (24) and lower than the results from Bowyer et al. study (73%) (25).

Regional researches conducted in Riyadh (26), Abu Dhabi (27), and Bahrain (28) also recorded comparable figures (34.5%, 29%, and 31.3% respectively).

Our findings suggested lower awareness and poorer knowledge of HPV vaccination among the Egyptian subjects. This might be accompanied byseveral factors, including low education levels, traditional thought, and poor governmental role concerning increasing the knowledge level.

However, the awareness about the vaccine was higher than that reported in preceding researches conducted by Yu et al. and Zhang et al. who recorded that only 19.33% and 25.1%, respectively of all females in their works were aware of HPV before the study (22, 23) and lower than the results from Bowyer et al. study (73%) (25).

In spite of the low level of awareness about the vaccine among our population, the majority of females (278 females; 68.1%) accepted to be vaccinated. This was consistent with studies from other countries (65.7–96%) (29, 30). Nearly half of the females (49.3%) received the Gardasil vaccine which protects against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) (31). Regarding the vaccine schedule, 209 females (51.2%) knew about all schedules.

We found that 130 females refused the vaccination owing to a number of factors. First of all, the cost of vaccine in 104 females (80%). Previous studies have emphasized cost concerns as a main issue impeding the uptake of HPV vaccine (32, 33). In addition, an Australian study demonstrated that 38% of women wouldn't be vaccinated if they needed to pay the charge of vaccination(34). Another study in China demonstrates that only 25.4% of parents accepted a price (23). Unfortunately, the price might be an essential factor to interfere with the HPV vaccination rate if the HPV vaccines are approved in Egypt. Secondly, an absence of confidence in the safety of the vaccine in 46 females (35.4%), reflecting the doubts about vaccine efficiency and safety. This is because when a novel vaccine was approved to be used, subjects became more cautious as regards vaccination.

In a recent Egyptian study, Zakzook et al. disagreed with our findings. They revealed that more than three-quarters of female university students refused the vaccine due to many factors such as it being very expensive, a fraid of taking it, proposing it increases the possibility of cervical cancer, and the risk of HPV infection, besides, they didn't prefer to have too many vaccines and it is inconvenient for them to have three injections within six months (35).

Also, Farsi et al. displayed that less than half of the studied participants were interested in receiving the HPV vaccine (36). Liu et al. revealed that nearly one-quarter of students accepted to take the vaccine (37).

In this work, more than half of the participating females (60.3%) confirmed that they would allow their daughter to get the vaccine while 39.7% refused, suggesting vaccine unsafely in 89 females (54.6%) or because they are against vaccine in 74 females (45.4%). This may be owing to the distrusting issues as regards a novel vaccine and trust in their spouses to not give them sexually transmitted diseases. However, in Egypt, mothers influence decisions, in particular for their young female children; as a result places with a high concentration of mothers such as antenatal classes, markets, and parent-teacher forum meetings could be engaged to enhance HPV awareness.

A systematic review measuring parents' attitudes towards the HPV vaccine for their children demonstrated that the vaccination choice was mainly reliant on the child's age. Some of the comprised researches demonstrated that parents favored not to vaccinate their children if they through them to be very young or sexually inactive, on the other hand parents were keener on vaccination of their children when they were older or sexually active (38).

In a Chinese study by Choi et al., regarding acceptability, 37.6% (34.5–40.8%) of the mothers were willing to have their daughters vaccinated, however, this is linked to the cost of the vaccine (8).

In our study, concerning the effect of vaccines, 68 females (16.6%) believed that vaccines have no impact on daily activity. Among the participating females,23 females (22.1%) confirmed that no side effects of the vaccine

while 41 females (39.4%),38 females (36.5%), one females (0.7%), and one female (0.9%) reported that vaccine causes erythema, pain, induration, and myalgia, respectively. Nearly three-quarters of females (302 females; 74%) did not know about the effect of the vaccine on fertility, while 87 females (21.3%) believed that the vaccine impacts fertility, and 19 females (4.7%) answered no effect of the vaccine on fertility. 26 females (6.3%) reported that the vaccine has an impact on early menopause, in addition, 108 females (26.4%) thought that the vaccine affected promiscuity. However, all participating females believe that our community is appropriate for vaccines.

Systemic review and meta-analysis, evaluating HPV vaccine safety and adverse effects, Gonçalves et al2014. found that pain was the commonest detected adverseevent. Such effects could be owing to a potential related inflammation process. Fatigue has been considered as the most related effect noticed then fever, intestinal manifestations, swelling, and headache (39).

Based on a Japanese study by Ozawa et al2017.,it was suggested that HPV vaccination is associated with the transiently high prevalence of chronic regional pain syndrome, impaired cognition and affection of autonomic functions among vaccinated cases(40).

On the other hand, Schuler et al stated that there is a great concern about vaccine-associated infertility with the HPV vaccine (41). However, a number of studies showed no effect of the HPV vaccine on fertility, concluding that the vaccine is safe even in pregnant females. Besides, some authors stated that if a woman has received an HPV vaccine and is planning to become pregnant, there is no need to postpone pregnancy, as the HPV vaccines are inactive (42, 43).

We observed some relationships between accepting vaccines and different factors. There were statistically significant relations between accepting the vaccine and age ($p= 0.005$), residence ($p= 0.004$), marriage duration ($p= 0.01$), vaginal discharge ($p< 0.001$), and husband age ($p= 0.003$).

In agreement with the current results, Alsous et al found a strong relationship between the acceptance of vaccines and age (20). Also, in other researches, age, education, and residence were demonstrated to be accompanied by HPV awareness (44, 45). Contrary to our results, a Saudi study demonstrated that the acceptance of vaccines is strongly related to marital status (46).

Ebu et al., analysing the causes for a negative attitude towards vaccination, demonstrated that the greatest percentage of unvaccinated subjects agreed with the statement that there was limited dataas regards HPV vaccination. In addition, in the same study, significant associations were demonstrated between age, marital status, education level, and work duration in a health facility with the acceptance of HPV vaccination (47).

Raiz et al. noticed that there was a significant correlation between the participants' age, marital status, education level, and positive attitude as regards cancer cervix screening and prevention. Subjects, who were of the younger age group, were married, and those who had higher education were observed to have a positive attitude than their counterparts. There was no significant relation demonstrated between positive attitude and the socioeconomic status of subjects(18).

This study is strengthened by including a large sample size for analyzing the awareness, knowledge, and acceptability of the HPV/ HPV vaccine in a major sample of Egyptian females. This will help identify specific factors that affect acceptance, and to develop tailored vaccination strategies. In addition, conduction of face-to-face meetings confirmed the inclusion of illiterate subjects and as a result greater cure rates to all questions.

Despite the promising results of the current study, the cross-sectional nature of the study has been considered the main limitation owing to the lacking a control group, which may lead

to some bias regarding the results. In addition, our study was conducted only at Mansoura University Hospitals and wasn't a multi-center study.

Conclusion

Despite the low level of awareness about the vaccine among our population, we reported the potential acceptability of the vaccine. However, the majority of the subjects agreed to vaccination, it might not essentially indicate their true intent to receive it even when the HPV vaccine is recommended and available. This indirectly relates to the lack of knowledge as regards the virus and its correlation with cancer cervix as well as with different malignant tumours.

Additional studies to assure the existing HPV vaccines is required. An organized vaccination program is recommended to increase vaccination coverage and improve the completion of the vaccination schedule, especially among sexually active females .A national HPV awareness campaign must be stratified in Egypt to raise knowledge about the HPV vaccine.

Table 1.Demographic characteristics, medical history, and special habits of the studied females.

	N	%
Age/years Mean ± SD (min-max)	34.77±6.65 (15-40)	
Residence Rural Urban	 54 354	 13.2 86.8
Occupation Housewife Employee Manual worker	 231 127 50	 56.6 31.1 12.3
Marital status Married Divorced	 407 1	 99.8 0.2
Duration of marriage(years) Median (min-max)	12(1-25)	
Number of marriages (two)	1	0.2
Smoking	0	0.0
Abnormal Sexual offense	0	0.0
Vaginal Discharge no vg bleeding offensive yellowish whitish creamy	 231 2 81 94	 56.6 0.5 19.9 23.0
Pain duration intercourse	175	43
Age of husband(years) Mean ± SD (min-max)	40.09±6.98 (25-52)	
Occupation of husband Employee Manual worker	 255 153	 62.5 37.5
Traveling abroad	192	47.1

Smoking	176	43.1
Number of marriage One Two	 402 6	 98.5 1.5
Abnormal sexuality	2	0.5
Genital warts	183	44.9

Table 2. The knowledge about HPV

	N=408	%
What is HPV **Don't know** **Know**	 341 67	 83.5 16.5
HPV cause **Genital warts** **Don't know**	 67 341	 16.5 83.5
HPV spread **Sexual transmitted ,skin content** **Don't know**	 44 364	 10.7 89.3
Having Genital wart	98	24
Think about cervical cancer **Don't know** **I know**	 150 258	 36.8 63.2
Persons can be infected by HPV **Don't know** **Male &Female**	 368 45	 90.1 10.9
HPV related to cancer cervix **Don't know** **Yes**	 371 37	 90.9 9.1
HPV related to other cancer **No** **Yes** **Don't know**	 11 13 384	 2.7 3.3 94
Prevention of HPV **Don't know** **Cervical screening** **Vaccination & cx screening**	 372 16 20	 91.2 3.9 4.9
History of Pap smear test **Don't know** **Yes**	 347 61	 85.1 14.9

Table 3. The Knowledge about HPV vaccine among studied cases.

	N=408	%
Knowledge about HPV vaccine		
Yes	48	12
Don't know	359	88
Accept to be vaccinated after awareness	278	68.1
If No, Why?	**N=130**	
Harm	26	20
Cost	104	80
If Yes, What is type of vaccine after awareness?		
Don't know	304	74.5
Gardasil	106	26
Vaccine schedule		
Don't know	304	74.5
0,2,6 months	106	26
Need for Pap smear screening after Vaccine		
Don't know	304	74.5
Yes	16	2.4
No	96	23.52
vaccine protect against cancer cervix after awareness		
-ve	162	39.7
+ve	246	60.3
Allowing daughter to get vaccine		
No	162	39.7
Yes	246	60.3
if No, Why?	**N=162**	
Not safe	70	43.2
I'm against	92	22.54
Effect of vaccine on daily activities		
Don't know	340	83.3
No disruption	68	16.6
Protection period		
I don't know	374	91.6
>10 years	61	14.9

Table 4.Knowledge about HPV vaccine side effects among studied cases.

	N=408	%
Side effects		
No	23	22.1
Pain	38	36.4
Myalgia	1	0.96
Erythema	41	39.5
Induration	1	0.96
Effect of HPV vaccine on fertility		
No	19	4.7
I don't know	302	74.0
Yes	87	21.3
HPV vaccine on early menopause		
No	60	14.7
I don't know	322	78.9
Yes	26	26.4
Vaccine to promiscuity		
No	40	9.8
I don't know	260	63.7
Yes	108	26.4
system appropriate for vaccine (community)	278	68.1
Regular cervical cancer screening		
Don't' know	318	77.9
yes	90	22

Table 5.The relation between demographic characteristics and vaccine acceptance among studied cases

	Accepting vaccine		Test of significance
	No N=130(31.9%)	**Yes N=278(68.1%)**	
Age/years Mean±SD	33.42±7.16	35.41±6.31	t=2.83 p=0.005*
Residence			
Rural	8(6.2)	46(16.5)	$\square^2$=8.33
Urban	122(93.8)	232(83.5)	P=0.004*
Occupation			
Housewife	82(63.1)	149(53.6)	
Employee	30(23.1)	97(34.9)	$\square^2$=5.77
Manual worker	18(13.8)	32(11.5)	P=0.06
Marital status			
Married	130(100)	277(99.6)	FET=0.469
Divorced	0	1(0.4)	P=1.0
Duration of marriage(years) Median (min-max)	10(1-23)	12(1-25)	Z=2.58 P=0.01*

Number of marriage One Two	 130(100) 0	 277(99.6) 1(0.4)	 FET=0.469 P=1.0
Vaginal Discharge No Vaginal bleeding Offensive yellowish Whitish creamy	 51(39.2) 0 33(25.4) 46(35.4)	 180(64.7) 2(0.7) 48(17.3) 48(17.3)	 MC=26.68 P≤0.001*
Pain duration intercourse	73(56.2)	173(62.2)	$\square^2$=1.37 P=0.242
Age of husband (years) Mean±SD	 38.58±7.61	 40.79±6.58	t=3.01 p=0.003*
Occupation of husband Employee Manual worker	 74(56.9) 56(43.1)	 181(65.1) 97(34.9)	 $\square^2$=2.53 P=0.112
Traveling abroad	65(50.0)	127(45.7)	$\square^2$=0.662 P=0.416
Smoking	61(46.9)	115(41.4)	$\square^2$=1.12 P=0.291
Number of marriage One Two	 130(100) 0	 272(97.8) 6(2.2)	 $\square^2$=2.85 P=0.09
Abnormal sexuality	0	2(0.7)	FET=0.940 P=1.0
Genital warts	54(41.5)	129(46.4)	$\square^2$=0.847 P=0.357

t: Student t-test, FET: Fisher exact test, *statistically significant

Z:mann Whitney U test, MC: Monte Carlo test, $\square^2$=Chi-Square test

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Comparative study between levels of maternal serum Cell Free Fetal DNA and Uric acid in pregnant women with and without Preeclampsia

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Short title: maternal serum cffDNA Vs uric acid in preeclampsia

Abstract

Objectives: In this study, we aimed to compare the value of cell-free fetal DNA (cffDNA) and uric acid in maternal serum as markers for pre-eclampsia and subsequently as possible predictors in the future.

Study Design: This cross-section study including pregnant women attending Cairo University maternity hospital, Cairo, Egypt. This study included 120 patients in two groups; study group and control group with 60 patients each.

Results: The mean level of CffDNA was 19.6 ± 5.4 and 578.9 ± 185.3 mg/dl in the control and preeclampsia patients respectively; p<0.01. The mean level of cell free fetal DNA was significantly higher among primigravida with severe preeclampsia; 743.2 mg/dl compared with 295.3 mg/dl in multiparous women with severe preeclampsia; p<0.01. Similarly, the mean level of cell free fetal DNA was significantly higher among primigravida with mild preeclampsia; 543.3900 mg/dl compared with 372.2464 mg/dl among the multiparous women with mild preeclampsia; p<0.01.

The mean level of uric acid in control group was 2.9 mg/dl compared with 4.7 mg/dl in the preeclampsia group; p<0.01. The mean level of uric acid was significantly higher among primigravida with severe preeclampsia; 749.6 mg/dl compared with 295.3 mg/dl in multiparous women with severe preeclampsia; p<0.01. Similarly, the mean level of uric acid was higher among primigravida with mild preeclampsia; 3.6 mg/dl compared with 3.4 mg/dl among the multiparous women with mild preeclampsia; however, there was no significant difference, p= 0.072.

Conclusion: We found that cffDNA is a better marker of pre-eclampsia than uric acid. Compared with uric acid, cffDNA is more sensitive as it has shown elevated levels with mild pre-eclampsia and more elevations with severe pre-eclampsia. Different age groups did not affect

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the levels of both markers. However, parity seemed to affect Cell-Free Fetal DNA level as it had higher values in primigravida.

Keywords: fetal DNA, cffDNA, uric acid, Preeclampsia.

Introduction

Pre-eclampsia is a disease specific to humans, characterized by hypertension and proteinuria. The disease has a high incidence of 7 % in most populations and it is one of the leading causes of maternal and perinatal morbidity and mortality in developing countries (1,2).

Multiple theories tried to explain why pre-eclampsia happens, yet the exact pathogenesis remains unclear and that explains the difficulty to predict pre-eclampsia. In order to establish a reliable pre-eclampsia predictor from the maternal serum, one should identify first a strong marker (3,4).

In 1997, a new approach of non-invasive prenatal diagnosis appeared when Lo et al. discovered the existence of cell-free fetal DNA (cffDNA) in maternal plasma by detecting Y chromosome-specific DNA sequence in pregnant women bearing male fetuses (5).

Current data suggest that fetal DNA is detectable in virtually all pregnant women. In case of pre-eclampsia, a five-fold elevation of plasma fetal DNA has been reported (6–8). The exact mechanism for such elevation, like the etiology of the disorder itself has not been fully understood.

Another marker/predictor has been suggested for decades, that is Uric acid. The association between elevated serum uric acid and pre-eclampsia was reported for the first time early in the 20th century by Slemmons et al. in 1917 (8). Interest has been renewed over the role of uric acid in the pathogenesis of hypertension, endothelial dysfunction and renal dysfunction, which are all features of pre-eclampsia. Recent studies pointed that uric acid measurement is considered a component in the work up of pregnant women with pre-eclampsia to monitor the severity of the disease and to help management (9–11).

Hence, in this study, we aim to investigate the predictive role of cffDNA and uric acid in preeclampsia.

Materials and methods

This is a case control study including pregnant women attending Cairo University maternity hospital, Cairo, Egypt. This study included 120 patients in two groups; study group and control group with 60 patients each.

A) Study group:

Inclusion criteria:

Singleton, viable pregnancy with no obstetrical or medical complications of pregnancy apart from severe pre-eclampsia (with the presence of any of the following criteria):

1- B/P more than or Equal to 160/110 in 2 separate occasions without history of hypertension prior to pregnancy and not responding to treatment. 2- Urine analysis showed persistent proteinuria of 3+ or 4+. 3- IUGR or oligohydramnios. 4- Placental separation. 5- HELLP Syndrome. 6- Abnormal kidney or liver functions. 7- Eclampsia. 8- Gestational age ≥ 28 weeks.

Exclusion criteria:

1- Any maternal complication found other than Preeclampsia. E.g: diabetes mellitus. 2- Past history of Hypertension. 3- Pregnancy with detected fetal congenital anomalies.

B) Control group:

Inclusion criteria:

1- Singleton, viable pregnancy, 2- No obstetrical or medical complications of pregnancy, 3- Gestational age ≥ 28 weeks, 4- Pregnancy with fetal congenital anomalies will be excluded.

All patients were subjected to history taking, general examination including blood pressure management and fetal ultrasound scanning. Blood and urine samples were collected afterwards for the detection of Albumin in urine, serum Uric acid and Cell Free Fetal DNA. Uricase method was used to determine the level of uric acid. Real time 7500 fast SDS software v. 2.05 (Applied biosystems, Foster City, USA) was used to monitor the cffDNA. It should be noticed that routine investigations were also done.

Statistical Analysis:

All of the statistical indices were done using statistical package: SPSS version 18 and Microsoft Excel 2007. Mean, Median, Mode, Standard Error, Standard Deviation, and Interquartile Range. Maternal peripheral blood samples (3ml of blood) were collected and serum is separated in a plain tube. For uric acid level in serum, uricase method is used.

Results

For better evaluation of the two markers, the study group was subdivided into mild (22 patients, 36.7%) and severe (38 patients, 63.3%) groups. In order to understand the relation of the Cell Free Fetal DNA and Uric acid to the parity of the women of the study, we divided the cases into Primigravida (35 control and 41 pre-eclamptic including 30 severe cases), and Multiparas (25 control and 19 pre-eclamptic including 8 severe cases), **figures 1 and 2.**

CffDNA characteristics: (Table 1)

The mean level of CffDNA was 19.6 ± 5.4 and 578.9 ± 185.3 mg/dl in the control and preeclampsia patients respectively. There was a statistically significant difference between preeclampsia patients compared with the control group; p<0.01. The mean level of cell free fetal DNA was significantly higher among primigravida with severe preeclampsia; 743.2 mg/dl compared with 295.3 mg/dl in multiparous women with severe preeclampsia; p<0.01. Similarly, the mean level of cell free fetal DNA was significantly higher among primigravida with mild preeclampsia; 543.3900 mg/dl compared with 372.2464 mg/dl among the multiparous women with mild preeclampsia; p<0.01.

	CffDNA Characteristics among different groups		
	Parameter	**Mean ± SD**	**p-value**
	Control (n=60)	19.6 ± 5.4	<0.01
Pre-eclampsia severity	**Pre-eclampsia patients (n=60)**	578.9 ± 185.3	
	Mild preeclampsia subgroup (n=22)	457.8 ± 101.2	
	Severe preeclampsia subgroup (n=38)	648.9 ± 187.5	
Gravidity and preeclampsia levels	**Primigravida with Severe preeclampsia (n=30)**	743.2 ± 34.3	<0.01
	Multi para with Severe preeclampsia (n=8)	295.3 ± 3.3	
	Primigravida with mild preeclampsia (n=11)	543.4 ± 68.8	<0.01
	Multi para with mild preeclampsia (n=11)	372.2 ± 25.4	

Table 1: Shows characteristics of CffDNA among different groups.

Uric acid characteristics: (Table 2)

The mean level of uric acid in control group was 2.9 mg/dl compared with 4.7 mg/dl in the preeclampsia group. There was a statistically significant difference between preeclampsia patients compared with the control group; p<0.01. The mean level of uric acid was significantly higher among primigravida with severe preeclampsia; 749.6 mg/dl compared with 295.3 mg/dl in multiparous women with severe preeclampsia; p<0.01. Similarly, the mean level of uric acid was higher among primigravida with mild preeclampsia; 3.6 mg/dl compared with 3.4 mg/dl among the multiparous women with mild preeclampsia; however, there was no significant difference, p= 0.072.

	Uric acid Characteristics among different groups		
	Parameter	**Mean ± SD**	**p-value**
	Control group (n= 54)	2.9 ± 0.39	<0.01
Pre-eclampsia severity	**Pre-eclampsia patients (n=60)**	4.7 ± 1.2	
	Mild preeclampsia subgroup (n=22)	3.5 ± 0.5	
	Severe preeclampsia subgroup (n=38)	5.5 ± 1	
Gravidity and preeclampsia levels	**Primigravida with Severe preeclampsia (n=30)**	5.7± 0.92	<0.01
	Multi para with Severe preeclampsia (n=8)	4.7 ± 0.83	
	Primigravida with mild preeclampsia (n=11)	3.6 ± 0.5	0.072
	Multi para with mild preeclampsia (n=11)	3.4 ± 0.5	

Table 2: Shows characteristics of uric acid among different groups.

