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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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Examples of correct form of references

1- Standard journal article

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

2- Books:

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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.

3- Agency publication

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Contents :

Letter from the Editor:

Dear colleagues,

very interesting subjects are included in this edition. The etonogestrel implant users have a significant rate of amenorrhea at 1-yer use. A significant increase in the BMI, decreases in the uterine and ovarian volume. The woman should be counselled for the revealed predictors to increase the continuation and satisfaction rate. The use of letrozole in addition to misoprostol was associated with shorter induction to complete expulsion interval, higher complete abortion rate and less curettage rate compared to misoprostol group in patients undergoing induction of first trimester missed abortion (less than 14 weeks). Maternal serum amyloid A levels are increased in women with Placenta Accreta Spectrum.

Post-Void Residual (PVR) urine was found to be higher in parous women after vaginal delivery and complaining of pelvic organ prolapse (POP). We recommend using PVR evaluation as a screening approach for all women complaining of lower urinary tract symptoms and with history previous vaginal delivery.

Hysteroscopy is considered as a routine step in the fertility work-up program and becomes obligatory before the final diagnosis of unexplained infertility. It is an ideal diagnostic approach to several undiagnosed intrauterine pathologies after failure of different routine approaches.

No trimester is immune from rupture uterus. Careful use of prostaglandins for induction of miscarriage is required in patients with previous caesarean delivery even in early pregnancy. Previous history of rupture uterus requires more attention as the risk of repeat rupture is high and it recurs at an earlier gestation. Diagnosis of the ruptured uterus in early pregnancy can be challenging.

Best regards.
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The rate and predictors of amenorrhea at 1-year follow-up in women using etonogestrel implant

Running title: Amenorrhea at 1-year follow-up with etonogestrel implant

Disclosure statement: The authors report no conflicts of interest

Clinical trial.gov: NCT05040282

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Abstract

Objective: To identify the rate and the predictors of amenorrhea related to 1-year use of etonogestrel implant (ESI).

Material and methods: It was a single-center; longitudinal study conducted at The Dairut Central Hospital, Assiut, Egypt from 1st of October 2021 to August 2023 included women who requested ESI for pregnancy prevention for at least 1 year. The rate of amenorrhea associated with 1-year use of ESI was reported. The changes of body mass index (BMI), the uterine and ovarian volume as well as the uterine blood flow during ESI use were also documented. Finally; the predictors associated with amenorrhea were also explored. The data were analyzed by Independent sample t-test, means of non-parametric tests and Chi-square test. Multivariate logistic regression was conducted to test for the predictors.

Results: Three hundred women were included in the study. The rate of amenorrhea at 1-year use of ESI was 38.6%. The predictive model found that fewer bleeding days, the shorter cycle, smaller uterine and ovarian volume, and higher uterine artery pulsatility index were significant predictors for amenorrhea at 1-year of ESI use.

Conclusion: The ENG implant users have a significant rate of amenorrhea at 1-yer use. A significant increase in the BMI, decreases in the uterine and ovarian volume and the uterine blood flow were also observed. The woman should be counseled for the revealed predictors to increase the continuation and satisfaction rate.

Key words: Amenorrhea; Etonogestrel Implant; Implanon; Progesterone only methods.

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Introduction

The use of progestin-only contraceptive methods (POCs) has been increased evidently and progressively over the world in the last few years [1]. POCs are an option for breastfeeding women or for whom an estrogen-containing contraceptive is either contraindicated or causes significant health problems [2, 3]. POCs include progestin-only pills, depot-medroxyprogesterone acetate, ESI, and levonorgestrel intrauterine devices (LNG-IUS) [4].

Unscheduled vaginal bleeding among women using POCs is high and it is responsible for dissatisfaction and discontinuation in the majority of the users [5]. Bleeding patterns associated with POCs have different forms such as amenorrhea, vaginal spotting, pronged heavy bleeding, and sometimes normal monthly menses [6].

The ESI has been available worldwide for more than 15 years [7]. The action of ESI is principally via suppression of ovulation, but it also has effects on cervical mucus and in some women induces a suppression of endometrial proliferation [8]. ESI discontinuation is common in many countries and the majority of those discontinuers is in the childbearing period and is still in need of contraception [9]. ESI discontinue is up to 43% of women prior to completion of the 3 years and a considerable number of those women request early removal because of amenorrhea [10, 11].