Discussion

Studying the control group showed a level of Cell Free Fetal DNA with a mean of 22.28 Genome equivalent/mL which is consisting with most of other studies as shown by Lo et al. (5) and Smid et al (12) with their mean levels of 76 and 24 Genome equivalent/mL respectively.

Same studies have shown mean levels of Cell Free Fetal DNA of 381 and 256 Genome equivalent/mL respectively denoting 6- and 12-folds increase, compared to our study having a mean of mild cases of 412 and 500 Genome equivalent/mL in severe cases which is showing an increase of 17 and 20-fold approximately. Our study has shown higher levels than those 2 studies yet lower than other studies as Swinkels at al (13) with a mean of 781 Genome equivalent/mL and 1599 Genome equivalent/mL by Zhong et al (8). But it should be clear that these two studies showed an increase of 6 to 7 folds of the mean level of Cell Free Fetal DNA in cases of pre-eclampsia comparing it with its equivalent in the control group, taking into consideration that some cases in these studies showed an increased level of Cell Free Fetal DNA by more than 25 folds compared to the level of Cell Free Fetal DNA of the same patient before and after the onset of pre-eclampsia.

Due to this great variation in the results using the Genome equivalent/mL as a unit for our research, we decided to focus on the

proportional increase in the level of the Cell Free Fetal DNA instead of its absolute value. It is important to denote that all of the studies showed an increase of the mean of the Cell Free Fetal DNA between the control and the study group of 5 to 20 folds (6–8).

The normal Uric acid level with pregnancy is still controversial. This is because it differs throughout pregnancy, being very low in its beginning (2.8 mg/Dl) and reaching 3.6 mg/dL in late pregnancy (14). Our study has shown results consistent with these numbers, having a level of uric acid of 2.9 mg/dL in the control cases, rising to 3.5 and 5.1 mg/dL in mild and severe cases of pre-eclampsia respectively.

There are no studies determining a specific value above which we can precise that Uric acid is abnormally elevated. That is why Uric acid level has prognostic value not a diagnostic one. Although mean serum uric acid values are elevated in women with preeclampsia, its clinical utility of identifying pre-eclampsia seems to be limited, however, a serum uric acid level of ≥5.5 mg/dL could identify women with preeclampsia (15).

For better understanding of our results, we decided to clarify if the levels of Cell Free Fetal DNA and Uric acid are influenced by other factors as parity.

An interesting finding was found in the interpretation of the levels of Cell Free Fetal DNA. We noted that the mean of mild and severe cases of primigravidas with pre-eclampsia was higher that its correspondent in multiparous women, though the mean level of Cell Free Fetal DNA in control multiparous is exceeding that of primigravidas in the control group (25 and 15 Genome equivalent/mL respectively). This should be further evaluated as most studies denoted that the fetal DNA is cleared very rapidly from maternal plasma, with a half-life in minutes (5). These results suggest that maternal plasma DNA analysis would not be complicated by fetal DNA persistence from a prior gestation, making false-positive results unlikely. Apart from the diagnostic importance of this observation, these data also raised questions with regard to the possible organ system(s) that is (are) responsible for the rapid clearance of circulating fetal DNA. Recent intriguing results suggest that some circulating fetal DNA may pass through the glomerulus and then be detectable in maternal urine (16). The incomplete understanding of this clearance gives rise to the importance of the re-evaluation of this topic.

No marked differences were noted between levels of Uric acid in primigravidas versus multiparous women in any of our 3 groups of patients.

It is clear that Uric acid level is not influenced by the factors of maternal age and parity, as most studies noted, it is surely influenced by the duration of pregnancy (14,17) which is not included in our studies as all of our cases were in their third trimester of pregnancy. On the other hand, it is not clear whether Cell Free Fetal DNA could be influenced by maternal age and parity as specific patterns were proven statistically in our study with no backup medical explanation raising the importance of more studies in this field.

Conclusion

To sum up our results, we concluded that Cell Free Fetal DNA is a better marker of pre-eclampsia than Uric acid. It is more sensitive as it rises with mild preeclampsia having even higher levels with severe preeclampsia. The uric acid shows no rise with mild preeclampsia. Different age groups did not affect the levels of both markers. Parity seems to have an effect on Cell Free Fetal DNA level as it has higher values in primigravida which needs further future evaluation.

Study Approval: this study protocol was reviewed and approved by the Fayoum university ethical committee, Fayoum, Egypt.

Consent to participate: Informed consent was obtained from all patients according to the ethical committee of Fayoum University.

Conflict of interest Statement: All authors declare that there are no conflicts of interest

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Data Availability:

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from B. H.M badranhm@yahoo.co.uk upon reasonable request.

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Tables Legends:

Table 1: Shows characteristics of CffDNA among different groups.

Table 2: Shows characteristics of uric acid among different groups.

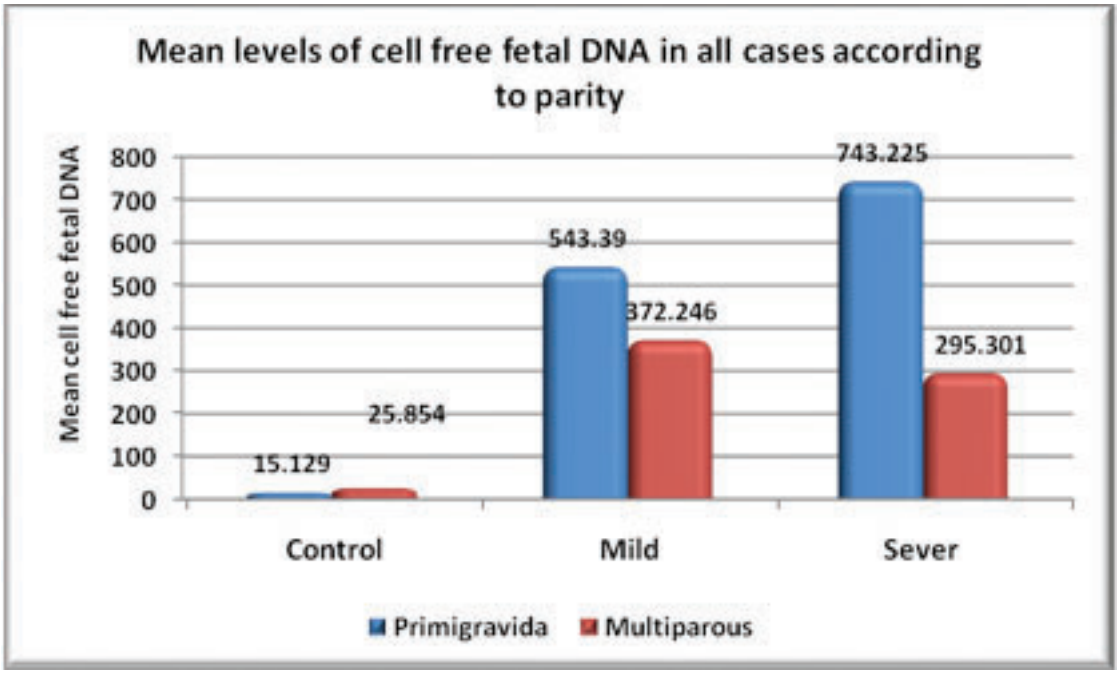

Figure 1 shows mean levels of cell free fetal DNA in all cases according to parity

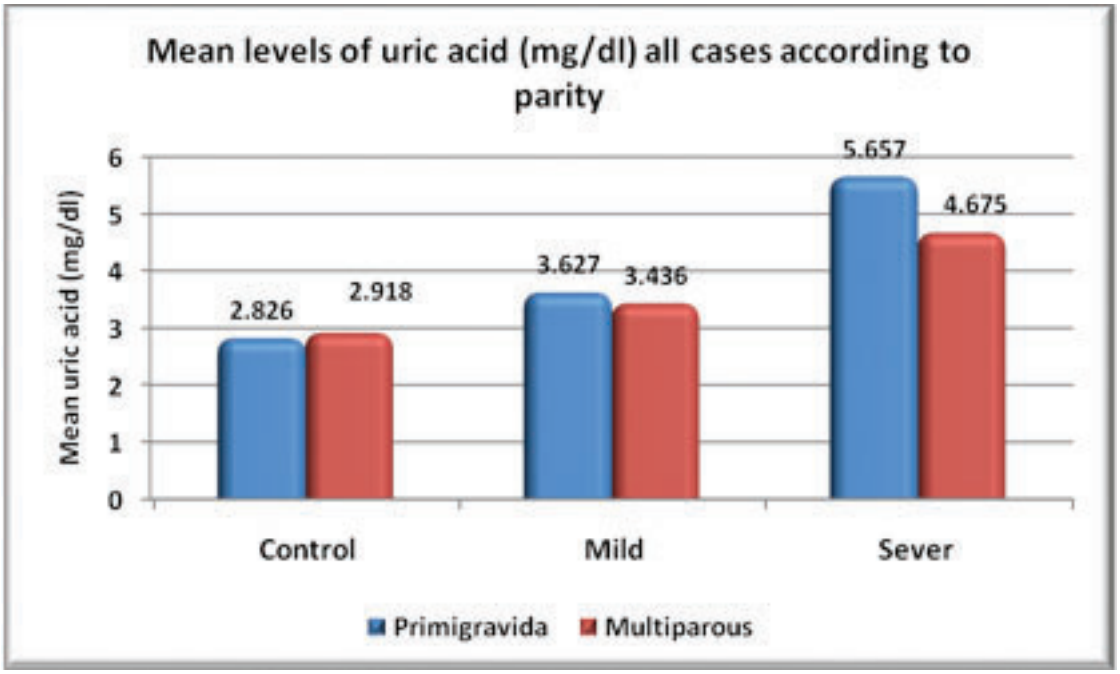

Figure 2 shows mean levels of uric acid (mg/dL) in all cases according to parity

Atypical presentation of placenta accreta spectrum: a case series of spontaneous hemoperitoneum in the third trimester

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Abstract

Background: The indications of emergent termination of pregnancy in placenta accreta spectrum (PAS) include vaginal bleeding, true labor pain or premature rupture of membranes (PROM). Some cases may have atypical presentation as a result of presence of intra-abdominal bleeding rather than vaginal bleeding. Delayed diagnosis of these cases leads to catastrophic complications to both mother and fetus.

Patients and Methods: This was a case series of patients with PAS who underwent emergent delivery due to atypical presentation by hemoperitoneum with absence of any of the classic symptoms that indicate urgent delivery, including vaginal bleeding, true labor pain or PROM. Hemoperitoneum was diagnosed by finding free fluid in the abdomen or pelvis by ultrasonography.

Results: Seven patients were included in this study. The atypical presentation included: 1) shortness of breath; 2) chest tightness; 3) vague abdominal pain and discomfort; 4) shoulder pain; 5) repeated vomiting and sweating; 6) syncope; and 7) cardiac arrest. Laparotomy was performed for all patients and variable amounts of intra-abdominal bleeding were found. The cause of bleeding was either rupture of surface vessel of uterovesical neovascularity or minute focal penetration of the placenta. Cesarean hysterectomy was performed in 5 patients while resection of lower uterine segment with uterine preservation was performed in 2 patients. The newborn was living in 6 patients and dead in one patient who had presented by cardiac arrest.

Conclusion: Any patient with PAS who have atypical presentation must be put under observation with close monitoring of the general condition for signs of hypovolemia, and ultrasonography should be performed by expert sonographer for early detection of hemoperitoneum. Confirmation of the diagnosis indicates emergent laparotomy, better via longitudinal incision, considering cesarean hysterectomy as a first line treatment.

Keywords: PAS, Placenta previa, Placenta accreta, Hemoperitoneum.

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Introduction

There was a dramatic increase in the incidence of placenta accreta spectrum (PAS) over the past several decades as a direct result of increased rates of cesarean delivery (CD), with reported incidence of 1 in 533 deliveries in 2002 (1, 2), compared to 1 in 4000 deliveries in 1970 (3). Massive peripartum bleeding is the real danger and at the same time, the main challenge associated with this problem, as it can lead to multisystem organ failure, disseminated intravascular coagulopathy (DIC), need for intensive care unit (ICU) admission, hysterectomy and even maternal mortality (2, 4-7).

Multiple retrospective cohort studies of PAS disorders have documented that the maternal morbidity was reduced when care was provided in centers of excellence. These centers should provide a dedicated management plan through a multidisciplinary team (MDT) that is experienced in management of such cases (8-11). The components of the team cooperate in order to improve the outcome through providing accurate prenatal diagnosis, dealing with complex pelvic surgery, managing all anesthetic considerations regarding these patients including establishing safe massive transfusion protocols if needed, solving transfusion problems, and finally caring of the patient during postpartum period and managing any complications during this critical period (12).

It was found that emergent delivery of patients with PAS was associated with poorer outcomes and increased maternal morbidity when compared with planned scheduled delivery even when performed in specialized centers by well-trained MDT (13). This had led to controversy about the optimal timing of delivery in PAS, as it should balance the maternal risks of emergent delivery against the neonatal complications of prematurity. The suggested time for delivery is between 34 and 36 weeks of gestation with consideration of earlier delivery in the presence of recurrent attacks of vaginal bleeding, uterine contractions and premature rupture of membranes (PROM) (12).

Although applying these guidelines had led to reduction in emergent deliveries in PAS, there are still some cases in which the diagnosis of the presence of emergent situation indicating delivery may be difficult and not straightforward due to presence of a typical presentation making these cases easily missed with catastrophic maternal and neonatal complications. Therefore, we aimed in this study to highlight the importance of suspicion, early detection and management of cases of PAS presented with atypical clinical picture.

Patients and Methods

This was a case series of patients with PAS who were presented during the period from September 2018 through August 2023 in Mansoura University Hospital (MUH), Egypt. The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. R.23.07.2274. R1). The main inclusion criterion was women with PAS who underwent emergent delivery due to atypical presentation by hemoperitoneum with absence of any of the classic symptoms that indicate urgent delivery, including vagina bleeding, true labor pain or PROM. The diagnosis of PAS was made by presence of signs of invasive placentation by ultrasonography in the form of intraplacental lakes, loss of retroplacental hypoechoic line, myometrial thinning, and uterovesical hypervascularity. Hemoperitoneum was diagnosed by finding free fluid in the abdomen or pelvis by ultrasonography.

Results

Seven patients were included in this study. Table 1 presents the demographic and clinical characteristics of the patients. All patients had history of at least one prior CD. Three patients were presented in emergency unite

while the other 4 patients were admitted from the outpatient clinic for elective delivery, but the emergency presentation occurred in the inpatient department. The clinical presentation of hemoperitoneum included: 1) shortness of breath; 2) chest tightness; 3) vague abdominal pain and discomfort; 4) shoulder pain; 5) repeated vomiting and sweating; 6) syncope; and 7) cardiac arrest. All patients presented in the third trimester (32-37 weeks of gestation). The fetus was living in 6 patients before delivery with no signs of fetal compromise. The fetus was dead in the seventh case that arrived to hospital with cardiac arrest. Also, the uterine wall appeared intact with no evident hole as evaluated by ultrasonography just before delivery.

The operative and postoperative characteristics of the patients were displayed in table 2. Longitudinal abdominal incision was performed in 6 patients and transverse incision was performed in only one patient. Cesarean hysterectomy was performed in 5 patients while resection of the lower uterine segment (LUS) and uterine preservation was performed in 2 patients. All patients needed transfusion of variable amounts of packed red blood cells (RBCs) and fresh frozen plasma (FFP). Only 2 neonates required admission to neonatal care unite (NCU) due to premature delivery at 32-33 weeks and low birth weight below 2500 gm.

Table 1. Demographic and clinical characteristics of the 7 patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	30.12	31.37	26.75	25.98	30.58	29.73	25.16
Height (cm)	162	164	164	167	166	168	165
Weight (kg)	68	66	70	92	79	102	72
BMI (kg/m^2)	25.91	24.54	26.03	32.99	28.67	36.14	26.45
Gravidity	4	5	2	4	5	3	4
Parity	2	4	1	3	3	2	2
Prior cesarean delivery	2	4	1	3	3	2	2
Prior vaginal delivery	0	0	0	0	0	0	0
Prior miscarriage	1	0	0	0	1	0	1
Underwent MRI	No	Yes	Yes	No	No	Yes	No
Site of presentation	Inpatient department	Inpatient department	Inpatient department	Emergency unit	Emergency unit	Inpatient department	Emergency unit
Clinical presentation	Shortness of breath and syncope	Chest tightness and shortness of breath	Shortness of breath and syncope	Vague abdominal pain and discomfort	Chest tightness, shortness of breath and shoulder pain	Repeated vomiting and sweating	Cardiac arrest
Gestational age at delivery (weeks)	32.14	37.71	32.71	35.71	37.14	36.14	32.14

Table 2. Operative and postoperative characteristics of the 7 patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Abdominal incision	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Longitudinal	Transverse	Longitudinal
Operative procedure	Cesarean hysterectomy	Cesarean hysterectomy	Cesarean hysterectomy	Resection of LUS and uterine preservation	Resection of LUS and uterine preservation	Cesarean hysterectomy	Cesarean hysterectomy
Intraoperative transfusion							
Packed RBCs (units)	8	7	9	3	6	6	10
FFP (units)	8	7	9	2	6	6	10
Intraoperative complications	Bladder injury	No	No	No	No	No	Bladder injury and DIC
Postoperative packed RBCs transfusion (units)	0	0	0	0	2	2	5
Neonatal weight (gm)	2100	3200	1800	2500	3100	3000	2000
NICU admission	Yes	No	Yes	No	No	No	IUFD

Discussion

The PAS usually manifests itself by vaginal bleeding while the occurrence of intra-abdominal bleeding is an unusual finding in PAS patients leading to delayed diagnosis of such life threatening condition. Deficiency of decidua basalis is the hallmark pathologic finding present in PAS which gives access to extravillous trophoblast to invade larger vessels beyond the junctional zone. The presence of hypervascularity at placental bed observed by prenatal imaging and at time of delivery is suggestive of presence of neovascularization around the scar area in invasive placentation (14).

This intra-abdominal bleeding that occurs with invasive placentation may result from spontaneous rupture of a surface vessel of this neovascularity or minute focal penetration of the placenta through the markedly thinned hypervascular uterine serosa over an area of few millimeters of the LUS. The rate of accumulation of blood is variable and may be rapid leading to early manifestations of hypovolemic shock or it may be gradual, and with this later condition, the patient may be in a stable general condition until late in the disease (mimicking the subacute disturbed ectopic pregnancy), making another difficulty in the diagnosis.

The atypical presentation of our patients was in the form of chest tightness, difficulty in breathing, vague abdominal pain, repeated vomiting, sweating, shoulder pain syncopal attack and cardiac arrest. In all patients, the diagnosis was made by presence of free fluid in the abdomen, especially in the hepatorenal and lienorenal gutters by transabdominal sonography or in Douglas

Pouch by transvaginal sonography (Figure 1). The seventh case had cardiac arrest once arrived to the hospital that was reversed after cardiopulmonary resuscitation and there was massive hemoperitoneum.

At time of presentation, there was no obvious abnormality in fetal heart beat pattern, and fetal movements were good in 6 patients and in the seventh patient who presented after cardiac arrest, the fetus was dead. Also, there was no gapping of the myometrium when assessed by ultrasonography.

The gestational age at occurrence of this condition was variable between 32 and 37 weeks of gestation which highlights the importance of presence of high index of suspicion when dealing with PAS patients even at earlier gestational ages. Also, the antenatal follow up was unremarkable in all patients except in one patient (patient number 3) who had a diagnosis of cesarean scar pregnancy in the first trimester and this patient had history of only one prior CD. After counselling, the patient decided to continue pregnancy despite the risk. Early hospitalization since 28 weeks of gestation was done and ultrasonography in the third trimester revealed marked thinning of the myometrium and placental bulge (Figure 2).

We have reviewed several case reports in literature of uterine rupture in PAS (15-19). The data of these cases are inconsistent as some of them were not be directly related to pathophysiology of PAS. Also, in our opinion, we think that the use of term of rupture uterus in our patients may be misleading. This term is used frequently by obstetricians to describe complete loss of the integrity of the uterine wall. At time of diagnosis of rupture uterus, the fetus is usually dead or severely compromised and dies within very short time. Also, the fetus with the amniotic sac may be present outside the uterus.

In our patients, as described earlier, there was either rupture of surface vessel or minute focal penetration of the placenta (Figures 3 and 4) which is a unique complication of invasive placentation. The overall integrity of the uterus was not lost with the fetus and placenta remained intrauterine. In one of our patients, we had about 3 hours between the time of diagnosis and the laparotomy as this case was Rh negative and there was no available blood, and despite this, the fetus was born living with no obvious hypoxemia. Only in the last patient, the fetus was dead because the mother had cardiac arrest.

In all of our patients, laparotomy was done depending on the presence of free fluid by ultrasonography and in all patients, variable amounts of hemoperitoneum were found (about 3 liters in the most critical one). We think that there is no role for expectant management because we found the bleeding site to be active in all cases. Also, the theoretical risk of presence of non-obstetric source of bleeding, like rupture spleen, must not delay the decision of laparotomy.

We had preferred longitudinal incision for opening the abdomen except in one patient (patient number 6) who was morbidly obese (BMI was 36.14 kg/m2) and in who, transverse incision was performed. Longitudinal incisions have many advantages. First, they are less time consuming and provide rapid access to the abdomen than transverse incisions especially all these patients had one or more prior CD with adhesion formation. Second, longitudinal incisions give access to fundal hysterotomy avoiding the placenta and minimizing the blood loss. Third, they are more exploratory than transverse incisions allowing better gain to retroperitoneal space if needed and also evacuation of all collected blood.

Cesarean hysterectomy was performed in 5 patients and resection of LUS with uterine preservation was performed in 2 patients. In hemodynamically unstable patient, performing cesarean hysterectomy is the safest method and should be done without hesitation. Also, the presence of more severe forms of PAS (Federation of Gynecology and Obstetrics grades 3a diffuse disease, 3b, and 3c) (20) indicates radical treatment.

The problem is that performing cesarean

hysterectomy is very difficult and needs much experience in placenta percreta. The condition is more dramatic and challenging in such cases as the presence of hemoperitoneum may obscure the surgical field and makes dissection in correct planes difficult. Also, the patient instability adds more tension to the surgeon. The most experienced personnel should deal with such cases and follow the well-known rules of peripartum cesarean hysterectomy as delayed bladder dissection and the start by clamping and cutting the upper pedicles first (21). The presence of huge amount of intra-abdominal bleeding should not be frustrating and the surgeon should keep in mind that all active bleeding will be controlled after bilateral clamping of uterine vessels and should keep stable and active until reaching this step. In case of sever hemodynamic instability, surgeon can apply manual aortic compression (22) and we had used this maneuver by the assistant in patient number 3 while performing the hysterectomy.

Hiramatsu described a case of placenta percreta that was presented with massive hemoperitoneum due to rupture surface vessel. Hemostasis was done at bleeding site after delivery of the fetus with delayed hysterectomy after 3 days with interventional radiologic intervention (23). Five of our patients were discharged after a period of 7 to 10 days in stable general condition. Patient number 1 was discharged after 21 days due to presence of bladder injury that was repaired by urologist and the integrity of bladder was confirmed with no fistula before discharge. Patient number 7 had presented with cardiac arrest that was reversed after cardiopulmonary resuscitation had severe intra-operative DIC and had cardiac arrest again in ICU and died after 12 hours of delivery.

Conclusion

Patients with PAS may present with atypical manifestations due to presence of intra-abdominal bleeding rather than vaginal bleeding. These include chest tightness, difficulty in breathing, repeated vomiting, sweating, vague abdominal pain, shoulder pain, syncope, and even cardiac arrest. Any patient with PAS having any of these manifestations must be put under observation with monitoring of the general condition for signs of hypovolemia and ultrasonography should be performed by expert sonographer for early detection of free fluid in abdomen or pelvis. Confirmation of diagnosis of hemoperitoneum indicates emergent laparotomy better through longitudinal incision and cesarean hysterectomy should be the first line of treatment.

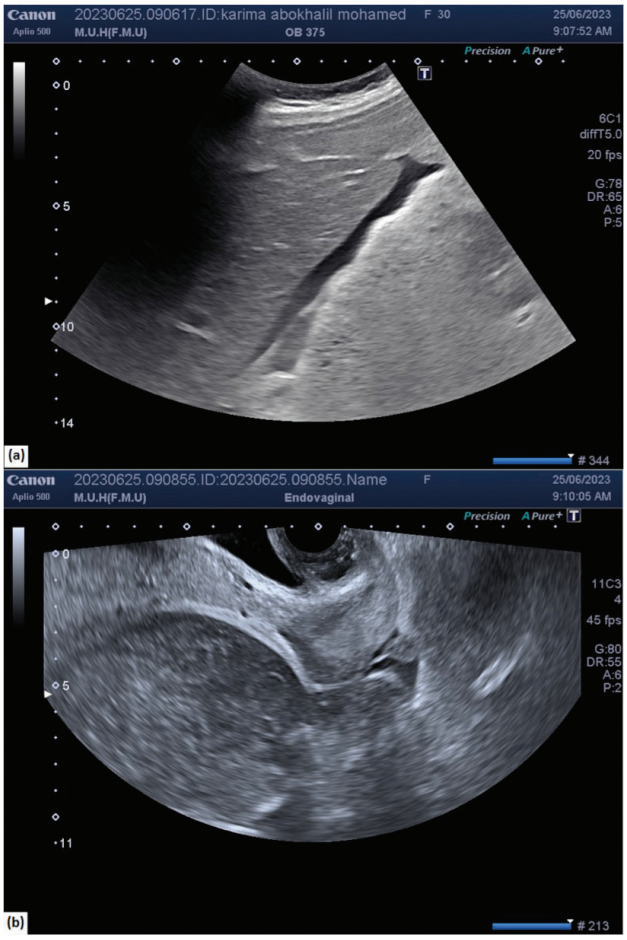

Figure 1. Ultrasonographic diagnosis of hemoperitoneum in patient number 5 through presence of free fluid in hepatorenal gutter by transabdominal sonography (a) and presence of free fluid in Douglas Pouch by transvaginal sonography (b).

Figure 2. Marked myometrial thinning and placental bulge by ultrasonography in third trimester in patient number 3.

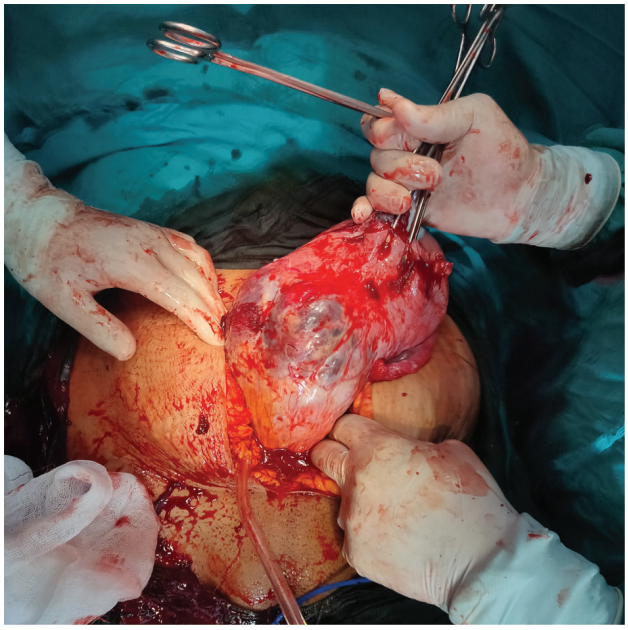

Figure 3. Intraoperative photo of patient number 5 showing placenta previa percreta with the cause of hemoperitoneum (rupture of surface vessel over placental penetration area).

Figure 4. Cesarean hysterectomy specimen of patient number 3 that had intraoperative massive hemoperitoneum due to focal placental penetration.

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Conflicts of Interest

The authors declare that they have no competing interests.

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Violence and Female Sexual Dysfunction in Infertile Women

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Abstract

Background: In our eastern society, having children is a social responsibility for couples, thus, infertility is a significant life stressor that negatively impacts the couple's life. The relationship between both sexuality& violence and infertility is a topic of great significance. However, little research had opened that gate and there is paucity of published data about infertile female sexual dysfunction and partner violence against Egyptian females.

Objective: To evaluate the prevalence of domestic violence and sexual dysfunction among the infertile women and their fertile counterparts.

Subjects and methods: This study was a case-control study that was conducted 205 infertile cases and 205 fertile control counterparts. The Arabic validated version of NorVold Domestic Abuse Questionnaire (NORAQ) was used to assess four categories of abuse: emotional, physical, and sexual, violence. Moreover, Arabic translated version of Female Sexual Functioning Index (FSFI) that comprised six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) was utilized to evaluate the female sexual dysfunction of the enrolled cases.

Results: Regarding NorVold Domestic Abuse Questionnaire (NORAQ) analysis, results showed that regarding the emotional violence, there was non-statistically significant difference between the percentage of cases who reported emotional violence the infertile cases (42.0%) and controls (40.5%). Regarding physical violence, 30.7% of the infertile cases in the current research reported that they had a physical violence compared to only 15.6% in the fertile controls ($P<0.001$). Regarding sexual violence it was the least represented in our work (21.5% and 14.6% in the infertile and fertile controls respectively) ($P=0.07$). As regard analysis of FSFI score, it was found that all its components; (Libido (desire), Sexual arousal, Lubrication, Orgasm, Satisfaction and Pain) were all significantly lower among infertile group ($p<0.001$) and also the total score was significantly lower among infertile group ($p<0.001$).Moreover, the univariate linear regression analysis reveals that BMI, frequency of emotional and physical violence were significant predictors

for FSFI total score, while in the multivariate linear regression only frequency of physical violence was significant predictors for it.

Conclusion: Infertile women are more likely to be exposed to physical, sexual and psychological violence. Psychological violence was found to be the most common type of reported violence against infertile women followed by physical and sexual violence. Moreover the infertile women had a significantly higher prevalence of sexual dysfunctions than their fertile counterparts.

Keywords: Infertility, Violence, Sexual Dysfunction.

Introduction

Millions of couples across the world suffer from Infertility[1]. In other words, it is estimated that approximately one in seven couples in the developed countries and one in four couples in the developing countries are subfertile[2].

In Egypt, infertility is a major health matter distressing about 12% to 25% of couples with a subsequent great psychosocial impact [3].

As having children is a social task of the family, failure in this concern negatively affects the all aspects of couple's life due to the excessive stress they face specially the wife as she feel more accountable for infertility[4].

The sub-fertile couple is more predisposed to stress, depression, and anxiety that would adversely affect the marital satisfaction in their sexual health. In addition, the medical procedures used for investigation or treatment of subfertility may create a sense of anxiety and thus influence sexual functioning [5]. The association between sexuality and infertility is an issue of critical significance [6].

Intimated partner violence (IPV) occurs at variable rates and by the World Health Organization (WHO) it is reported by 37% in the Arab world. Yet, it is still underestimated in Egypt [7].

Moreover, it's reported that infertility is among of the factors that lies behind all forms of domestic violence anti women. Therefore, it is crucial to determine infertility-induced psychosocial and sexual consequences distressing female life [8].

The present study aimed to evaluate the prevalence of domestic violence and sexual dysfunction among the infertile females versus their fertile counterparts.

Subjects and Methods

This study was a case-control study that was conducted at the Department of Obstetrics and Gynecology, Benha University Hospitals and Private Infertility Clinic during the period of study that extended from December 2021 till May 2023. Study groups were female aged 18–45 years with continuous marital relationship and complaining of infertility either primary or secondary and matched control group of fertile women who attended the outpatient clinics for any concern. Infertile couples with male factor infertility and women who refused to participate in our research were excluded from the study.

The study protocol was approved by the ethical committee of Benha University Hospitals, Benha University. An informed written consent was obtained from all patients participating in this.

Sample size:

The sample size was be calculated using EPI-Info (Epidemiological information package) software version 7.2.4, C.I (Confidence Interval) 95%, power of the study 90%, ratio of cases to control was 1:1, Hypothetical proportion of controls with exposure was 25% while in cases was 40% (9). The sample size was 205 in each group (fertile and infertile groups).

Demographic parameters were gathered in details. Also, Partners' data included age, level of education, occupation and socioeconomic level. Infertility data: type

(primary or secondary) and duration of infertility were evaluated. Any clinical data about infertility cause was gathered.

Then, women were asked to complete the Arabic validated version of NorVold Domestic Abuse Questionnaire (NORAQ) that was described by ***Haddad et al***., [10] to assess four categories of abuse: emotional, physical, sexual, in addition to violence in the healthcare system, the last one being excluded in the current research. Validation was done to guarantee that the questions were reliably sent to women with the intended meaning they were formulated for. The entire types were classified into three categories of severity (mild, moderate, and severe) except for sexual abuse that was classified into four categories: mild abuse (absence of genital contact), mild (emotional or sexual humiliation), moderate abuse (genital contact), and severe abuse (penetration) (Arabic version appendix1).

Moreover, Female sexual dysfunction evaluation was completed via Arabic translated version of Female Sexual Functioning Index (FSFI) ***Anis et al.***, [11] that comprised six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) with score ranged of 0 (or 1) to 5 for each parameter so the entire FSFI score ranged from 2 to 36 **(Box1)**: . Every single question in the FSFI questionnaire was explained to cases to be answered in an appropriate and silent private environment and they were asked to feel free to explain about the meaning of some words. Higher scores indicate a better sexual functioning with a cut off 26.55 or less is indicative of sexual dysfunction according to a validation study (Arabic version appendix1).

All the answers for both questionnaires were collected and revised to make sure that they were complete. The full scale score is obtained by adding the six domain scores to obtain the full scale score.

Statistical analysis

The data was collected, reviewed, coded and entered into an excel sheet. Data will be analyzed by using SPSS software. Des**s at w**

NA: Not applicable. ^Independent t-test. #C

Table (6) showed that: Cases with menstrual abnormalities and postmenstrual spotting had significantly higher nich depth.

Box (1): Female Sexual Function Index domain scores and full scale score (12).

Domain	Item Number	Score range	Factor	Minimum score	Maximum score
Desire	1, 2	1-5	0.6	1.2	6.0
Arousal	3, 4, 5, 6	0-5	0.3	0	6.0
Lubrication	7,8, 9,10	0-5	0.3	0	6.0
Orgasm	11,12, 13	0-5	0.4	0	6.0
Satisfaction	14,15, 16	0 or 1-5*	0.4	0.8	6.0
Pain	17,18, 19	0-5	0.4	0	6.0
	Full scale score			2.0	36.0

Statistical analysis

Analysis of data as conducted using SPSS (statistical program for social science version 23) software (Spss Inc, Chicago, ILL Company). Quantitative data were statistically represented in terms of mean ± standard deviation (± SD) while categorical data were represented as frequency and percentage. Comparison of quantitative data was done using (Mann Whitney U) test for independent samples while categorical data were compared using (Chi squared test) or (Fisher exact test) when appropriate. A probability value (p value) > 0.05 was considered statistically insignificant, a probability value (p value) < 0.05 was considered statistically significant & a probability value (p value) < 0.001 was considered statistically highly significant.

Results

Regarding demographic characteristics of the studied 205 infertile cases and 205 fertile control counterparts, results of the current work revealed that there was non-statistically significant difference between the infertile and control groups regarding age, marriage years, residence, female genital mutilation, educational level, employment and husband education. However BMI was significantly higher among the infertile group as the mean BMI of the infertile ladies was 27.33±3.11 kg/m2 versus 24.87±3.69 kg/m2 in their fertile peers (P<0.001). Husband age was statistically significant higher among the control group (P<0.001) and the percentage of the unemployed husbands was significantly higher among the infertile group (25.9%) than the control group (16.6%) (P=0.02) (Table 1).

Regarding the infertility data, the mean duration of infertility was 4.13 ± 2.25 years and 151 (73.7%) of participants had Primary infertility while 54 (26.3%) had secondary infertility in the infertile group (Table 1).

Regarding NorVold Domestic Abuse Questionnaire (NORAQ) analysis, results showed that regarding the emotional violence, there was non-statistically significant difference between the percentage of cases who reported emotional violence the infertile cases (42.0%) and controls 40.5%. However, the frequency of emotional violence occurrence was statistically significant higher among infertile group (the median was higher than that in the fertile peers). Mild emotional violence was the most prevalent grade of violence in nearly one fifth (20%) of the population "fertile and infertile were equal" (Table 2).

Regarding physical violence, 30.7% of the infertile cases in the current research reported that they had a physical violence compared to only 15.6% in the fertile controls (P<0.001) and there was statistically significant difference between infertile and control groups regarding occurrence, frequency and grades of physical violence as they were higher among infertile group (Table 2).

Regarding sexual violence it was the least represented in our work as only 21.5% of the infertile cases in our research reported that they had a sexual violence compared to only 14.6% in the fertile controls and the difference was non-statistically significant (P=0.07). Mild abuse, no genital contact was the most reported complain in this category of violence by 11.6% of the infertile cases versus 8.3% by controls but without a statistical significance (Table 2).

As regard analysis of FSFI score, it was found that all its components; (Libido (desire), Sexual arousal, Lubrication, Orgasm, Satisfaction and Pain) were all significantly lower among infertile group (p<0.001) and also the total score was significantly lower among infertile group (p<0.001) (Table 3).

Moreover, the univariate linear regression analysis reveals that BMI, frequency of emotional and physical violence were significant predictors for FSFI total score, while in the multivariate linear regression

only frequency of physical violence was significant predictors for it (Table 4).

Discussion

Regarding demographic characteristics of the studied 205 infertile females and 205 fertile counterparts groups, the elected healthy fertile women were age-matched with the study group and nearly the same socio-demographics in terms of residence and educational level to exclude environmental and age effect on their sexual life. Moreover, marriage years, educational level, employment and husband education were comparable among both studied groups. However BMI was significantly higher among the infertile group as the mean BMI of the infertile ladies was 27.33±3.11 kg/m2 versus 24.87±3.69 kg/m2 in their fertile peers (P<0.001). Husband age was statistically significant higher among the control group (P<0.001) and the percentage of the unemployed husbands was significantly higher among the infertile group (25.9%) than the control group (16.6%) (P=0.02).

Regarding NorVold Domestic Abuse Questionnaire (NORAQ), there was non-statistically significant difference between the infertile and control groups regarding occurrence of emotional violence and its grades however frequency of it was statistically significant higher among infertile group. Regarding physical violence, there was statistically significant difference between infertile and control groups regarding occurrence, frequency and grades of physical violence as they were all higher among infertile group. As regard sexual violence, the occurrence, frequency and grades of sexual violence were higher among infertile group but there was non-statistically significant difference between the infertile and control groups.

These results agreed with Egyptian work conducted by Ghoneim et al., [7] who reported that, 50.98% of their infertile patients were subjected to violence, although difference in violence exposure was not statistically significant in comparison to the fertile ones with mild emotional abuse was predominating (35.29%) like our findings followed by mild physical abuse in 19.61%. Moreover, sexual violence was the least recounted by participants as mild abuse, no genital contact, reported by 5.88% of the infertile cases versus 8.43% by controls but without a statistical significance.

Several studies on this subject matter showed clearly that domestic violence was higher among the infertile women compared to their fertile counterparts. In concordance to our results too, a study conducted in Iran by Poornowrooz et al., [8] reported that entirely the three varieties of violence (physical, sexual, and psychological) were significantly higher in the infertile cases than fertile counterparts. These data indicated that the uppermost proportion of violence against infertile women was in psychological domain (52.4%) and the lowest rate was in the sexual domain (24.5%).

Sheikhan et al., (13) found a closer physical, emotional and sexual violence rates of 34.7%, 5.3%, 74.3% and 47.3%, respectively.

Mansour and Mohdy, [14] in another Egyptian study also reported that psychological violence was the most common type of reported violence against infertile women followed by sexual and physical violence. Abstaining from sexual relationship was the most frequent type of sexual violence in 33.3% and 22.8% of the infertile and fertile cases respectively.

In the same line, a similar study conducted in Valiasr infertility center in Tehran by Iliyasu et al., [15] as they reported that 61.8% of infertile women were exposed to domestic violence due to their infertility problem. Psychological violence was described in 33.8% followed by physical violence in 14% and sexual violence in 8%.

Also Sami and Ali, (16) reported that a

psychological violence was reported in 60.8% including the verbal violence that includes the threat of separation or divorce.

Our results were also consistent with results from other studies as the prevalence of all the subclasses of violence (physical, verbal, emotional and sexual) was higher among the infertile group in contrast to their fertile counterparts [13, 17-21].

Budh et al., [22] found a lower domestic violence rate of 11.3% among infertile women. However, a study by Pasi et al., [23] gave higher domestic violence rates of 76.3% and 65.9% among infertile women and their fertile counter parts respectively.

In contrast, Solanke and colleagues, [24] in 2018 reported that husband violence was higher among women who have children versus their child deprived counterparts. This controversy may be due to the alteration in cultural and economic circumstances as more children may bear economic burden on their father life and instigating further violence in their families.

Therefore, conflicting results exist regarding the rates of IPV among infertile women but most findings were in line to ours.

The more domestic violence in the infertile cases can be elucidated by that gender unfairness reinforces male violence against women. In a male-controlled construct, either the family or the entire society, men often consider women as their private belongings and also consider marriage as a means to have offspring. The infertile couples are more predisposed to depression, distress, and mental disorders. At the same time, infertile women may deny exposure to violence predominantly sexual violence because of the shame, fear, or guilt about their infertility [25]. Physical violence reported at inferior rates as it can be demonstrated in courts besides the shame the women may feel while revealing their physical violence experiences [26].

The prevalence of IPV among infertile women is a controversy matter and is hard for evaluation precisely due to variable definitions for infertility and IPV used among studies [27].

Regarding Female Sexual Function Index of the fertile and infertile cases in our study, the components of FSFI score (libido (desire), sexual arousal, lubrication, orgasm, satisfaction and Pain) were statistically significant lower among infertile group ($p<0.001$) and also the total score was statistically significant lower among infertile group ($p<0.001$). The total score was 15.74±1.66 in the infertile cases compared to 27.35±1.45 in the fertile ones. Univariate linear regression analysis revealed that BMI, frequency of Emotional and physical violence were significant predictors for FSFI total score, while in Multivariate linear regression only frequency of Physical violence was significant predictors for it.

Ghoneim et al., [7] also reported that their studied population had female sexual dysfunction. They differed significantly in terms of arousal and satisfaction which were impaired in infertile women than the fertile group ($p= 0.001$ and 0.003, respectively). Besides, infertility significantly affected both domains in their study (p-value 0.004 each). These conclusions also corresponded with previous researches [28-30].

Poornowrooz et al., [8] results were nearly similar to the finding of the current work as they reported that sexual problems in the infertile women were more than fertile ones as contents of each domains of sexual function and the mean of entire sexual function in the infertile women were significantly lower than fertile women. Like our findings the total score was 22.53±6.63 in the infertile cases compared to 16.31±9.98 in the fertile ones ($p<0.001$).

Other research [9,29,31,32] also reported lower scores of total sexual function, arousal, desire, satisfaction, orgasm, and lubrication in infertile women compared with fertile women ($P < 0.005$).

Most studies show that infertile women have some degree of sexual dysfunction with FSFI scores lower than 26. This is consistent with findings from former literature [33,34] .

This may be justified by the increased stress levels allied to infertility that would negatively impact the marital life as well as sexual health. Whether sexual dysfunction is the trigger or after-effect of infertility is challenging to establish. The psychological stress concomitant with the wish for getting pregnant besides getting sex on demand for a designed timed intercourse that focus for coitus only for the purpose of conception could result in a reduction in enjoyment of sex loss of a couple's intimacy and would aggravate sexual dysfunction [14].

Mirblouk et al., [35] reported similar finding in their comparison of sexual dysfunction in women with infertility and without infertility referred to Al-Zahra Hospital in 2013-2014. However their individual and total scores were higher than the reported in the current work. There was significant differences between desire (3.93±0.94 vs. 3.62±0.91, p=0.004), arousal (4.12±0.90 vs. 3.71±1.06, p=0.001), satisfaction (4.99±0.87 vs. 4.74±1.00, p=0.022) and total sexual dysfunction (26.33±3.82 vs. 34.40±25.13 p=0.011) in infertile and fertile groups but in lubrication (p=0.266), orgasm (p=0.61) and pain (p=0.793) were not significant. The reason of difference can be related to age differences of participating women. Factors such as age, duration of marriage and partner age have been considered as central causes of sexual complaints in infertile women.

Yet, one of the studies, Peterson et al., [36] found better sexual function among infertile women, however, the difference on the FSFI was very small (infertile women achieved a mean of 24.83±4.72 and fertile ones 23.85±4.34 points). Another study published in 2017 by Emec et al. [37] did not approve the negative influence of infertility on sexual function as their infertile and fertile women achieved 17.49±7.20 and 17.86±6.41 points on the FSFI, respectively. The last two studies had smaller sample size of population than others.

The evaluated studies also like our findings show that fertile women also experience some degree of sexual dysfunction despite obtaining higher scores.

Karakaya et al., [38] also reported that correlation values between domestic violence and sexual function index scores were found to be inversely significant ($p < 0.05$). The research denotes that infertile females who are exposed to violence suffer from more sexual dysfunction. It also indicates that women who are not pleased with their sexual life are more subjected to sexual violence.

At last, the discrepancies between the formerly mentioned studies and the present one could be owing to the study cases' cultural diversities, sample selection criteria differences and dissimilar tools of data collection. As the preponderance of the research was performed in non-eastern cultures as India, Turkey, and Iran…etc. Thus, the nature of the culture could have its influence the results of this point of research. In our Egyptian culture talking about marital bond and sexual life represent a very sensitive matter to discuss and may cause shame especially if their spouse are present at the time of the examination.

The strengths of this research is summarized in that that there is a paucity of studies in our country that opened that gate and the published data about sexual dysfunction and partner violence among Egyptian females are still scare due to the shame or the fear of most cases to discuss this matter. Also sample size was relatively adequate with recruiting a relatively matched fertile control group.

Some of the limitations of our study include that most cases were selected from few centers. Therefore, the results cannot be generalized to the entire population. So, we recommend a large multi-center study to target the various aspects of infertile couples' quality

of marital and sexual life for both partners from multitude of cultures and customs and thus; the results can be representative to the entire population. Furthermore, this study did not take into account the effects of various infertility etiologies on sexual function. In addition the interview with case to fulfill the questionnaires face-to-face might have resulted in stress and discomfort to the case and may be bias resulted.

Conclusion

Infertile women are more likely to be exposed to physical, sexual and psychological violence. Psychological violence was found to be the most common type of reported violence against infertile women followed by physical and sexual violence. Moreover the infertile women had a significantly higher prevalence of sexual dysfunctions than their fertile counterparts.

Ethical approval: Approval of ethical committee was obtained from quality education assurance unit, Faculty of Medicine, Benha University Egypt.

Conflict of interest: The authors declare that they have no conflicts of interest.

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Tables' legend:

Table (1): Comparison of study groups regarding demographic characteristics

Table (2): Comparison of study groups regarding NorVold Domestic Abuse Questionnaire (NORAQ)

Table (3): Comparison of study groups regarding Female sexual dysfunction (FSFI score).

Table (4): Univariate and Multivariate logistic regression analyses of various variables for prediction of FSFI total score.

Table (1): Comparison of study groups regarding demographic characteristics.

Characteristics		Infertile group (n=205)		Control group (n=205)		Test of sig.	p-value
Age (mean ± SD)		27.53	3.85	28.27	4.17	1.9	0.06
BMI (mean ± SD)		27.33	3.11	24.87	3.69	7.3	<0.001*
Marriage years (mean ± SD)		5.02	2.90	4.89	3.10	0.4	0.7
Duration of Infertility (years)		4.13	2.25	---	---	---	---
Infertility type No. (%)	Primary	151	73.7%	---	---	---	---
	Secondary	54	26.3%	---	---	---	---
Husband age (mean ± SD)		31.58	4.87	33.32	4.83	3.6	<0.001*
Residence No. (%)	rural	99	48.3%	97	47.3%	0.1	0.8
	urban	106	51.7%	108	52.7%		
Female genital mutilation No. (%)	no	88	42.9%	89	43.4%	0.1	0.9
	yes	117	57.1%	116	56.6%		
Educational level No. (%)	Primary	9	4.4%	12	5.9%	5.4	0.1
	Preparatory	18	8.8%	7	3.4%		
	Secondary	34	16.6%	36	17.6%		
	University	144	70.2%	150	73.2%		
Employment No. (%)	Employed	127	62.0%	135	65.9%	0.7	0.4
	Housewife	78	38.0%	70	34.1%		
Husband education No. (%)	Primary	3	1.5%	2	1.0%	1.6	0.7
	Preparatory	9	4.4%	5	2.4%		
	Secondary	35	17.1%	39	19.0%		
	University	158	77.1%	159	77.6%		
Husband employment No. (%)	Employed	152	74.1%	171	83.4%	5.3	0.02*
	Unemployed	53	25.9%	34	16.6%		

Table (2): Comparison of study groups regarding NorVold Domestic Abuse Questionnaire (NORAQ).

		Infertile group (n=205)		Control group (n=205)		Test of sig.	p-value
Emotional violence (No. & %)		**86**	**42.0%**	**83**	**40.5%**	**0.1**	**0.8**
Frequency (median & IQR)		2	2-3	1	1-2	5.2	<0.001*
Grade No. (%)	mild	42	20.5%	41	20.0%	0.4	0.9
	moderate	29	14.1%	30	14.6%		
	severe	15	7.3%	12	5.9%		
Physical violence (No. & %)		**63**	**30.7%**	**32**	**15.6%**	**13.2**	**<0.001***
Frequency (median & IQR)		2	1-2	1	1-1	3.6	<0.001*
Grade No. (%)	mild	34	16.6%	17	8.3%	14.9	0.002*
	moderate	25	12.2%	12	5.9%		
	severe	5	2.4%	2	1.0%		
Sexual violence (No. & %)		**44**	**21.5%**	**30**	**14.6%**	**3.3**	**0.07**
Frequency (median & IQR)		1	1-1	1	1-1	0.7	0.5
Grade No. (%)	Mild abuse, no genital contact	24	11.7%	17	8.3%	3.7	0.5
	Mild abuse, emotional/sexual humiliation	6	2.9%	5	2.4%		
	Moderate abuse, genital contact	7	3.4%	4	2.0%		
	Severe abuse, penetration	6	2.9%	3	1.5%		

Table (3): Comparison of study groups regarding Female sexual dysfunction (FSFI score)

Characteristics	Infertile group (n=205)		Control group (n=205)		Test of sig.	p-value
	mean	±SD	mean	±SD		
Libido (desire)	2.07	0.44	4.74	0.55	13.6	<0.001*
Sexual arousal	1.58	0.24	3.87	0.31	10.7	<0.001*
Lubrication	1.80	0.34	2.06	0.35	7.7	<0.001*
Orgasm	2.20	0.37	4.41	0.38	5.7	<0.001*
Satisfaction	1.07	0.44	2.43	0.42	8.5	<0.001*
Pain	1.02	0.37	2.83	0.29	5.6	<0.001*
Total	15.74	1.66	27.35	1.45	9.8	<0.001*

Table (4): Univariate and Multivariate logistic regression analyses of various variables for prediction of FSFI total score.

	Univariate analysis		Multivariate analysis	
	β	p-value	β	p-value
Age	-0.032	0.523		
BMI	-0.158	0.001*	0.005	0.965
Residence	0.069	0.163		
Female genital mutilation	0.063	0.204		
years of marriage	-0.058	0.241		
Infertility type	0.012	0.862		
years of infertility	-0.020	0.776		
Educational level	0.004	0.937		
Employment status	-0.014	0.770		
Husband age	-0.021	0.674		
Husband education	0.002	0.972		
Husband employment	-0.013	0.796		
Emotional violence	-0.241	0.002*	-0.138	0.191
Physical violence	-0.254	0.013*	-0.261	0.015*
Sexual violence	-0.080	0.506		

ملحق ١: ''استبيان نورفولد للعنف المنزلي"

الإيذاء العاطفى	
إيذاء معتدل	هل قد عانيت من أى شخص بانتظام أو لفترة أطول يحاول كبتك أو إهانتك أو إذلالك؟
إيذاء متوسط	هل قد عانيت من أى شخص بانتظام وبتهديد أو بقوة يحاول أن يحد من تواصلك مع الآخرين أو يتحكم كليةً فيما يجب أن تفعله وما لا يجب أن تفعله؟
إيذاء قاسى	هل قد عانيت من الحياة فى خوف لأن شخص ما هددك أنت أو شخص قريب لك بشكل منتظم ولفترة طويلة؟
الإيذاء البدنى	
إيذاء معتدل	هل قد عانيت من أى شخص يضربك أو يصفعك على وجهك أو يعوقك بثبات ضد رغبتك؟
إيذاء متوسط	هل قد عانيت من أى شخص يضربك بقبضته أو قبضاته أو بشيء صلب أو يركلك أو يدفعك بعنف أو يعطيك عقاب أو يجلدك أو يفعل بك أى شيء مشابه لذلك؟
إيذاء قاسى	هل قد عانيت من أى شخص يهدد حياتك, على سبيل المثال يحاول أن يخنقك باستخدام سلاح أوسكينة أو أى فعل آخر مشابه؟
الإيذاء الجنسى	
إيذاء معتدل, بدون اتصال تناسلى	هل هناك أى شخص ضد رغبتك قد لمس أجزاء من جسمك غير الأعضاء الجنسية "بطريقة جنسية" أو أجبرك على لمس أجزاء أخرى من جسمه "بطريقة جنسية"؟
إيذاء معتدل, مع إذلال عاطفى أو جنسى	هل ذللت بطريقة أخرى جنسياً, مثال لذلك: بإجبارك على رؤية فيلم إباحى أو ما شابه ذلك وكان ذلك ضد رغبتك أو أجبرك على المشاركة فى فيلم إباحى أو ما شابه أو أجبرك على أن ترى جسمك عارياً أو أجبرك على رؤية شخص آخر عارياً؟
إيذاء متوسط, مع اتصال تناسلى	هل هناك أى شخص ضد رغبتك قد لمس أجزاء من جسمك غير الأعضاء التناسلية "بطريقة جنسية" أو أجبرك على لمس أجزاء أخرى من جسمه "بطريقة جنسية"؟
إيذاء قاسى, مع اخترق	هل هناك أى شخص ضد رغبتك قد لمس أجزاء من مهبلك أو فمك أو مستقيمك أو حاول فى أى منهم أو وضع أو حاول أن يضع شيء أو جزء آخر من الجسم فى مهبلك أو الفم أو المستقيم؟

ملحق ٢: "مؤشر الوظيفة الجنسية لدي إناث"

مع مراعاة اختيار اجابة واحدة لكل سؤال

١- على مدار الأسابيع الأربعة الماضية ، كم مرة شعرت بالرغبة في العلاقة الزوجية؟

٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١= لا يحدث

٢- في الشهر الأخير ، ما هي درجة الرغبة في العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية ،
٥ =عالي جدا
٤ = عالي
٣ = متوسط
٢ = منخفض
١ = منخفض جدًا أو منعدم

٣- في الشهر الأخير ، كم عدد المرات التي شعرت فيها بالإثارة أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

٤- في الشهر الأخير ما هي درجة شعورك بالإثارة أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية ،
٥ =عالي جدا
٤ = عالي
٣ = متوسط
٢ = منخفض
١ = منخفض جدًا أو منعدم

٥- في الشهر الأخير ، ما مدى ثقتك في وصولك للاثارة أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد نشاط جنسي
٥ =عالي جدا
٤ = عالي
٣ = متوسط
٢ = منخفض
١ = منخفض جدًا أو منعدم

٦- في الشهر الأخير ، كم عدد المرات التي كنت فيها راضيًةعن وصولك للاثارة أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

٧- في الشهر الأخير ، كم عدد المرات التي شعرت فيها بحدوث بلل "تزلق" المهبل أثناء العلاقة الزوجية الجنسية ؟

٠= لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

٨- في الشهر الأخير ، ما مدى صعوبة حدوث بلل "تزلق" المهبل أثناء العلاقة الزوجية الجنسية؟

٠= لا يوجد علاقة زوجية جنسية
١ = مستحيل
٢ = صعب جدا
٣ = صعب
٤ = صعب بعض الشيء
٥ = لا يوجد صعوبة

٩- في الشهر الأخير ، كم عدد المرات التي تكونين فيها قادرة علي المحافظة علي حدوث بلل "تزلق" المهبل أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
= لا يحدث

١٠- في الشهر الأخير ، ما مدى صعوبة المحافظة علي حدوث بلل "تزلق" المهبل أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
١ = مستحيل
٢ = صعب جدا
٣ = صعب
٤ = صعب بعض الشيء
٥ = لا يوجد صعوبة

١١- في الشهر الأخير ، كم عدد المرات التي وصلتي فيها الي الشبق "النشوة أو الذروة" أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

١٢- في الشهر الأخير ، ما مدى صعوبة الوصول الي الشبق "النشوة أو الذروة" أثناء العلاقة الزوجية الجنسية ؟

٠=لا يوجد علاقة زوجية جنسية
١ = لا يوجد علاقة زوجية جنسية
١ = مستحيل
٢ = صعب جدا
٣ = صعب
٤ = صعب بعض الشيء
٥ =لا يوجد صعوبة

١٣- في الشهر الأخير ، ما مدى رضائك عن قدرتك علي الوصول الي الشبق "النشوة أو الذروة" أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = راضِية جدًا
٤ = راضِية إلى حدٍ ما
٣ = راضية أو غير راضية يستويان
٢ = غير راضِية إلى حدٍ ما
١ = مستاء جدا

١٤- في الشهر الأخير ، ما مدى رضائك عن قربك العاطفي أثناء النشاط الجنسي من زوجك أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = راضِية جدًا
٤ = راضِية إلى حدٍ ما
٣ = راضية أو غير راضية يستويان
٢ = غير راضِية إلى حدٍ ما
١ = مستاء جدا

١٥- في الشهر الأخير ، ما مدى رضائك عن علاقتك الجنسية مع زوجك؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = راضِية جدًا
٤ = راضِية إلى حدٍ ما
٣ = راضية أو غير راضية يستويان
٢ = غير راضِية إلى حدٍ ما
١ = مستاء جدا

١٦- في الشهر الأخير ، ما مدى رضائك عن الجانب الجنسي في حياتك عموما؟

٠= لا يوجد علاقة زوجية جنسية
٥ = راضِية جدًا
٤ = راضِية إلى حدٍ ما
٣ = راضية أو غير راضية يستويان
٢ = غير راضِية إلى حدٍ ما
١ = مستاء جدا

١٧- في الشهر الأخير ، كم مرة شعرت بعدم الراحة أو الألم أثناء الإيلاج أثناء العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

١٨- في الشهر الأخير ، كم مرة شعرت بعدم الراحة أو الألم أثناء الإيلاج بعد العلاقة الزوجية الجنسية ؟

٠ = لا يوجد علاقة زوجية جنسية
٥ = دائمًا
٤ = غالبا (أكثر من نصف عدد المرات تقريبا)
٣ = أحيانًا (نصف عدد المرات تقريبا)
٢ = نادرا (أقل من نصف عدد المرات تقريبا)
١ = لا يحدث

١٩- في الشهر الأخير ، ما هي درجة عدم الراحة أو الألم أثناءأو بعد الإيلاج بعد العلاقة الزوجية الجنسية ؟

٠ = لا يوجد نشاط جنسي
٤ = عالي
٢ = منخفض
٥ =عالي جدا
٣ = متوسط
١ = منخفض جدًا أو منعدم

Role of transcerebellar diameter in prediction of gestational age in IUGR pregnancies

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Abstract

Background: Ultrasound measurement of biparietal diameter "BPD", head circumference "HC", abdominal circumference "AC" and femur length "FL" can accurately detect gestational age "GA" in normal pregnancies. The study aims to assess the accuracy of transcerebellar diameter "TCD" in estimating the GA in normal and intra-uterine growth restriction "IUGR" pregnancies.

Methods: A cross-sectional study was carried out on 30 pregnant women with normal pregnancy (group A) and 30 pregnant women with IUGR (group B). Ultrasound measurement of fetal biometry was done, including the following parameters: BPD, HC, AC, FL and TCD.

Results: Regression analysis for GA by date using different measures among the normal group showed that TCD had the highest determination (0.886), which increased to 0.958 when TCD was combined with FL and AC. On the other hand, regression analysis for GA by date among the IUGR group showed that TCD had the highest determination (0.988), which increased to 0.990 when TCD was combined with BPD.

Conclusion: Fetal TCD is a more reliable method in the 3rd trimester of gestation to determine the GA than BPD and other biometric measures, especially in IUGR pregnancies.

Keywords: Transcerebellar diameter; Gestational age; IUGR; Fetal biometry.

INTRODUCTION

Accurate estimation of the gestational age "GA" is important for evaluating pregnancy progress and fetal development, as well as for proper planning of adequate intervention or management. Before sonography, obstetricians had relied on the last menstrual period (LMP) to estimate the GA (1).

Though LMP has been shown to correlate with GA, it may be a deceptive indication because only approximately half of women can reliably recall their LMP (2). Therefore, ultrasound has been used to detect GA accurately (3). The biometric parameters, including biparietal diameter

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"BPD", head circumference "HC", abdominal circumference "AC" and femur length "FL", could be reliable in measuring GA. The accuracy of these metrics is dependent on the fetal skull shape, placental location, fetal head flexion, engagement, maternal adiposity, and gestational multiplicity. However, such measurements are affected by abnormal fetal growth (4).

Intra-uterine growth restriction (IUGR) is considered when the estimated fetal weight "EFW" is below the 10th percentile and the AC is below the 2.5th percentile for the GA by dates. It is believed that, under normal conditions, each fetus has a precise growth potential appropriate with GA. However, in IUGR cases, the neonate is born with a smaller head and/or abdomen than normal (5). Antenatal recognition of IUGR is crucial because of being linked with increased intra-uterine fetal death "IUFD" and fetal morbidity, including brain damage, fetal distress, newborn hypothermia, hyperbilirubinemia, hypoglycemia, and reduced immunological function (6).

Owing to the brain-saving phenomena that lead to prolonged brain blood flow at the expense of systemic supply, the cerebellum is least affected by IUGR. Moreover, it is relatively resistant to hypoxia. Transcerebellar diameter (TCD) is the distance between the cerebellar lateral aspects that includes the breadth of the cerebellar vermis on the axial scan (7). Because of its anatomical placement in the posterior cranial fossa, the cerebellum is less susceptible to anomalies in embryonic growth, such as growth acceleration or limitation (8). TCD is considered a reliable parameter for estimating the GA, as there is a link between the dimension of the fetal cerebellum, particularly the TCD, and the GA (9).

Consequently, this study was conducted and aimed to assess the accuracy of TCD in estimating the GA in normal and IUGR pregnancies.

METHODS

This cross-sectional study was carried out at the Department of Obstetrics and Gynecology, Kasr El Aini Hospitals, Cairo University, from January 2022 to January 2023, during which about 60 pregnant women were included for antenatal care. The Research Ethics Committee (REC), Faculty of Medicine, Cairo University approved this study under registration number (MS-631-2021). The included women had signed written informed consent before participating in the study after being informed of its purpose. All participants had the right to withdraw from the study without being adversely impacted regarding the medical care they should receive.

Eligibility criteria for the enrolled pregnant women in this study included singleton pregnancy, GA of 28- 40 weeks (based on the first day of LMP of regular menstrual cycles or documented first-trimester or early second-trimester ultrasound scan). Women were excluded if they were unsure of dates or in case of fetal anomalies, multifetal pregnancy, or intrauterine fetal death (IUFD).

Women were allocated into 2 equal groups; "Group A" which included pregnant women with normal fetuses, and "Group B" which included pregnant women with IUGR fetuses. All women were subjected to detailed medical history and clinical examination to ensure adherence to inclusion criteria. During antenatal transabdominal ultrasonography, patients were positioned with the head of the bed elevated 30 degrees and a little cushion under their right loin procedures. To assure the accuracy of the test results, all ultrasound exams were performed utilizing 2-dimensional ultrasonography by knowledgeable and experienced medical experts.

Ultrasound measurements of fetal biometry included the following parameters:

- BPD was measured on a section plane

that passed across the thalami and 3rd ventricle. In the sectional plane, the calvarium seemed symmetrical and smooth. The abdominal transducer was positioned perpendicular to the fetal parietal bones in order to get the proper picture. Next, the cursors were positioned on the inner and outer edges of the distal and proximal skulls, respectively. This length was indicative of the BPD.

- HC was obtained in the plane passed across the thalami and 3rd ventricle, similar to the plane for the BPD. To achieve the most accurate measurement, we cared to visualize other intracerebral markers, such as the cavum septum pellucidum anteriorly and the tentorial hiatus posteriorly. This view depicted the cranium's greatest anterior-posterior length and resembled an "arrow" with the anterior portion appearing as tail feathers, the third ventricle and Sylvian aqueduct as the shaft, and the actual arrowhead comprised of the ambient and quadrigeminal cisterns and the tentorial hiatus as the actual arrowhead. The cerebellum and lateral cerebral ventricles were not included in the usual picture.
- FL was obtained in line with the femur long axis. The proximal end of the femur's greater trochanter or the proximal end of the femur's femoral condyle were visible to achieve the correct image. To measure solely ossified bone, the calipers were positioned at the point where bone and cartilage meet.
- AC was obtained at the level of the fetal liver's maximum diameter, which was identified by the "hockey stick"-shaped site where the right and left portal veins united. This plane was selected because there is a strong correlation between the liver's size and the total fetal growth. The proper plane was verified by observing the left portal vein's umbilical segment at its smallest length.
- TCD was obtained by rotating the transducer to about 30º from the trans-axial plane, identifying the thalamus, the cavity of the septum pellucidum, the third ventricle, and the cisterna magna. This was done after locating the cerebellum in the posterior fossa. The largest measurement was obtained by positioning the electronic calipers on the cerebellar hemispheres' outside borders.
- The ultrasound machine derived GA and EFW from the measured biometric parameters. The GA and EFW were estimated according to the following formulas:

  - GA (weeks) = 10.6 − 0.168×BPD + 0.045×HC + 0.03×AC + 0.058×FL + 0.002×BPD2 + 0.002×FL2 + 0.0005×(BPD×AC) − 0.005×(BPD×FL) − 0.0002×(HC×AC) + 0.0008×(HC×FL) + 0.0005×(AC×FL).

  - Hadlock-1 formula: Log10 (EFW) = 1.3596 + 0.0064 × HC+0.0424 × AC+0.174 × FL+0.00061 × BPD × AC-0.00386 × AC × FL [g, cm].

The primary outcome was to assess the accuracy of TCD as a predictor of GA in normal and IUGR pregnancies, while the secondary outcome was to determine the correlation of TCD with BPD, HC, AC and FL in normal and IUGR pregnancies.

Sample size calculation: Sample size was calculated by using PASS 11 program for sample size calculation, setting the confidence level at 95%, margin of error ±0.05, and after reviewing previous study results (10), in which the correlation between TCD and GA was (0.993) in normal pregnancy and (0.995) in intrauterine growth retardation. Based on that, a sample size of at least 60 pregnant women of GA of 28 to 40 weeks was sufficient to achieve the study objective. They were divided into two equal groups: the normal pregnancy group and the IUGR group according to ultrasound fetal biometry and the EFW in relation to GA.

Statistical methods: Data was analyzed using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Numerical data were presented in terms of mean ± standard deviation or median and range. Categorical data were presented in terms of frequencies and percentages. Correlations between quantitative variables were done using the Pearson correlation coefficient in normally distributed data and Spearman correlation coefficients in data that are not normally distributed. P-values < 0.05 were considered statistically significant.

RESULTS

Two groups of patients were studied; "Group A" which included normal pregnant women (n=30), and "Group B" which included pregnant women with IUGR fetuses (n=30). Demographic data of the pregnant women and ultrasound measurements of the fetal biometry in both groups are shown in "Table 1".

Table 1: Maternal demographic characteristics and fetal ultrasound measurements

	Normal group "n=30"	IUGR group "n=30"
Maternal age (years)	28.97 ± 6.60 30.5 (18 - 42)	29.70 ± 6.42 30.5 (18 - 40)
GA by date (weeks)	31.03 ± 2.85 30.5 (28 - 38)	31.83 ± 3.50 31 (28 - 39)
BPD (mm)	79.37 ± 6.51 79.5 (69 - 95)	73.60 ± 7.90 71 (62 - 90)
BPD (weeks)	31.73 ± 2.91 32 (27 - 39)	29.43 ± 3.33 28 (25 - 37)
HC (mm)	287.57 ± 23.74 285.5 (259 - 350)	253.03 ± 25.79 248 (223 - 302)
HC (weeks)	32.87 ± 2.57 32.5 (30 - 39)	28.77 ± 3.17 28 (25 - 35)
FL (mm)	59.37 ± 6.03 58 (50 - 75)	54.73 ± 7.19 53.5 (45 - 67)
FL (weeks)	30.40 ± 2.94 30 (26 - 38)	28.33 ± 3.40 27.5 (24 - 34)
AC (mm)	268.83 ± 28.29 265.5 (230 - 344)	238.37 ± 30.53 232 (195 - 295)
AC (weeks)	30.40 ± 2.87 30 (27 - 38)	27.33 ± 2.92 27 (23 - 33)
TCD (mm)	38.23 ± 5.24 36.5 (32 - 50)	38.80 ± 5.31 37.5 (32 - 49)
TCD (weeks)	30.87 ± 2.89 30 (27 - 37)	31.37 ± 2.95 30.5 (27 - 37)
GA by U/S (weeks)	31.10 ± 2.77 30 (28 - 39)	28.23 ± 3.05 27 (25 - 34)

Regression analysis for GA by date using different measures among the normal group showed that TCD had the highest determination (0.886), followed by FL (0.880), then HC (0.841), then AC (0.828), then BPD (0.769). Combining TCD with FL and AC increased the determination to 0.958. On the other hand, regression analysis for GA by date using different measures among the IUGR group showed that TCD had the highest determination (0.988), followed by HC (0.954), then FL (0.949), then BPD (0.920), then AC (0.886). Combining TCD with BPD increased the determination to 0.990.

The correlation between the estimated GA and GA by date in both groups is shown in Table 2. In the normal group, the correlation coefficient was highest in regression combined (0.981), followed by ultrasound combined (0.961), and then regression TCD (0.943). While in the IUGR group, the correlation coefficient was highest in regression combined (0.995), followed by regression TCD (0.994) and then ultrasound TCD (0.986).

Table 2: Correlation between the estimated GA and GA by date in both groups

	Normal group "n=30"		**IUGR group "n=30"**	
	r	P-value	r	P-value
Ultrasound BPD (weeks)	0.883	<0.001*	0.961	<0.001*
Ultrasound HC (weeks)	0.915	<0.001*	0.980	<0.001*
Ultrasound FL (weeks)	0.937	<0.001*	0.984	<0.001*
Ultrasound AC (weeks)	0.897	<0.001*	0.923	<0.001*
Ultrasound TCD (weeks)	0.928	<0.001*	0.986	<0.001*
Ultrasound combined (weeks)	**0.961**	<0.001*	0.985	<0.001*
Regression BPD (weeks)	0.881	<0.001*	0.960	<0.001*
Regression HC (weeks)	0.920	<0.001*	0.977	<0.001*
Regression FL (weeks)	0.940	<0.001*	0.975	<0.001*
Regression AC (weeks)	0.913	<0.001*	0.985	<0.001*
Regression TCD (weeks)	**0.943**	<0.001*	**0.994**	<0.001*
Regression combined (weeks)	**0.981**	<0.001*	**0.995**	<0.001*

The agreement between the estimated GA and GA by date in both groups is shown in Table 3. In the normal group, the interclass correlation coefficient was highest in regression combined (0.990), followed by ultrasound combined (0.980), and then regression TCD (0.970). While in the IUGR group, the interclass correlation coefficient was highest in regression combined (0.998), followed by regression TCD (0.997).

Table 3: Agreement between the estimated GA and GA by date in both groups

	Normal group "n=30"		IUGR group "n=30"	
	Cronbach's alpha	P-value	Cronbach's alpha	P-value
Ultrasound BPD (weeks)	0.938	<0.001*	0.980	<0.001*
Ultrasound HC (weeks)	0.953	<0.001*	0.988	<0.001*
Ultrasound FL (weeks)	0.967	<0.001*	0.992	<0.001*
Ultrasound AC (weeks)	0.946	<0.001*	0.952	<0.001*
Ultrasound TCD (weeks)	0.963	<0.001*	0.985	<0.001*
Ultrasound combined (weeks)	**0.980**	<0.001*	0.988	<0.001*
Regression BPD (weeks)	0.933	<0.001*	0.979	<0.001*
Regression HC (weeks)	0.957	<0.001*	0.988	<0.001*
Regression FL (weeks)	0.968	<0.001*	0.987	<0.001*
Regression AC (weeks)	0.953	<0.001*	0.969	<0.001*
Regression TCD (weeks)	**0.970**	<0.001*	**0.997**	<0.001*
Regression combined (weeks)	**0.990**	<0.001*	**0.998**	<0.001*

DISCUSSION

The brain-sparing phenomenon indicates that blood flow to the brain is sustained at the expense of systemic supply. Therefore, the cerebellum is the least affected in IUGR cases. Moreover, it is relatively resistant to hypoxia. Therefore, we aimed to evaluate the accuracy of TCD in GA assessment, especially in IUGR cases. Our study revealed that TCD had the highest determination for GA in normal pregnancies, followed by FL, then HC, then AC, and then BPD. When TCD was combined with FL and AC, GA determination increased. Additionally, TCD had the highest determination among the IUGR group, followed by HC, then FL, and then BPD. When TCD was combined with BPD, GA determination increased.

Many studies suggested that the TCD could be valuable when GA is unknown or intrauterine growth restriction is suspected. Mishra et al. (2020) determined the precision of TCD measurement in estimating GA in healthy babies in order to create a TCD reference chart based on GA. Ultrasonographic measurements in 300 singleton pregnant women, including BPD, HC, AC, FL and TCD, were studied in a retrospective cross-sectional study. They found that TCD shows a linear correlation to progressing GA in typically growing fetuses. (11).

Kumar et al. (2020) studied 100 cases between

15-40 weeks of gestation. They found that TCD was associated well with other indicators such as BPD, HC, AC, and FL in normal pregnancies. TCD was shown to have the greatest connection with GA when compared to other measures in both normal pregnancies (r = 0.993, p 0.001) and IUGR pregnancies (r = 0.995, p 0.001) (10).

Vedpathak et al. (2020) compared the efficacy of fetal TCD and FL in predicting GA in their study, which included 100 pregnant women. The participants were divided into groups according to their GA. TCD is associated well with other indicators such as BPD, HC, AC, and FL in normal pregnancies. TCD was shown to have the greatest connection with GA when compared to other measures in both normal pregnancies (r = 0.993, p 0.001) and IUGR pregnancies (r = 0.995, p 0.001) (12).

Using the LMP as a reference for the actual gestation time, Sersam et al. (2019) assessed the accuracy of fetal TCD in determining GA in the third trimester of pregnancy. Fetal TCD was measured ultrasonographically in addition to standard measures. GA was estimated using TCD and contrasted with the estimated GA derived from LMP. A statistical investigation revealed a substantial and robust relationship between the estimated GA by LMP and BPD, FL, and TCD, with TCD exhibiting the greatest correlation coefficient (13).

Dashottar et al. (2018) studied 200 pregnant women in the second and third trimesters, including normal and IUGR pregnancies. The results showed that TCD exhibited substantial correlations at 16–20, 20–24, and 24-28 weeks; moderate correlations at 28–32 weeks; and low correlations at 32–40 weeks (14).

Singh et al. (2018) studied 500 pregnant women from 14 to 39 weeks of gestation. The results revealed a statistically significant relationship between TCD and GA in normal and IUGR pregnancies. TCD showed a good correlation with GA in the case of normal pregnancies (correlation coefficient=0.979) and a correlation coefficient of 0.942 in cases of IUGR pregnancies. GA calculated by TCD measurements correlated well with GA calculated by BPD, HC, AC and FL (15).

The study conducted by Eze et al. (2017) included pregnant women in the second and third trimesters of pregnancy. It revealed a significant linear association between TCD and GA acquired from LMP (16). In addition, a previous Egyptian study by Alalfy et al. (2017) was conducted on 60 Egyptian pregnant women in the second and third trimesters of gestation. The study revealed a significant positive correlation between the TCD and the GA by dates (17).

This study's strengths were that it was a cross-sectional analytic study design and that no participants were lost throughout the study period. To assure the accuracy of test results, all ultrasound exams were performed by skilled and competent medical experts. On the contrary, our study had certain limitations. This was a hospital-based research. Another drawback is that our study is limited to the third trimester of pregnancy.

CONCLUSION

Fetal TCD is a more reliable method in the 3rd trimester of gestation to determine the GA than BPD and other biometric measures, especially in pregnancies with fetal growth restriction. Future studies on a large scale could emphasize using combined TCD with femur length and abdominal circumference to determine GA in late pregnancy accurately.

DECLARATIONS

Competing interests: The author has no financial or other conflicts of interest.

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Informed consent: All women gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

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Evaluation of different methods for pain management in office hysteroscopy

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Abstract

Objective: : to detect the most effective pain control modality for the performance of office Hysteroscopy.

Methods: This was a double-blind randomized comparative study. Both sample size and randomization were done by a computer program. Patients were classified into four groups: Group one received 50 mg diclofenac potassium orally 30 minutes before hysteroscopy, group two received lidocaine 2% gel applied to cervix 5 minutes before hysteroscopy, group three received 10 ml 2% lidocaine solution injection in the cervix, group four received placebo drugs before hysteroscopy. Adjustments were made so that the 4 groups receive the 3 forms of analgesic drugs either in active form or placebo to ensure the integrity of double-blind study. The woman was asked by an independent observer to evaluate the pain felt at different stages of the procedure using VAS.

Results: There was a statistically significant difference in two groups (oral NSAIDs and paracervical block) in the VAS.

Conclusion: oral NSAIDs is an effective method in reducing pain during hysteroscopy. paracervical block reduce pain significantly only during introduction of hysteroscopy through the cervix, hindered by the time it takes, bleeding, lack of effectiveness through other stages of the procedure, while application of anesthetic gel though is proved to be an ineffective way to control pain during the procedures.

Keyword: office hysteroscopy, pain management, oral NSAIDs, paracervical block.

INTRODUCTION

Hysteroscopy is the best method used for evaluation of endometrium in cases of vaginal bleeding, recurrent miscarriage, and anomalies of the uterus, cervix, and vagina (1).

When it comes to hysteroscopy, a novel technique known as "office hysteroscopy" has evolved since early nineties. The "see and treat" procedure, which blurs the separating line between diagnosis of uterine pathology and operative

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maneuvers, reveals the concept of one procedure which integrate the management with the diagnosis (2).

In comparison to operating room-based hysteroscopy, office hysteroscopy has various benefits, including the omission of hospital stay, preoperative tests, and general anesthesia (3). Notably, it has decreased the duration needed for improvement after operation, the overall expenses of the therapy, and the how common are problems such as lacerations of the cervix, perforation of the uterus, and those brought on by the media that will be used for distending the uterus (4).

Despite being largely accepted to a great level, unpleasant painful stimuli, vaso-vagal attacks, falling of blood pressure, and loss of ease are frequently narrated by patients have hysteroscopy performed to them (4). Pain is still by far considered the most important factor in office hysteroscopy failure, despite the truth that a "no-touch" modality may be done easily in the majority of instances without anesthetics (3).

The origin of the painful stimuli sensed during hysteroscopy are currently not well understood. Also, there is no consensus on the use of medications for treating pain and anesthetic modalities for hysteroscopy in the ordinary clinic room because there is a deficiency of enough high-quality evidence in this area (4).

84% of failed hysteroscopies, according to Nagele et al, were caused by severe discomfort and pain during the procedure (5).

It is stated that around 35% of individuals who have a hysteroscopy for getting pathology diagnosed without anesthetic claim a very severe painful experience (6).

Around 68% of patients revealed feeling intermediate to agonizing level of discomfort (detected by (VAS) scoring system of five or above) right away by the time their assessment has ended (3).

When we try to understand the pathophysiology of discomfort during hysteroscopic maneuvers, one must have a sufficient knowledge of the female genital tract anatomy (7, 8). The tissues of the female pelvis are supplied by two nervous systems (8, 9). The upper part of the uterus is supplied by the sympathetic system from the tenth thoracic to the second lumbar segment by the inferior hypogastric plexus of nerves (7). That get access to the uterine body by two ligaments of the uterus, and they are sacro-cervical ligament and the suspensory ligament of the ovary, forming together the ovarian plexuses (8).

The upper part of the vagina, cervical tissue, and inferior part of the uterus are supplied by parasympathetic nerves from second to fourth sacral, which combine together to give rise to the uterovaginal plexus of nerves, which get access to the uterus through the mackenrodt's ligament (8,9).

While performing hysteroscopic techniques, discomfort is for the most part arise from the use of instruments to grasp cervix, dilatation of the cervical canal, passage of the hysteroscope through the canal of the uterine cervix, and separation of the two uterine walls from each other by media (10,11). Operative techniques which destroy the endometrial tissue, such as getting tissue biopsy of the endometrium, removal of a polyp or excision of myoma can also cause a great deal of discomfort (10,11).

This intricate nerve supply means that good anesthesia and pain control demands targeting of many sites at the same time, such as paracervical and intracervical anesthetic modalities as well as topical medicines for the lining of the cervix and uterine cavity (9).

Pain during office hysteroscopy remains a determining factor for patient acceptability of the procedure.in our study we investigate the most common pain control modalities to control pain during office hysteroscopy and they are oral NSAIDs, paracervical block, topical anesthetics applied to the cervix.

MATERIALS AND METHODS

Our study is prospective randomized double-blind study. This study was conducted in the outpatient clinics of Mansoura University Hospitals in the period from September 2021 to September 2022. Ninety-two women were enlisted for hysteroscopy in Mansoura gynecological center outpatient clinic and that comes after good counselling and signing their consent. The 92 patients were randomized into four groups using a computer program designed for research purposes. Group one got 50 mg diclofenac potassium orally 1 hour before hysteroscopy and 10 ml normal saline injection in the paracervical region and 5 mg placebo gel applied to the cervix 10 minutes before hysteroscopy, group two received placebo drug orally 1 hour before hysteroscopy and 10 ml normal saline injection in paracervical region and 5 mg lidocaine 2% gel applied to cervix 10 minutes before hysteroscopy, group three received placebo drug orally 30 minutes before hysteroscopy and 10 ml 2% lidocaine solution injection in the paracervical region and 5 mg placebo gel applied to cervix 10 minutes before hysteroscopy, group four received placebo drug orally 1 hour before hysteroscopy and 10 ml normal saline injection in the paracervical region and 5 mg placebo gel applied to cervix 10 minutes before hysteroscopy.

The random division of the groups and preparation of the drugs were made by a health care worker who did not attend the hysteroscopy setting. The physician who performed the procedure, physician assistant and the patient did not recognize the medication used. The patient was asked to lie in the lithotomy position and gynecologic examination using the two hand simultaneously through the vagina and over the abdomen was performed. A speculum was then introduced through the vagina to show the cervix, then disinfection the cervix takes place. The upper cervical lip was held firmly with volsellum forceps by the physician. Paracervical anesthesia was then achieved by the use of spinal needle and the drug was injected at third, fifth, seventh and ninth o'clock of the junction between cervix and vagina, in four equally divided doses. The gel was then put on the Ectocervix. Hysteroscopic procedure began 5 minutes after the application of the gel. Dilatation of the cervix was not performed before the start of the hysteroscopy. The type of the hysteroscopy in this study is the rigid type. And its diameter is 5 mm with 30-degree angle. The hysteroscopy was advanced through cervical canal till the uterine cavity vision is attained. Saline solution was used to distend the uterus and to maintain the separation of the uterine walls. The patient was demanded to give a pain score to another independent attendant to evaluate the discomfort during every single stage of the hysteroscopy using VAS. Discomfort was evaluated when the cervix was held firm by volsellum; during advancement of hysteroscope through the cervical canal; just after the procedure was finished; and half hour after the procedure was performed. Blood pressure and pulse were recorded during the same stages of the procedures during which pain was recorded.

RESULTS

Table 1: The baseline characteristics of the study participants.

characteristics	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Age/years mean±SD	30.83±9.78	36.52±13.6	34.61±9.43	35.35±7.81	0.281
BMI(kg/m^2) mean±SD	28.58±2.18	28.79±2.34	29.79±3.05	28.65±1.61	0.316
Residence Urban Rural	9(39.1) 14(60.9)	8(34.8) 15(65.2)	7(30.4) 16(69.6)	9(39.1) 14(60.9)	0.915

Used test : One Way ANOVA test , Chi-Square test

First table leads to the conclusion that there is no difference between studied groups that signify importance in relation to statistics as regard age , body mass index and residence. Mean age is 30.83 , 36.52 , 34.61 & 35.35 years for the local lidocaine group , Diclofenac group, Paracervical block and placebo groups. Mean body mass index is 28.58 , 28.79 , 29.79 and 28.65 kg/m^2 . Rural residence is detected among the following; 60.9% , 65.2% , 69.6% & 60.9% , respectively for local lidocaine group , Diclofenac group, Paracervical block and placebo groups.

Table (2): comparison of obstetric history between studied groups.

characteristics	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Parity	**0(0-3)**	**1(0-6)**	**2(0-5)**	**0(0-4)**	**0.226**
Gravidity	**1(0-7)**	**2(0-7)**	**2(0-5)**	**2(0-7)**	**0.364**
Previous vaginal delivery	**2(1-3)**	**4(1-6)**	**2(1-5)**	**2(1-3)**	**0.784**
Previous cs	**2(1-3)**	**1(1-3)**	**2(1-3)**	**1(1-3)**	**0.412**
Previous miscarriage	**2(1-7)**	**1(1-5)**	**1(1-2)**	**1(1-7)**	**0.461**

Used test : Kruskal Wallis test

Second table help us conclude that the groups don't differ to the level that signify value in the fields of statistics as regard median parity , gravidity , previous vaginal , CS and miscarriage.

Table (3): comparison of medical and surgical history between studied groups.

characteristics	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Medical history -ve +ve	**18(78.3) 5(21.7)**	**18(78.3) 5(21.7)**	**13(56.5) 10(43.5)**	**18(78.3) 5(21.7)**	**0.249**
Surgical history -ve +ve	**13(56.5) 10(43.5)**	**16(69.6) 7(30.4)**	**8(34.8) 15(65.2)**	**10(43.5) 13(56.5)**	**0.09**

Used test: Chi-Square test

Third table demonstrates the relation that there is no significant differentiation between studied groups when it comes to statistics as regard medical and surgical history. Positive medical history is detected among 21.7% , 21.7% , 43.5% &21.7% , for local lidocaine group , Diclofenac group, Paracervical block and placebo groups , respectively.

Table (4): Vas score among studied groups.

outcomes	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
VAS when the cervix was grasped	5.09±0.85[a]	3.17±1.11	5.87±1.01	5.22±1.31a	F=26.29 p<0.001*
VAS at the time of insertion of hysteroscopy	7.13±0.81	4.30±0.76	3.74±0.86	6.13±0.86	F=83.22 p<0.001*
VAS immediately after hysteroscopy	5.83±0.98[a]	4.30±0.82	6.04±0.92[a]	5.09±0.85	F=17.74 p<0.001*
VAS 30 minutes after hysteroscopy	4.0±0.85	1.78±1.24[a]	2.78±0.79	2.22±1.24[a]	F=19.13 p<0.001*

Used test: ANOVA test.

Fourth table demonstrates the relation that there is a significant differentiation between studied groups when it comes to statistics as regard VAS score when the cervix was grasped, at the time of insertion of hysteroscopy, immediately after hysteroscopy and 30 minutes after hysteroscopy. Post Hoc Tukey test was used to assess within group significance and demonstrates that for VAS when cervix was grasped; no significant difference between local lidocaine gel group & Placebo group, for VAS immediately after hysteroscopy no significant difference detected between Local lidocaine gel group & Paracervical block group, for VAS 30 minutes after hysteroscopy; no significant difference is detected between Diclofenac & placebo groups

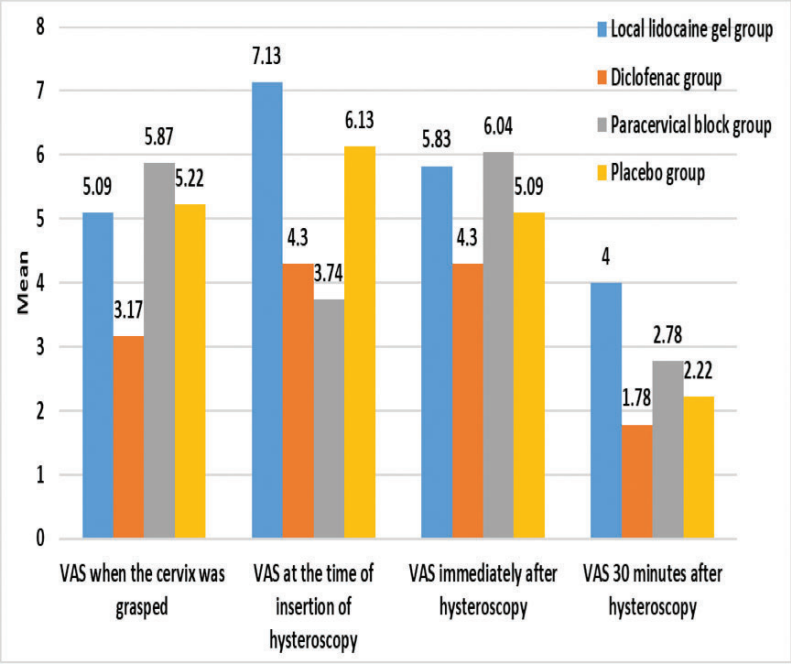

Figure (1) distribution of the studied groups according to VAS score during follow up.

Table (5): systolic blood pressure among studied groups.

Systolic blood pressure	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Basal	112.17±12.78	114.78±122.17	122.17±13.47	118.69±16.04	F=1.89 P=0.137
When the cervix was grasped	123.04±11.85[a]	120.87±15.86[a]	134.56±11.77	136.96±9.7	F=9.61 p<0.001*
At the time of insertion of hysteroscopy	134.35±8.95	128.91±14.77	125.22±10.38	131.74±11.14	F=2.66 P=0.053
Immediately after hysteroscopy	127.61±11.66	133.47±13.93	136.08±10.66	129.13±13.11	F=2.28 P=0.085
30 minutes after hysteroscopy	117.61±12.78	118.69±16.94	123.91±13.05	125.22±12.01	F=1.71 P=0.171

Used test: One Way ANOVA test, *statistically significant, similar superscripted letters denote non-significant difference between groups.

Fifth table demonstrates that there is statistically significant difference between studied groups as regard systolic blood pressure when cervix was grasped except between Local lidocaine gel group & Diclofenac group.

Table (6): diastolic blood pressure among studied groups.

diastolic blood pressure	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Basal	76.09±7.22	74.35±6.62	76.52±6.47	76.96±5.58	F=0.711 P=0.548
When the cervix was grasped	78.91±6.56[a]	78.04±8.22[a]	86.74±7.48[b]	85.22±5.11[b]	F=9.19 p<0.001*
At the time of insertion of hysteroscopy	86.74±6.68[ab]	82.95±8.54 [acd]	80.43±6.38[ce]	83.48±6.47[bde]	F=3.10 P=0.03*
Immediately after hysteroscopy	81.30±7.57[a]	86.74±7.01[bc]	87.83±6.71[bd]	84.35±5.07[acd]	F=4.34 P=0.007*
30 minutes after hysteroscopy	75.87±6.34[a]	75.65±8.02	81.09±6.73[b]	80.0±6.03[ab]	F=3.87 P=0.012*

Used test: One Way ANOVA test, *statistically significant, similar superscripted letters denote non-significant difference between groups.

Sixth table shows that there is statistically significant difference between studied groups as regard diastolic blood pressure at the following studied periods; when the cervix was grasped, at the time of insertion of hysteroscopy, immediately after hysteroscopy and 30 minutes after hysteroscopy.

Table (7): pulse distribution among studied groups.

pulse	Local lidocaine gel group N=23	Diclofenac group N=23	Paracervical block group N=23	Placebo group N=23	P value
Basal	78.35±5.87	78.61±5.34	76.26±5.54	79.56±6.87	F=1.27 P=0.291
When the cervix was grasped	90.09±7.45	85.56±5.66	94.61±7.92[a]	95.22±7.30[a]	F=9.14 p<0.001*
At the time of insertion of hysteroscopy	105.65±7.88	91.22±6.02[a]	86.0±4.94	90.87±5.15[a]	F=44.41 p<0.001*
Immediately after hysteroscopy	94.35±8.43[a]	96.25±6.45[ab]	99.57±8.79[b]	89.13±5.15	F=8.11 p<0.001*
30 minutes after hysteroscopy	86.22±5.20	83.83±5.22	84.96±5.22	85.48±4.68	F=0.899 P=0.445

Used test: One Way ANOVA test, *statistically significant, similar superscripted letters denote non-significant difference between groups.

Seventh table demonstrates statistically significant change in pulse among the following follow up periods; when the cervix was grasped, at the time of insertion of hysteroscopy, immediately after hysteroscopy and 30 minutes after hysteroscopy.

DISCUSSION

Because it can be performed in an office environment lacking anesthesia, office hysteroscopy is now less complex, faster, and cheaper and poses less complications for the patient. Even while technological advancements, including as the use of thinner, flexible equipment and no-touch procedures, have tremendously decreased patient pain and discomfort during office hysteroscopy, pain is still an important factor in configuring whether this procedure is accepted for most women (12).

In our study, we evaluate how three distinct pain management techniques affect pain and discomfort both during and following office hysteroscopy procedures.

Additionally, a 10 cm VAS was utilized to assess how uncomfortable the treatment was both during and immediately following various process stages.

In contrast to the paracervical block group, which only experienced pain reduction during hysteroscopy advancement through the cervical canal, the group that received diclofenac K preoperatively demonstrated reduced pain scores using VAS during various stages of the procedure and postoperatively.

However, the pain scores in the group that had lidocaine gel applied locally to the cervix are not decreased during or after the procedure.

Our outcome was consistent with these studies regard the effectiveness of diclofenac as a pain control modality for office hysteroscopy:

Abbas and his colleagues come to the conclusion that, VAS scores during hysteroscopy were much less in diclofenac group than placebo group (13).

El-Gamal and his colleagues come to the result that using with 100 mg diclofenac orally one hour before office hysteroscopy decreased median pain scores during and after the procedure (14)

Mohammadi and his colleagues found that the mean pain score was much lower during advancement of the hysteroscope through the cervical canal and removal of the hysteroscope from cervix in the diclofenac group (15)

Our study matched the result of these studies regard the ineffectiveness of paracervical block and topical cervical anesthesia:

Vercellini and colleagues, examined the effect of paracervical anesthetic modality in pain decreasing during hysteroscopy in the outpatient and concluded that it is not effective modality of anesthesia in finishing the procedure without discomfort (16).

Lau and his colleagues found that Paracervical block modality fails to decrease discomfort and agony during outpatient hysteroscopy in addition to posing a tremendous risk of decreasing heart rate and hemodynamic instability that may be originated from accidental injection of anesthetics into the vessels in the cervix (17)

Wong and his colleagues found that there were no differences that signify significance in VAS score of each step and the collective discomfort score between the group that used the local anesthetic gel lignocaine and the control group in their study and concluded that the use of lignocaine gel locally applied to the cervix is not a reliable method in decreasing pain and discomfort at the time of performing hysteroscopy in outpatient setting. (18)

Van den Bosch and colleagues tested the application of lidocaine gel locally to the cervix before performing office hysteroscopy and come to the conclusion that it does not decrease the pain and agony resulting from the procedure (19)

But this result runs counter to these studies regards the effectiveness of diclofenac as a pain control modality for office hysteroscopy:

Yuen and colleagues come to the consensus that there were no positive effects regarding decreased pain neither during performing hysteroscopy nor after the procedure if hysteroscopy is performed one to two hours after diclofenac taken orally by the patients (20).

Hassa and colleagues come to the conclusion that there was no benefit regards decreasing pain by the rectal use of one hundred milligrams of diclofenac one hour before the performance of hysteroscopy in ordinary clinic settings in a trial in which test subject were aligned in two groups in a random controlled fashion. (21)

Our study results were different from these studies regard the effectiveness of paracervical block and topical cervical anesthesia:

Cooper and his colleagues come to the result that Paracervical anesthesia injected into the cervix is the most effective modality to decrease pain and discomfort for female patients getting hysteroscopy performed to them in the office setting in a huge meta-analysis research study; around twenty studies were performed (around 29 hundred patients were enrolled). Included data in fifteen studies were analyzed. Intracervical modality of anesthesia and the local use of anesthetic material for paracervical injections significantly decrease the discomfort and pain in a great deal in female patients underwent hysteroscopy in the office, whereas application of anesthetics locally to the cervical canal and ectocervix resulted in no decrease regard pain scores. Further analysis shows that paracervical injection was by far the most effective pain control modality (22).

Bendary and colleagues examined how effective the use of topical anesthetic agents in a randomly aligned research. They examined the use of EMLA cream, an emulsion mixture, containing two and half percent each of lidocaine/prilocaine to control discomfort and agony during the performance of hysteroscopy in the outpatient

setting, and come to the conclusion that the local application of EMLA cream as an anesthetic modality for hysteroscopy in the outpatient facility is effective, reliable, and easy to use by gynecologists (23).

Chudnoff and colleagues examined the use of paracervical anesthetic injection modality by the use of one percent lidocaine before office hysteroscopic sterilization in a randomly aligned controlled trial and come to the conclusion that the use of lidocaine injected paracervically decreased pain scores tremendously for grasping the cervix and advancement of the hysteroscopy through the cervical canal. At the end they come to the result that Paracervical anesthetic modality by injecting one percent lidocaine give us an effective method to decrease discomfort, agony and pain during different phases of performing hysteroscopy in the outpatient facility, on the other hand it had no effect on reducing discomfort related to distension media use and distending the upper part of the uterus. (24)

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The role of corticosteroids in prevention of neonatal respiratory morbidity in term elective cesarean section: A prospective: observation study

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Abstract

Background : Caesarean sections continue to increase day by day in both developed and developing countries, which is associated with increased respiratory distress syndrome (RDS), the key reason for early neonatal morbidity and mortality.

Objective: To assess the effect of routine prophylactic corticosteroids before elective caesarean section after 37 weeks of gestational age, on neonatal respiratory morbidity. Methods: A prospective observational study was conducted on all pregnant women undergoing elective caesarean sections between 37-42 weeks at Ain Shams University Maternity Hospital. Over an 8- month period (from November 2020 to June 2021), 1105 cases were divided into the exposed group (A), (N = 877) who received prophylactic dexamethasone, and 228 cases in the non-exposed group (B) who did not receive dexamethasone. Outcome measures were the incidence of transient tachypnea of the newborn, and NICU admissions due to respiratory morbidity. Data were analyzed using SPSS 22.

Results: Overall, there was no statistically significant difference in the incidence of TTN or RDS. No cases of TTN were found in exposed subgroup, versus 1 (0.4%) in non-exposed group (p= 0.745). The respiratory distress (RDS) in the exposed subgroup was 4 cases (16.7%) versus 18 (7.9%) in

non-exposed group (p = 0.148). While the admission to the neonatal intensive care unit (NICU) due to respiratory morbidity after an elective caesarean section was 4 cases (16.7%) in the exposed subgroup versus 19 cases (8.3%) in the non-exposed group (p = 0.178).

Conclusion: Routine administration of prophylactic antenatal corticosteroids before elective caesarean sections at term does not reduce the risk of admission to the NICU compared to non- administration.

Key Words: elective cesarean delivery; antenatal corticosteroid; respiratory morbidity.

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INTRODUCTION

Caesarean section is the most common major surgical intervention in many countries and a lifesaving intervention for women and newborns when complications arise, such as antepartum hemorrhage, fetal distress, abnormal presentation of the fetus, and hypertension. Therefore, the global concern about caesarean section rates is understandable when it is medically justified. [1]

According to a WHO survey, the percentage of caesarean sections (CS) performed around the world is constantly rising, with a recent upward trend, when compared to newborns delivered vaginally or by emergency cesarean delivery. [2]

Term pregnancy is defined as a delivery between 37 and 42 weeks (259–293 days) of gestation, according to the international classification of diseases, which is optimal timing for a good outcome for the mother and babies. However, neonatal outcomes vary within this wide gestational age [3,4].

Furthermore, the guidelines issued by the American Council of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists (RCOG), and (NICE) recommend that an elective lower segment caesarean section (EL-LSCS) should be planned at 39 weeks [5, 6].

A systematic review of the literature and meta-analysis by Tefera et al. 7 showed that, babies born at term (at or after 37 weeks) by planned (elective) caesarean section and before onset of labour are more likely to develop respiratory complications than babies born vaginally.

Steroids are effective drugs with a variety of side effects, even if they improve outcomes when used appropriately. If not, side effects such as decreased fetal and placental growth, brain apoptosis, and increased infection may occur. On the other hand, steroid side effects appear to be related to both average dosage and cumulative duration of usage [8, 9].

The World Health Organization recommends that antenatal corticosteroids should not be routinely administered in instances where the gestational age cannot be verified (especially when thought to be more than 34 weeks) because the risk of harm would exceed the benefits 10. While, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists **RANZCOG** [11], advised that, if an elective lower segment caesarean section (EL-LSCS) is required before 39 weeks, prophylactic dexamethasone should be administered at least 48 hours before the caesarean section to reduce the incidence of infant respiratory morbidity (NRM).

The evidence for administration of corticosteroids after 34 weeks is still controversial since there is a lack of properly conducted trials of antenatal corticosteroids in mothers delivered by elective caesarean section at this gestational age. This current study is planned to compare the incidence and pattern of neonatal respiratory morbidity in neonates delivered by elective caesarean section between 37+ 0 to 41+ 6 weeks, whether they received antenatal routine prophylactic corticosteroids, or not.

PATIENTS AND METHODS

Study setting and design:

A prospective observational study was conducted on all pregnant women undergoing elective caesarean sections between 37-42 weeks, at Ain Shams University Maternity Hospital, over an 8- months' period (from November 2020 to June 2021).

Study participants:

Inclusion criteria: For all patients undergoing elective caesarean sections between 37+º to 42+º weeks an informed written consent was obtained for participation after reading the patient information sheet or having it discussed with patients.

Exclusion criteria: Congenital fetal anomalies conditions as: (Congenital diaphragmatic

hernia (CDH), congenital pulmonary airway malformation (CPAM), tracheo-esophageal fistula (TOF), pulmonary hypoplasia and congenital pneumonia). Also, cases with chorioamnionitis, fetal hydrops, persistant pulmonary hypertension of the newborn, evidence of fetal distress, APH, and maternal DM, or HTN were excluded.

Sample size:

A sample size of 1105 pregnant women achieve 80% power to detect equivalence in NICU admission rate between two groups with margin of equivalence range from (-5% to 5%) with significance level 0.05%.

After enrollment, there will be two groups:

Exposed group (A): 877 pregnant women who received complete or incomplete course of antenatal corticosteroid, in an appropriate manner.

Complete course is defined as: either 2 doses of 12 mg, 24 hours apart of betamethasone (Glomethasone ampoule Betamethasone - 8 mg/2 ml, Global Pharmaceutical Industries, GPI) or, 4 doses of 6 mg, 12 hours apart, of dexamethasone (Dexamethasone ampoule as sodium phosphate, 8 mg/2 ml, Amriya Pharmaceutical Industries). Both are given intramuscularly. Appropriate manner means that, delivery occurred between 24 hour up to one week after last dose of steroids.

Incomplete course is defined as: Failed to complete the above-mentioned doses or delivery before (24 hour) from last dose or after one week from last dose.

Unexposed group (B): 228 pregnant women who have not received any corticosteroids before caesarean section.

Procedure of the study:

All pregnant women undergoing elective caesarean sections between 37+º to 42+º weeks at Ain Shams University Maternity Hospital, (ASUMH) were included, after signing an informed consent to participate in this study [consent form 2] after explaining the study aims and objectives [form 1]. Also, we observed the patient hospital records and interviewed patients, in case of incomplete records to obtain the necessary data as listed in the data record form [form 3].

A neonatology specialist attended all deliveries; details of the resuscitation at the operative theatre were recorded. Apgar scores at 1 and 5 minutes were recorded.

All neonates were assessed for signs of RDS [defined as the presence of at least 2 of the following criteria: tachypnea, central cyanosis in room air, expiratory grunting, and subcostal, intercostal, or jugular retraction, and nasal flaring] or transient tachypnea of the newborn (TTN) [defined as a period of rapid breathing higher than the normal range of 40-60 times per minute].

All neonates admitted to the NICU were subjected to chest X-ray for exclusion of other associated pathologies and confirmation of diagnosis of RDS. All data about the need for admission to the neonatal intensive care unit (NICU) or the need for mechanical ventilation within 24 hours after birth were recorded.

Study outcomes:

Primary outcome: Admission to the NICU for respiratory morbidity.

Secondary outcome: Incidence of TTN, RDS, and need for mechanical ventilation.

Statistical analysis:

The data were analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). Numerical data were expressed as a mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using an independent sample t-test. Odd risk (OR) with it 95% confidence interval (CI) were used for risk assessment.

For all the above-mentioned statistical tests done, the threshold of significance was fixed at 5% level. The results were considered significant when $p \leq 0.05$.

RESULTS

The study investigators reviewed the records of 1105 women who met the eligibility criteria and were enrolled in the study as shown in the participant's flow chart; Figure 2.

Participants flow chart:

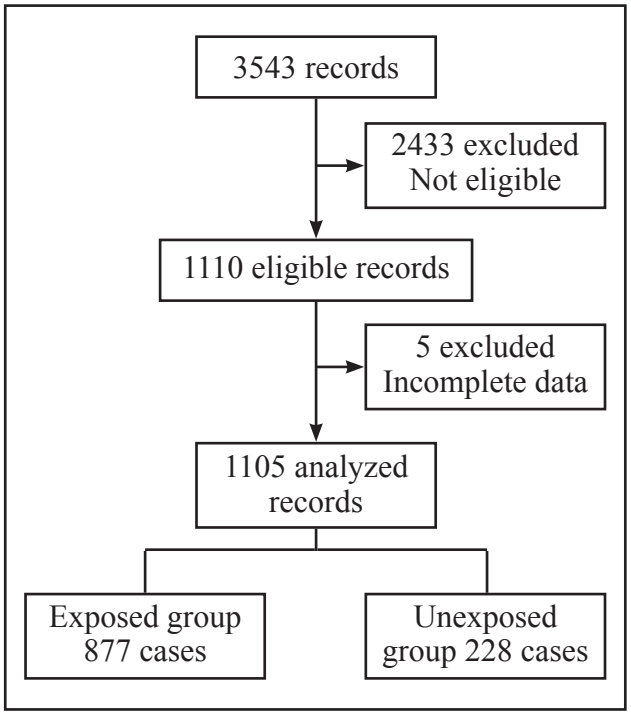

Figure 1. Flow chart of the studied cases.

There were no significant differences between the two groups regarding their age and parity at the time of enrollment table 1.

As shown in figure 2, collective analysis of the indications for elective caesarean section showed that the majority of elective caesarean section in both groups were done for previous caesarean section (72.39%), and the other common indications for caesarean section in patients were found to be malpresentation (3.17%), cephalopelvic disproportion (0.63%), maternal request (0.81%), and others (22.99%) on the study.

Table 2, shows that, there was no statistically significant difference regarding fetal and neonatal parameters.

We reviewed the records for the antenatal steroid courses received. We considered two doses of 12 mg each 24 hours apart of betamethasone, or four doses of 6 mg each 12 hours apart of dexamethasone, given intramuscularly a complete course. Also, we reviewed the interval between antenatal corticosteroids last dose and delivery. We considered 24 hours to 7 days between ANC last dose and delivery is a proper time for ANC administration.

Only 24 (2.74%) women were found to have received a complete course of dexamethasone in an appropriate time. On the other hand, 862 (98.29%) received single course versus 15 (1.71%) repeated courses before caesarean delivery. Regarding the time interval between the last ACS dose and delivery, an ACS-to-delivery interval of less than 7 days was found in 89 (10.15%) of cases, and more than 7 days in 788 (89.85%) of cases table 3.

There were no statistically significant differences between the outcomes of the two groups regarding respiratory distress, TTN, the length of hospitalization after caesarean delivery, and fetal outcomes (discharge from the NICU, neonatal sepsis, or death), as shown in table 4.

Further analysis was performed on the subgroup of patients (N = 24) who received complete (4 doses of 6 mg IM of dexamethasone12 hours apart), and proper (delivery occurred within 24 hours to 7 days after the last dose of dexamethasone) course of ACS. As shown in table 5, there was no statistically significant difference between the outcomes of this subgroup and no corticosteroids group regarding admission to the NICU, respiratory distress, TTN, and fetal outcome.

Furthermore, table 6 shows that there was no statistically significant difference between the outcomes of the subgroup with proper complete ACS and incomplete course of ACS regarding admission to the NICU, respiratory distress, TTN, and fetal outcome.

Table 1: Baseline maternal characteristics among studied groups

Demographic data	Group (A) Corticosteroids (n=877)	Group (B) No corticosteroids (n=228)	Test of Significance	P-value
Age (years)				
Mean ± SD	29.48 ± 5.42	29.28 ± 6.01	t= 0.497	0.619
Min-Max	18-46	18-44		
Age class				
≤25 y	242 (27.6%)	65 (28.5%)	χ^2 = 37.957	**0.079**
>25 y	635 (72.4%)	163 (71.5%)		
Parity				
Primigravida	71 (8.1%)	31 (13.6%)	χ^2 = 9.771	0.135
Multigravida	806 (91.9%)	197 (86.4%)		

χ^2: Chi square test, **t:** Independent sample t-test.
SD; Standard deviation

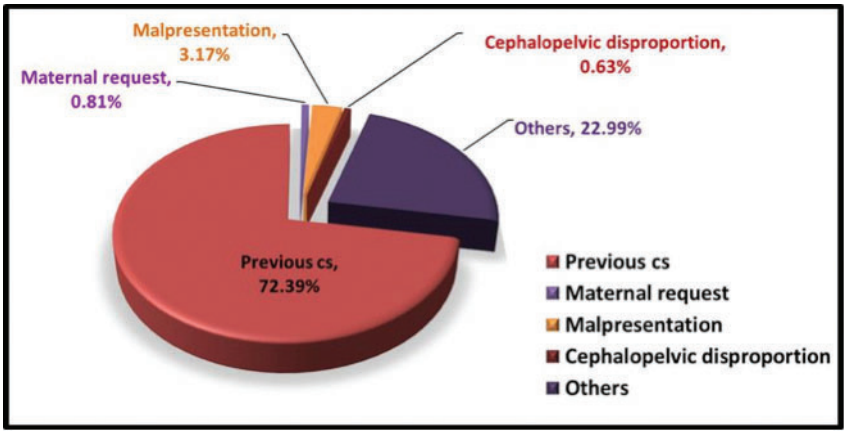

Figure 2 Indication of caesarean section among the studied groups.

Table 2: Baseline neonatal characteristics among the studied cases.

Characteristics	Group (A) Corticosteroids (n=877)	Group (B) No corticosteroids (n=228)	Test of Significance	P-value
Gestational age,				
Mean ±SD (week)	38.3 ± 6.91	38.5 ± 7.95		
Neonatal deliveries				
Single, no. (%)	856 (97.6%)	227 (99.6%)	χ^2= 3.548	0.060
Twins, no. (%)	21 (2.4%)	1 (0.4%)		
Neonatal gender				
Male, no. (%)	435 (48.4%)	112 (48.9%)	χ^2= 0.044	0.835
Female, no. (%)	463 (51.6%)	117 (51.1%)		
Birth weight				
Mean ±SD (gram)	3012.87±465.94	3071.51±489.61	t= 1.675	0.094
Range	1600-4800	1950-5300		

χ^2: Chi square test, **t:** Independent sample t-test.
SD; Standard deviation

Table 3: Corticosteroids characteristics received among the studied cases.

Characteristics		N	%
Dexamethasone received intramuscularly	Complete course & proper dose *	24	2.74%
	Incomplete course	853	97.29%
	Single course	862	98.29%
	Repeated course	15	1.71%
The time between last ACS dose and delivery > 7 days		788	89.85%
The time between last ACS dose and delivery ≤ 7 days		89	10.15%

Total =877
***Complete course:** means 4 doses of 6 mg IM of dexamethasone 12 hours apart.
***Proper dose:** means delivery occurred within 24 hours to 7 days after the last dose.

Table 4: Outcome of the two-studied groups and odds ratio of the dexamethasone treated group.

Outcome	Group (A) Corticosteroids (n=877)	Group (B) No corticosteroids (n=228)	OR	95% CI	p-value
Admission to NICU	104 (11.9%)	19 (8.3%)	1.48	0.887-2.470	0.132
RD	100 (11.4%)	18 (7.9%)			
Grade I	56 (6.3%)	10 (4.4%)			
Grade II	28 (3.2%)	4 (1.8%)	1.50	0.889-2.537	0.127
Grade III	16 (1.8%)	4 (1.7%)			
Grade IV	0 (0.0%)	0 (0.0%)			
TTN	4 (0.5%)	1 (0.44%)	1.04	0.116-9.351	0.972
Mechanical ventilation	15 (1.7%)	3 (1.3%)	0.77	0.220-2.670	0.675
Apgar - score					
At 1-min, mean ±SD	6.69 ± 1.18	6.71 ± 1.21			0.885
At 5-min, mean ±SD	8.83 ± 0.53	8.85 ± 0.55			0.679
NICU- stay					
<6h	12 (1.4%)	3 (1.3%)			0.476
6-48h	47 (5.4%)	8 (3.5%)			
>48h	45 (5.1%)	8 (3.5%)			
Fetal outcome					
Discharge	93 (89.42%)	17 (89.47%)			0.321
Sepsis	7 (6.73%)	3 (15.78%)			
Death	11 (10.58%)	2 (10.53%)			

NICU: Neonatal intensive care unit. **OR:** Odds ratio.
TTN: Transient tachypnea of newborn. **CI:** Confidence interval.
RD: Respiratory distress.

Table 5: Complete ACS versus no ACS group regarding neonatal outcomes.

Outcome	Complete ACS (n=24)	Group (B) No corticosteroids (n=228)	OR	95% CI	p-value
Admission to NICU	4 (16.7%)	19 (8.3%)	2.200	0.682-7.101	0.178
RD	4 (16.7%)	18 (7.9%)			
Grade I	1 (4.2%)	10 (4.4%)			
Grade II	2 (8.3%)	4 (1.8%)	2.333	0.719-7.567	0.148
Grade III	1 (4.2%)	4 (1.7%)			
Grade IV	0 (0.0%)	0 (0.0%)			
TTN	0 (0.00%)	1 (0.44%)	1.004	0.996-1.013	0.745
Fetal outcome					0.242
Discharge	3 (75.0%)	17 (89.47%)			
Death	1 (25.0%)	2 (10.53%)			

NICU: Neonatal intensive care unit. **OR:** Odds ratio.
TTN: Transient tachypnea of newborn. **CI:** Confidence interval.
RD: Respiratory distress. **ACS:** Antenatal corticosteroids.

Table 6 Complete course versus incomplete course of ACS regarding neonatal outcomes.

Outcome	Complete course (n=24)	In complete course (n=853)	OR	95% CI	p-value
Admission to NICU	4 (16.7%)	100 (11.72%)	1.506	0.505-4.495	0.460
RD	4 (16.7%)	96 (11.25%)			
Grade I	1 (4.2%)	55 (6.4%)			
Grade II	2 (8.3%)	26 (3.0%)	1.577	0.528-4.711	0.411
Grade III	1 (4.2%)	15 (1.8%)			
Grade IV	0 (0.0%)	0 (0.0%)			
TTN	0 (0.00%)	4 (0.47%)	1.005	1.000-1.009	0.737
Fetal outcome					0.403
Discharge	3 (75.0%)	90 (90.0%)			
Death	1 (25.0%)	10 (10.0%)			

NICU: Neonatal intensive care unit. **OR:** Odds ratio.
TTN: Transient tachypnea of newborn. **CI:** Confidence interval.
RD: Respiratory distress. **ACS:** Antenatal corticosteroids.

DISCUSSION

According to a recent guideline by the Royal College of Obstetricians and Gynaecologists **(RCOG),** [6] for a planned caesarean section between 37+0 and 38+6 weeks an informed discussion should take place about the potential risks and benefits of a course of antenatal corticosteroids. Although antenatal corticosteroids may reduce admission to the neonatal intensive care unit for respiratory morbidity, it is uncertain if there is any reduction in respiratory distress syndrome, transient tachypnea of the newborn, or NICU admission overall, antenatal corticosteroids may result in harms to the neonate, which include hypoglycaemia and potential developmental delay.

Furthermore, a study by **Crowther et al**. [12] reported increased rates of SGA with repeated doses ≥4 courses.

This prospective observational study was conducted at Ain Shams University Maternity Hospital to assess the effect of routine prophylactic corticosteroids before elective caesarean section, at 37-42 weeks of gestation on neonatal respiratory morbidity.

The present study compared neonatal respiratory morbidity between 877 cases in group (A), whose mothers received prophylactic antenatal dexamethasone, and 228 cases in group (B), whose mothers did not receive dexamethasone.

The majority of elective caesarean sections in both groups were done for previous caesarean section (72.39%), malpresentation (3.17%), cephalopelvic disproportion (0.63%), maternal request (0.81%), and others (22.99%).

Meticulous review of the dose regimens and ACS- delivery interval revealed that only 24 women was (2.74%) received the ACS doses strictly according to the guidelines and delivered within 24 hours to 7 days after the last dose.

In our study, there was no statistically significant difference in the incidence of TTN or RDS. No cases of TTN were found in exposed subgroup, versus 1 (0.4%) in non-exposed group (p = 0.745). The respiratory distress (RDS) in the exposed subgroup was 4 cases (16.7%) versus 18 (7.9%) in non-exposed group (p = 0.148). While the admission to the neonatal intensive care unit (NICU) due to respiratory morbidity after elective caesarean section was 4 cases (16.7%) in the exposed subgroup versus 19 cases (8.3%) in the non- exposed group (p = 0.178).

Jayawardane et al. [13] conducted a retrospective cohort study to investigate the effects of corticosteroid administration for respiratory morbidity in neonates delivered by elective caesarean section (ELCS) between 37 and 38+6 weeks. Of the 560 patients included, 23.2% received antenatal corticosteroids. The incidence of RD, NICU admissions in the study cohort was 10%, 0.9%, and 2.7% respectively. Relative risk for developing RD in the steroid group compared to no steroid group was 2.67 (95% CI 1.64-4.35). While 4.6% of the steroid group and 3.3% of the non-steroid group needed to be admitted to the NICU (p = 0.464). They agreed with the results of the present study and even stated that, there was an increase in respiratory morbidity in the dexamethasone-administered mothers. However, this effect had no clinical significance since the admissions to the NICU was not significantly different.

El-Berry and colleagues, [14] compared neonatal respiratory morbidity among exposed and non-exposed groups. They found that there were no significant difference between the corticosteroid exposed group and non-exposed group regarding admission to the NICU (p = 0.570), respiratory distress syndrome (no cases of RDS have been recorded), transient tachypnea of the neonate, need for mechanical ventilation (p = 0.701), outcome, and length of hospital stay. They agreed with our study that antenatal corticosteroids for elective caesarean delivery between 37 and 39 weeks is not effective in improving neonatal outcomes.

Also, **Ahmadpour-kacho and colleagues,** [15] compared an overall of 200 infants, with the age of 39-42 weeks, in two groups a control group (n = 100) and betamethasone group (n =100). They reported that nine neonates (9%) in the steroid group and 8 neonates (8%) in the control group had TTN (p = 0. 64), and one (1%) neonate in the steroid group and one neonate (1%) in the control group had RDS (p = 1). They found that, there were no significant differences in outcomes between the two groups.

In line with our results **Tan and colleagues,** [16] conducted a retrospective study of 674 patients undergoing elective caesarian sections between 37±0 and 38±6 and compared the respiratory morbidities before and after the implementation of single dose 12 mg IM dexamethasone given at least 24 hours before the elective caesarean section. They found that IM dexamethasone injection did not show any significant benefit with regards to reducing the admission to neonatal care (OR 0.97, p = 0.69), admission to the neonatal intensive care unit (OR 0.91, p = 0.80), the need for mechanical ventilation (OR 0.98, p = 0.95), and the incidence of transient tachypnea of the newborn (OR 1.01, p = 0.96). Also, there was no significant difference in the duration of admission to the neonatal intensive care unit for both groups (p = 0.17).

Arsad and colleagues, [17] conducted a study on women with singleton pregnancies planned for elective caesarean section between 37+0 and 38+6 weeks gestation.

Overall, 189 patients were recruited, 93 women in the intervention group and 96 as controls. In their study, infants with respiratory morbidities were primarily due to transient tachypnea of newborns (9.7% vs. 6.3%), but none had respiratory distress syndrome. Only four infants required NICU admission (2.2% vs. 3.1%, p = 0.63). Their average length of stay was not statistically different between the two groups; 3.5 ±2.1 days vs. 5.7 ± 1.5 days (p = 0.27).

They agreed with our results that antenatal dexamethasone did not diminish the number of infants needing respiratory support, NICU admission or the length of NICU stay.

In our study, the overall mortality in exposed group was 1 out of 24 (4.17%), while in non-exposed group was 2 out of 228 (0.88%). However, this was not a statistically significant difference (p = 0.242).

Contrary to our study, a recent cochrane review by **Sotiriadis et al.** [18] suggested that the administration of 2 doses of betamethasone 48 hours, before planned CS at term probably reduces neonatal respiratory morbidity compared with a placebo or no treatment. The incidence of TTN was 2.3% versus 5.4% (RR 0.43, 95% CI 0.29–0.65), RDS was 2.6% versus 5.4% (RR 0.48, 95% CI 0.27–0.87), and admission to the NICU for respiratory morbidity was 2.3% versus 5.1% (RR 0.45, 95% CI 0.22–0.90). However, they stated that the risk of bias for selective outcomes was unclear, and the overall certainty of the evidence for the primary outcomes was found to be low or very low.

Also, **Khushdil and colleagues,** [19] conducted a non-randomized experimental study and compared 240 patients (44.8%) who received steroids before their elective caesarean section at 37-39 weeks, to 295 patients (55.2%) who did not receive steroids. They reported that, 4.74% of newborns in group (2) developed transient tachypnea of newborns (TTN), which was higher than the newborns in group (1) (1.66%), (p = 0.049). Also, the number of neonates being admitted to the NICU was greater in group (2) than in group (1) [23 (7.79%) versus 6 (2.5%), respectively, p = 0.007]. They disagreed with our study that steroids significantly reduce the risk of respiratory morbidity in babies delivered by elective caesarian section between 37-39 weeks. However, this disagreement might be

due to the difference in gestational age, and the smaller sample size.

Similarly, **Elewa and colleagues,** [20] compared 200 cases who received two intramuscular doses of 12 mg dexamethasone 12 hours apart, 24 hours before elective caesarean section. To 200 cases who received IM saline as a placebo in the same regimen as the steroid group at gestational age 37-39 weeks. They reported that both TTN admission to the NICU, and neonatal need for CPAP were statistically significantly lower among group (A) than in group (B). However, their study used a prophylactic intramuscular injection of 12 mg of dexamethasone rather than 6 mg. The dexamethasone dose, and the gestational age of the study participants, may be behind the difference with our results.

Srinivasjois and colleagues, [21] conducted a systematic review and meta- analysis, including three randomized controlled trials (N = 2740 patients). They concluded that although steroid administration reduces neonatal morbidities, routine administration of steroids prior to scheduled cesarean section should be done cautiously because of the long-term risks related to steroids.

A recently published systemic review and meta-analysis by **Ninan et al.** [22] further alerts us to the potential long-term effects on neurodevelopment of antenatal exposure to corticosteroids. In this review, a total of 30 studies (more than 1.25 million children) were included, where the authors highlighted the risk of associated mental, behavioral, and neurocognitive disorders in late-preterm and full-term birth with antenatal corticosteroid exposure. The postulated explanation was that fetuses near term are exposed to an intrinsic increment of cortisol from self and from the maternal side. The dose of the injected exogenous corticosteroids is supraphysiological, which may interfere in the brain developmental programming, as well as the hypothalamic– pituitary–adrenal axis.

Among the strengths of this study is the large sample size (1105 patients). Furthermore, we observed the patients' hospital records and interviewed the patients in case of incomplete records to minimize recall bias. Also, we meticulously reviewed the dose regimens and ACS- delivery intervals to further target the subgroup of patients who received ACS strictly as per the guidelines.

Finally, we followed up the neonates admitted to the NICU, traced their respiratory needs (nasal oxygen, CPAP, mechanical ventilation), until they were either discharged home, or sadly perished.

The limitations of the current study is it's observational nature, that made it dependent on patient recall and self-reported exposure. So, a risk of bias may be found. However, the outcomes were objective, depending on the diagnosis made by clinicians at the time of delivery rather than radiological features. Also, we tried to minimize bias by confirmation of the data in the records by direct interview of the patient. Furthermore, the current study focused on short-terms rather than long-terms follow–up of babies whose mothers received dexamethasone.

CONCLUSION

According to our findings, routine administration of prophylactic antenatal corticosteroids before elective caesarean sections at term does not reduce the risk of admission to the NICU compared to non-administration.

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Association between vitamin D levels and menstrual irregularities in reproductive age women

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Abstract

Background: Vitamin D was found to be linked with many derangements in the human body. Its association with menstrual irregularities has been significantly reported.

Objective: Evaluation of the association between vitamin D deficiency and menstrual irregularities.

Study design: This cross- sectional study was conducted from March 2023- August 2023 at the outpatient clinic

of a tertiary hospital. We recruited women presented with menstrual irregularities according to predetermined inclusion and exclusion criteria. A control group of women with regular cycles was included. Vitamin D level was evaluated in both groups.

Results: This study recruited 104 women (52 participants per group). Vitamin D deficiency was noted in 46/104 participants (44.2%). Women with menstrual irregularities were younger than those with regular cycles (p-value 0.0001). The menstrual cycle length differed significantly between both groups (p-value 0.0001). Vitamin D level was significantly lower in the study group than in the control group (20.0 ± 11.9 and 28.7 ± 16.6, respectively, p-value 0.003). Younger age was a significant predictor for irregular cycles (p-value 0.005).

Conclusion: Vitamin D deficiency was noted significantly among women with irregular cycles. Age was a significant predictor for irregular cycles rather than vitamin D levels.

Keywords: Irregular cycles; Reproductive age; Vitamin D.

Introduction

The menstrual cycle is a physiological sign of women's well-being (1). The cycle length differs from one woman to another, with a reported range from 18- 35 days (2). At least one menstrual problem occurs in 64% of females. These problems might include menstrual irregularities, heavy menstrual bleeding, or oligomenorrhea (3). Evidence has shown that metabolic mechanisms may disrupt menstrual irregularity (4). Multiple metabolic mechanisms depend on vitamin D as an essential factor (5). Vitamin D affects reproductive hormone regularity and the menstrual cycle (6). It has been reported that vitamin D receptors were found in the reproductive organs (ovaries, endometrium, uterus, and placenta) (7). It was found that anti-mullerian hormone receptors included a domain for the vitamin D response element, which allows vitamin D to affect ovarian function (8). Accordingly, vitamin D deficiency was associated with a wide range of reproductive problems (9), particularly menstrual cycle irregularity and length (10). Other reported associations with vitamin D deficiency included endometriosis (11), polycystic ovary syndrome (12), uterine fibroids (13), and infertility (14). Another evidence reported an association between vitamin D deficiency and the severity of premenstrual symptoms (15). Also, it has been reported that estradiol levels are affected by fluctuations in vitamin D levels (1). Accordingly, this study evaluated the association between vitamin D levels and menstrual irregularities among Egyptian women.

Methods

This cross-sectional study was conducted at the outpatient clinics of obstetrics and gynecology at a tertiary hospital from March 2023 to August 2023. The study recruited women according to predetermined inclusion and exclusion criteria. The inclusion criteria were a) women aged 18- 40 years, b) women presenting with any menstrual complaint as follows:

- Oligomenorrhea: defined as a menstrual cycle length > 45 days (16)
- Heavy menstrual bleeding is defined as excessive menstrual blood loss interfering with women's physical, social, emotional, and quality of life (17).
- A bleeding/ spotting episode is defined as one or more consecutive days during which blood loss has been reported (18)
- Polymenorrhea: defined as intervals of up to 21 days (19).

The exclusion criteria included a) women taking vitamin D supplementation, b) women refusing to participate in the study, c) women taking hormonal contraceptive methods, d) women with a known cause of menstrual

irregularities such as thyroid disorders, hyperprolactinemia, polycystic ovary syndrome, or ovarian tumors. A control group of women presenting to the outpatient clinic without any menstrual-related complaints was recruited. They had to be non-pregnant and not take any hormonal contraceptive methods to be eligible for the study.

Eligible women were subjected to history taking and examination, including (age, weight, height, BMI, occupation, and education). They were asked to report the following:

- number of bleeding/ spotting episodes
- cycle length in days
- number of menstrual bleeding days
- the presence or absence of dysmenorrhea.

Bleeding was evaluated using a bleeding diary that was given to each participant. Women were instructed to mark ○ for spotting and ● bleeding days. The usual menstrual bleeding was marked as /. Women were instructed to use standard disposable pads and to report the number of pads each day.

A blood sample was collected to measure serum Vitamin D after recruitment. Vitamin D was measured by ELISA (20). Results were interpreted as sufficiency (30–100 ng/mL), insufficiency (21–29 ng/mL), and deficiency (< 20 ng/mL) (21).

The sample size was calculated at a significance level of 99% and an error level of 10% using a difference in mean vitamin D level in women with irregular cycles (14.56 ng/ml) (22) and the mean vitamin D level in women with regular cycles (21.9 ng/ml) (22). The estimate of the pooled standard deviation of vitamin D was 8.76 ng/ml. So, by calculation, the minimum sample size required is 44 patients per group.

Ethical approval: This study was conducted after the approval of the research ethics committee on 21/3/2023 with a number of 5205#.

Statistical Analysis

Data was statistically described in terms of mean and standard deviation, frequencies (number of cases), and percentages when appropriate. P values less than 0.05 were considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 22 for Microsoft Windows. The chi-square test was used for categorical variables, and the (t) test was used for continuous variables with normally distributed data. Non-normally distributed data were tested using Fisher's exact for categorical variables, and Mann-Whitney U tests for continuous variables. The strength of association was measured with odds ratio. Logistic regression was performed to determine the predictors for irregular menstrual cycle and confirm the association between it and vitamin D levels.

Results

This study recruited 52 women in each group. The study group included women with irregular cycles, while the control group included women with regular ones. Vitamin D deficiency was noted in 46/104 participants (44.2%).

Younger women had irregular cycles than (p-value 0.0001). There was no statistically significant difference in the other demographic data of the studied population (Table 1).

The menstrual cycle length differed significantly between both groups (p-value 0.0001). The number of pads/day was significantly increased among the control group than the study one (2.8 ± 1.1 versus 2.3 ± 0.5, p-value 0.001). The menstrual cycle pattern varied among the study group, with oligomenorrhea (65.4%) as the predominant pattern (Table 2).

Vitamin D level was significantly lower in the

study group than in the control group (20.0 ± 11.9 and 28.7 ± 16.6, respectively, p-value 0.003). Also, the study group included more women with deficient and insufficient vitamin D (51.9% and 32.7% respectively) level than the control group (36.5% and 26.9% respectively) (Table 3).

Among the factors associated with irregular cycles, younger age was a significant predictor (p-value 0.005) (Table 4).

Discussion

Vitamin D deficiency was present in 44.2% of the studied population. Higher results were reported previously, where 80% of the studied population was vitamin D deficient (23). Another study conducted among Egyptian mothers reported vitamin D deficiency to affect 40% of the studied population (24), which is similar to the current results. This discrepancy would be attributed to different races among studies, different cultural behaviors as women tend to wear clothes covering the entire body, and different territories with variable sun incidence (25).

Women with irregular cycles were younger than those with regular cycles. An earlier study contradicted this finding (26). However, this agreed with another one as women with irregular cycles had a mean age of 27.65 ± 0.36, while those with regular cycles aged 30.57 ± 0.17 (p-value < 0.001) (27). This was due to the effect of age on maturing and stabilizing sex hormones and the reproductive organs (27).

Vitamin D level was significantly lower in women with irregular cycles than those with regular ones. This agreed with previous results, as insufficient vitamin D was associated with increased cycle length, oligomenorrhea, and amenorrhea (28, 29). Another study reported improved cycle regularity among women after vitamin D supplementation. However, this study recruited women with polycystic ovary syndrome and added calcium supplantation (30).

The mechanism behind vitamin D's effect on menstrual cycle regularity is unexplained. It was assumed that it affects anti-mullerian hormone (AMH), which has an essential role in oocyte maturation and ovulation (30), as evidenced by decreased primordial follicle production, delayed follicle atresia, and decreased follicle development (31). This effect is mediated through vitamin D control of AMH production because of a domain for vitamin D signaling pathways on AMH receptors (31). Vitamin D receptors are present in the ovarian tissue, which correlates with steroidogenesis and follicle maturation (32). It affects estrogen and progesterone production (1). Another mechanism regulates calcium homeostasis, paramount in oocyte activation and maturation (8).

Among the factors associated with irregular cycles, younger age was a significant predictor. This agreed with previous results, as increasing age was associated with decreased odds of having irregular cycles (27). Another study reported that vitamin D insufficiency was associated with 13.3 times the odds of reporting irregular cycles (29), contradicting our results. Another reported a significant association between low vitamin D levels and irregular cycles, with no significant association with short or long cycles (7).

Strength and limitations

The study included a control group of women with regular cycles to get conclusive results; however, the small sample size is a limitation. Another limitation is the study design (cross-sectional study), as a randomized trial would be more powerful. Menstrual cycle evaluation was done using a diary to avoid recall bias. We did not evaluate possible risk factors contributing to irregular cycles.

Conclusion

Vitamin D deficiency was noted significantly among women with irregular cycles. Age was a significant predictor for irregular cycles rather than vitamin D levels.

Conflict of interest: None

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Table (1): Basic demographic data of the studied population

		Study group (N= 52)	Control group (N= 52)	P value
Age (years) (Mean ± SD)		30.2 ± 7.3	35.1 ± 6.2	0.0001[a]
Parity (Mean ± SD)		2.5 ± 1.6	2.8 ± 1.5	0.324[a]
BMI (Mean ± SD)		27.2 ± 5.7	28.4 ± 5.2	0.275[a]
Education N (%)	**None**	6 (11.5%)	8 (15.4%)	0.096[b]
	Middle	26 (50%)	34 (65.4%)	
	High	20 (38.5%)	10 (19.2%)	
Occupation N (%)	**Housewife**	40 (76.9%)	38 (73.1%)	0.494[b]
	Employee	12 (23.1%)	14 (26.9%)	

[a] student t-test, [b] chi-square test

Table 2: Menstrual cycle characteristics between both groups:

		Study group (N= 52)	Control group (N= 52)	P value
Menstrual cycle length (days) (Mean ± SD)		58.4 ± 38.1	27.3 ± 2.8	0.0001[a]
Menstrual bleeding days (Mean ± SD)		5.57 ± 0.80	5.55 ± 0.77	0.901[a]
Number of pads/day (Mean ± SD)		2.3 ± 0.5	2.8 ± 1.1	0.001[a]
Number of bleeding episodes		0.09 ± 0.4	0.0 ± 0.0	0.093[a]
Menstrual cycle pattern N (%)	**Intermenstrual bleeding**	3 (5.8%)	0 (0.0%)	0.0001[b]
	Oligomenorrhea	34 (65.4%)	0 (0.0%)	
	Amenorrhea	7 (13.5%)	0 (0.0%)	
	Polymenorrhea	7 (13.5%)	0 (0.0%)	
	HMB	1 (1.9%)	0 (0.0%)	
Dysmenorrhea N (%)	**Yes**	3 (5.8%)	8 (15.4%)	0.111[b]
	No	49 (94.2%)	44 (84.6%)	

[a] student t-test, [b] chi-square test

Table 3: Vitamin D levels among both groups

		Study group (N= 52)	Control group (N= 52)	P value
Vitamin D level (ng/ml) (Mean ± SD)		20.0 ± 11.9	28.7 ± 16.6	0.003[a]
Vitamin D category N (%)	**Sufficient**	8 (15.4%)	19 (36.5%)	0.046[b]
	Insufficient	17 (32.7%)	14 (26.9%)	
	Deficient	27 (51.9%)	19 (36.5%)	

[a] student t-test, [b] chi-square test

Table 4: Factors associated with irregular cycles

Variable	B	95% CI	P value
Age	-0.166	0.754- 0.951	0.005
Parity	0.488	0.991- 2.676	0.054
BMI	-0.034	0.885- 1.054	0.440
Education	0.219	0.615-2.521	0.543
Occupation	-0.134	0.875- 0.520	0.614
Vitamin D level	-0.059	0.861-1.032	0.202

KHALAF maneuver, a new maneuver for management of shoulder dystocia.

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Abstract

Background : Shoulder dystocia is a vaginal cephalic delivery in which the foetus must be delivered via further obstetric procedures after the head has been delivered and gentle traction has failed. Even when the illness is well controlled, there may be severe prenatal morbidity and mortality.

Technique : Khalaf technique is a new technique that can be used as a second-line maneuver to resolve shoulder dystocia. It involves combined rotation and traction of the shoulders so that the biacromial diameter occupies the wider oblique diameter of the pelvis and at the same time traction will help delivery of the posterior shoulder followed by the anterior shoulder.

Patients and methods: We conducted this maneuver during the period from 2019 till 2023 on 35 women with shoulder dystocia only after failure of 1st line maneuvers to resolve the condition . Cases underwent vaginal delivery in Mouwasat hospital Qatif and Riyadh in collaboration King Faisal military hospital (Armed forces Hospital).

Results: Age of studied women ranged from (19-43) with a mean of 31.03 + 6.75 years .Their Gestational age ranged from (37-41) with a mean of 39.46+1.38weeks and BMI ranged from (23.60-42) with a mean of 32.67+4.39Kg/m2. Head to shoulder interval ranged from (45-120) seconds with a mean of 74.57 + 18.80 seconds. Fetal weight ranged from (3.40-4.40) with a mean of 3.94 + 0.27 Kg, APGAR score at first minute ranged from (5-8) with a mean of 6.54 + 0.82 and five minutes ranged from (8-10) with a mean of 9 + 0.49. Our new maneuver was successful in all cases of the case series , Khalaf maneuver was not associated with any maternal or fetal mortality . No cases of fetal injuries occurred in our case series and also no significant maternal morbidity.

Conclusion: Khalaf maneuver is a safe effective and not time consuming maneuver that can be used for cases of unresolved shoulder dystocia.

Keywords: labour , shoulder dystocia , Khalaf maneuver .

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Introduction

By definition, shoulder dystocia is a mechanical issue that arises during a vaginal birth and is indicated by one of the following characteristics:

- The shoulders of the foetus are not delivered utilising only little downward traction. To deliver the baby successfully, more delivery techniques are required.
- A head-to-body gap that is measured to be longer than a minute.

Following the delivery of the foetal head, the foetal head may retract towards the perineum. It is referred to as the "turtle sign." A risk factor for shoulder dystocia is the latter. [1,2]

It happens when one or both shoulders get impinged on the sacral promontory and/or symphysis pubis of the mother's pelvis.[3]

0.6 to 1.4% of all vaginal births are complicated by obstetric crises, which are unpredictable and frequently inevitable. The risk factors and treatment of shoulder dystocia must be understood by all obstetric professionals. [1,2]

There are a number of risk factors for shoulder dystocia. The main risk factor for shoulder dystocia is foetal macrosomia. Pregnant and gestational diabetes, a history of shoulder dystocia, and surgical vaginal birth, particularly when the vacuum is used, are further established risk factors. Due to inconsistent findings in research, other risk factors like maternal obesity, excessive maternal weight gain, and labour disruption are debatable. Based on these risk factors, attempts to predict shoulder dystocia have shown low predictive value and reliability.[4]

Shoulder dystocia, which is regarded as an obstetric emergency, can cause serious injury to both the mother and the foetus if it is not treated effectively and quickly. Cord pH decreases as the head-to-body delivery interval increases, but it takes about five minutes for the decline to become clinically meaningful. [5,6] A head-to-body delivery interval of less than or equal to 6 minutes has been shown to not increase the incidence of hypoxia ischemic encephalopathy (HIE) in otherwise healthy foetuses. [7] However, after that point, there is a higher risk of newborn depression, acidosis, hypoxia, injury to the central nervous system, and death. [8,9]

Shoulder dystocia may have negative effects on the mother and foetus. Postpartum haemorrhage and a higher incidence of third- or fourth-degree laceration are two maternal effects. The Zavanelli manoeuvre is one of the "heroic manoeuvres" that is strongly linked to considerable maternal morbidity. Foetal repercussions can include hypoxic ischemic encephalopathy syndrome, brachial plexus damage, clavicular or humeral fractures, and possibly foetal mortality. The majority of brachial plexus injuries heal over time and with physical therapy. Usually, foetal fractures heal without any problems.[10,11,12]

Various manoeuvres are now used to treat shoulder dystocia, however there haven't been any direct comparisons of their efficacy in randomised controlled studies or experiments. Some authors advocate a coordinated series of manoeuvres, like those listed in the HELPERR mnemonic. [13-15] The HELPERR [16,17] algorithm is as follows: Help, Evaluate (for episiotomy), Legs (McRoberts' position), Pressure (suprapubic), Enter (rotational maneuvers), Remove (posterior arm), and Roll (hands and knees).

However, the order in which these manoeuvres should be used lacks a solid empirical base .[18]

We introduce our technique to be used immediately if 1st line maneuvers failed to resolve this obstetric emergency.

Technique

1. Confirm the diagnosis : Observe for signs of shoulder dystocia which includes difficulty of delivery of the face and chin , the head remains tightly applied to the vulva or even retracting (turtle-neck sign) , failure of restitution of the fetal head , failure of the shoulders to descend .

2. Assess the need to do episiotomy.
3. If the face of the baby is towards the right maternal thigh , introduce the palmer aspect of the LT hand in the vaginal orifice below the posterior shoulder , then hook the index finger around the axilla of the posterior shoulder , (note that the palmer aspect of the index finger should be in contact with axilla not the tip of the finger to avoid any unnecessary trauma to brachial plexus) this will form C shaped hook around the axilla of the posterior shoulder and will provide good grip, now introduce the palmer aspect of the middle and index finger of the right hand to the anterior aspect of the anterior shoulder .
4. Both hands should work in synergy to do a combined movement of rotation and traction as the LT hand rotate posterior shoulder towards the maternal right thigh and right hand push the anterior shoulder towards the maternal left thigh and by that the shoulder will occupy the wider oblique diameter of the pelvis , only 15-30 degree is needed for rotation , note that this rotation movement is accompanied by traction in the direction of pelvic axis with the left hand that will help in delivery of the posterior shoulder followed by delivery of the anterior shoulder .
5. If the face of the baby is towards the left maternal thigh then the right hand will be behind the posterior shoulder and the LT hand will be in front of the anterior shoulder and the rest of the steps will be as above.
6. An assistant do support of the perineum with every case during performance of the maneuver to protect it from extended perineal injuries .

Patients and methods

- This case series was conducted at Mouwasat hospital , Qatif , Riyadh and King Faisal military hospital (Armed forces Hospital) during the period from August 2019 till September 2023. It included patients all of which fulfilling criteria of diagnosis of shoulder dystocia and have been subjected to 1st line maneuvers of management of shoulder dystocia which are McRobert and suprapubic pressure . After failure of 1st line to resolve the condition , so we implemented our technique , we did not discuss cases at which 1st line maneuvers succeeded to resolve the condition . The following factors are used to determine a shoulder dystocia diagnosis: delivery of the face and chin is difficult, the foetal head is still strongly attached to the perineum with the turtle neck sign, and the shoulder fails to deliver with . We call for help to provide extra support and it include the author , extra nurse , pediatric team , anesthesiologist , obstetric resident and a personnel assigned to record time and notify the team with it after every passing 30 seconds , after delivery of the baby , the pediatric team receives him APGAR score is done at minute 1 and minute 5 , resuscitation is done if needed , full examination is done to document any birth injury , if the pediatric team suspects injury , then additional radiological investigation to confirm . at the same time the obstetric team examines the mother to find out any maternal injury and to repair it . finally we documented the following : maternal age , parity , gestational age , Body mass index , fetal weight , any maternal risk factors such as diabetes mellitus or previous history of shoulder dystocia , names of staff persons present at delivery and their roles , documentation of any labor abnormality , type of anesthesia, if needed , timing of the delivery of the head , timing of the delivery of the shoulders , position of the fetal head at the time of delivery , which shoulder was the anterior shoulder , which maneuvers were used to achieve delivery and the order in which

they were used , whether episiotomy was performed and if any lacerations , whether maternal injuries were sustained , whether fetal injuries were identified , the condition of the baby at birth , the results of umbilical cord gas analysis. Our primary outcome is interval time between delivery of the head and delivery of the shoulder , secondary outcomes are maternal or fetal birth injuries and fetal condition at birth.

This study had been registered on PACTR with ID 24037

Ethical and legal aspect: Detailed informed written consent was given to women suspected to encounter shoulder dystocia while they are still in labor including their rights, nature, objectives, benefits and hazards of the study in a form understandable for her in Arabic language containing all locally required data and specifications. The original form was signed by personally dated signature, then retained by the investigator. If any woman was unable to read, oral presentation and explanation of the written consent in the presence of impartial witness was available. Alternatively, the participant could use the thumbprint or a mark in presence of witness who would also sign and personally date it. Nothing done till a valid consent was obtained. If the situation occur in patients without risk factors then verbal consent is taken before applying this maneuver .

All reports, evaluation forms didn't contain any personal data to ensure their confidentiality. Only patient number and initials were recorded, and if the name of patient was appearing in any document, its privacy was kept by the investigator who had the personal identification list.

The protocol and any corresponding element according to the local regulations was approved before the beginning of the study by the ethical committee of Mouwasat hospital Qatif and King Faisal military hospital (Armed forces Hospital). The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Results

Table 1: Patients' criteria

		Minimum	Maximum	Mean	SD
age in years		19.00	43.00	31.03	6.75
gestational age in weeks		37.00	41.00	39.46	1.38
maternal BMI		23.60	42.00	32.67	4.39
pre Hb		9.20	13.20	10.94	.92
		N		%	
Parity	PG	8		22.9%	
	P1	3		8.6%	
	P2	8		22.9%	
	P3	9		25.7%	
	P4	4		11.4%	
	P5	2		5.7%	
	P6	1		2.9%	

relevant maternal past or obstetric history	No	19	54.3%
	Previous vacuum delivery	2	5.7%
	Gestational diabetes	1	2.9%
	Pregestational diabetes	6	17.1%
	Previous forceps delivery	1	2.9%
	Induction of labor	5	14.3%
	Previous shoulder dystocia	1	2.9%
use of anesthesia	No	10	28.6%
	Local	17	48.6%
	Epidural	8	22.9%
use of episiotomy	No	12	34.3%
	Yes	23	65.7%
which shoulder was the anterior shoulder	Right	22	62.9%
	Left	13	37.1%

Age of studied women ranged from (19-43) with a mean of 31.03 + 6.75 years. Their Gestational age ranged from (37-41) with a mean of 39.46+1.38weeks and BMI ranged from (23.60-42) with a mean of 32.67+4.39Kg/m2. Hemoglobin level before labor ranged from (9.20-13.20) with a mean of 10.94+0.92gm/dl.

Eight women (22.9%) were PG, 19 women (54.3%) had no maternal medical or obstetric healthy and the most common relevant medical history was pregestational diabetes (17.1%). 10 women (28.6%) didn't need anesthesia and 48.6% needed local anesthesia.

Episiotomy was done in 23 women (65.7%) and the anterior shoulder was the right one in 62.9% of cases.

Table 2: Outcome

		Minimum	Maximum	Mean	SD
post Hb		7.80	12.50	9.83	1.01
Cord blood PH		7.18	7.36	7.25	.05
length of active phase in hours		3.00	7.00	5.14	1.00
length of 2nd stage in minutes		20.00	120.00	59.20	28.22
head to shoulder interval in seconds		45.00	120.00	74.57	18.80
fetal weight in kilograms		3.40	4.40	3.94	.27
APGAR 1 min.		5.00	8.00	6.54	.82
APGAR 5 min.		8.00	10.00	9.00	.49
		N		%	
mode of delivery	Spontaneous	26		74.3%	
	Vacuum	7		20.0%	
	Forceps	2		5.7%	

any labor abnormality	No	22	62.9%
	Protracted 1st stage	10	28.6%
	Protracted 2nd stage	3	8.6%
position of fetal head after delivery	Facing maternal right thigh	22	62.9%
	Facing maternal left thigh	13	37.1%
fetal birth injury	No	35	100.0%
	Yes	0	0.0%
Neonatal ICU admission	2 cases due to meconium stained liquor.		
maternal birth injury	No	17	48.6%
	1st degree perineal tear	5	14.3%
	2nd degree perineal tear	6	17.1%
	contralateral vaginal tear	6	17.1%
	paraurethral tear	1	2.9%

Post-labor hemoglobin level ranged from (7.80-12.50) with a mean of 9.83 + 1.01 gm/dl and cord blood PH ranged from (7.18-7.36) with a mean of 7.25 + 0.5.

Length of active phase ranged from (3-7) with a mean of 5.14 + 1.00 hours, length of second stage ranged from (20-120) with a mean of 59.20 + 28.22 minutes and head to shoulder interval ranged from (45-120) with a mean of 74.57 + 18.80 seconds.

Fetal weight ranged from (3.40-4.40) with a mean of 3.94 + 0.27 Kg, APGAR score at first minute ranged from (5-8) with a mean of 6.54 + 0.82 and five minutes ranged from (8-10) with a mean of 9 + 0.49.

Most of women (74.6%) had spontaneous delivery and 62.9% had no labor abnormality. Twenty-two fetuses (62.9%) had their head facing right maternal thigh and all of them had no birth injury.

Seventeen women (48.6%) had no maternal injury and among those with injury, the most common injuries were second degree perineal tear and contralateral vaginal tear (17.1% for each).

Discussion

Shoulder dystocia is one of the most challenging situations facing obstetricians because of its unpredictable and unpreventable nature and its association with significant maternal and fetal birth injuries . Our new technique was successful in all cases of the case series , it had been used after failure of 1st line maneuvers . Khalaf technique was not associated with any maternal

or fetal mortality , it provided a head to shoulder interval ranging between 45 to 120 seconds with mean 74.57 and SD 18.80 . It also provided 1 minute APGAR score ranging between 5 to 8 with mean 6.54 and SD 0.82 , moreover 5 minute APGAR score ranged between 8 to 10 with mean 9 and SD 0.49 . No cases of fetal injuries occurred in our case series and also no significant maternal morbidity.

Improvement of outcomes is linked to the use of simulation training and a methodical strategy. In order to achieve the greatest results for both mother and baby during shoulder dystocia management, a calm operator and skilled team are required.

Once the situation has been identified, a call for assistance should be made right away. It is not recommended to utilise maternal pushing or fundal pressure.(13) RCOG and ACOG both agreed that the McRoberts procedure should be used as a first line since it is a straightforward, quick, and successful intervention with a success rate of 24-62%. [13,18] The McRoberts manoeuvre involves flexing and abducting the mother's hips to place her thighs on her belly. [19] It raises the relative anterior-posterior diameter of the pelvis and straightens the lumbosacral angle. It also turns the mother's pelvis towards her head.[20] The McRoberts' move is a successful intervention, with success rates reached up to 90% in some series .[21,22] If at all possible, use it initially because it has a low likelihood of complications and is one of the least invasive manoeuvres. The McRoberts manoeuvre can be combined with suprapubic pressure to increase success rates. [23] The foetal biacromial diameter is decreased by suprapubic pressure, and the anterior foetal shoulder is rotated into the larger oblique pelvic diameter. Regular axial traction is then used to release the shoulder so that it can slide under the symphysis pubis. [21] An episiotomy is not usually required; it is mostly employed when the operator needs to do internal vaginal operations . [13]

Both McRoberts' maneuver and suprapubic pressure are considered 1st line maneuvers , if failed we go rapidly to 2nd line ones .

In an effort to decrease the risk of brachial plexus palsy and assist delivery, the Woods[24] manoeuvre was described in 1942. It involved presenting a screw-like rotation manoeuvre to avoid the need for excessive traction to the head during delivery. This method rotates the symphysis pubis, sacral promontory, and coccyx inside the body while simultaneously providing downward external pressure to the newborn's buttock . In 1964, Rubin's[25] manoeuvre was introduced and demonstrated a way to decrease the shoulder's transverse diameter. In order to abduct the shoulder towards the chest and reduce its overall circumference to enable delivery, finger pressure is applied to the posterior aspect of both the anterior and posterior shoulders during the Rubin's manoeuvre. Unfortunately, these methods frequently fail to treat the dystocia and instead merely change the location of the two shoulders, which continue to lie behind the symphysis pubis. Furthermore, in large cohort studies, these two manoeuvres were linked to greater injury rates.[23,26]

It is feasible to deliver the posterior arm, but doing so necessitates that the neonate's hand be available to sweep across the chest. When the mother's anatomy is constrained or the newborn is enormous, this can be exceedingly challenging.[27] Aggressive attempts during this process can also fracture the clavicle or the humerus. Delivery

Shoulder shrug manoeuvre is one of the newly created manoeuvres that has been used.

This technique is designed specifically for severe shoulder dystocia, which frequently occurs when the posterior shoulder is positioned behind the sacral promontory. The posterior shoulder is encircled by the thumb and index finger. Insert the posterior shoulder into the sacrum's hollow by moving it forward. The head-shoulder unit is formed by positioning the head in relation to the body's axis, then rotating the unit 180 degrees in the direction of the chest. The anterior shoulder has progressed in the pelvis and turned posterior during rotation. With little forward propulsion, delivery of the newborn is currently being carried out. [28] With a better success rate than other internal manoeuvres and no increase in maternal or newborn morbidity, axillary traction has been employed as many women's initial internal manoeuvre. [29]

Khalaf maneuver is a technique that can be added to obstetrician's flowchart for management of shoulder dystocia. The

manoeuvre is simple to master during simulation training and apply in cases of dystocia because it just requires the obstetrician's hands and no other tools. Furthermore , it did not necessitate change in position of the patient and is suitable for patients with restricted mobility like with epidural anesthesia unlike all four maneuver.

Conclusion

Khalaf maneuver is a safe , effective and rapid maneuver that can be used to manage unresolved shoulder dystocia after failure of 1st line maneuvers to do so . It can be considered as an effective option that combine both rotation and traction on shoulders . However , more studies are needed to validate the procedure and to compare it with other 2nd line maneuvers.

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