Despite the presence of many studies reported the prevalence of ESI associated bleeding [12, 13, 14], a little is known about the rate of amenorrhea and the predictive factors causing amenorrhea after ESI insertion. These predictive factors should be provided to the clients prior to the ESI insertion which may improve acceptance and continuation of ESI. So the aim of this study was to explore the rate and the predictors of amenorrhea related to 1-year use of ESI.

Material and methods

It was a single-center; longitudinal study. It was prospectively registered at Clinicaltrial.gov (NCT05040282). The study was conducted at Dairut Central Hospital, Assiut, Egypt from 1st of October 2021 to August 2023. The protocol of the study was approved by The Assiut University Medical Ethical Review Board (IRB17101567).

Eligible participants

We included women aged between 18-40 years who were not lactating) more than 12 month postpartum). Those women had regular menstrual cycles (21–35 days length with less than 7 bleeding days) and wanted to use ESI only for pregnancy prevention for at least 1-year. The women had any contraindications for progesterone only contraception in accordance with WHO eligibility criteria [15] or refused the participation in the study were excluded.

Enrollment

Written consent was obtained from all eligible participants. Then; women were subjected to detailed demographic, menstrual, obstetrics and contraceptive history. BMI was calculated. Transvaginal ultrasound (TVS) examination by the DP-10 ultrasound device (Mindray - China) using 4- to 7-MHz was used to assess the uterine and ovarian volume (Length x Width x antero-posterior diameter). Uterine artery was demonstrated by the color Doppler immediately after the crossing of the external iliac artery. The pulsatility index (PI) of both uterine arteries was measured and the average value was calculated [16].

After that; the principle investigator inserted ESI (etonogestrel 68 mg-Implanon NXT; Organon, USA Inc.) in all participants during their menses. The bleeding pattern was followed up by the menstrual diary which included bleeding and spotting days.

Follow-up plan

All women were instructed to come for follow-up at 6 and 12 months. The menstrual pattern was assessed by the menstrual diary. Amenorrhea was considered if the cycle stopped for three consecutive cycles. Most of the women brought their diaries during the follow-up visit which were reviewed by the principal investigator. Any women, who did not bring a diary, were asked to phone the principal investigator to complete the diary and they had to bring the missed diary at their next scheduled visit. BMI, the uterine and ovarian volume and uterine artery Doppler indices were also assessed. The side effects of ESI were also documented.

Termination visit

At study termination (12 month), the final status of the participants was classified as “completed study", "lost from follow up" or "discontinued the ESI”. Additional 4 weeks were needed for the participants who were lost from follow-up. Participants would continue the ESI and the follow-up visits if they wish so.

The study outcomes

The primary outcome was the rate of amenorrhea at the 1-year of ESI use. The secondary outcomes included the potential predictors of the amenorrhea at 1st year of ESI use and the changes in BMI, uterine volume, ovarian volume and uterine artery Doppler among ESI users.

Sample size

A previous study reported that the rate of amenorrhea with ESI at one year of use is 22% [17]. Using population size 1000000 and hypothesized % frequency of outcome factor in the population equal to 22% with confidence limits 5%, a total sample size of at least 300 women were needed in the study assuming the rate of lost from follow-up 10% (Epi-info™, CDC, USA).

Statistical analysis

The data was collected and analyzed by the Statistical Package for Social Science (SPSS Inc., Chicago, version 25). Shapiro-walik test was used first, to test for the distribution of the variables. Normally distributed variables were expressed in means ± standard deviation and compared either by Independent sample t-test. While abnormally distributed variables were presented by medians and compared using means of non-parametric tests. Chi-square was used to compare proportions. Multivariate logistic regression was conducted to test for predictors of amenorrhea among ESI users. The results of the logistic regression were expressed in Odds ratio, confidence interval (C.I.), and p-values. We constructed receiver operating characteristic (ROC) curves to evaluate the sensitivity, specificity, positive predictive value, negative predictive value, the accuracy of the potential predictors revealed by logistic regression. The p-value <0.05 was considered statistically significant.

Results

Three hundred twenty-three women were counseled for participation. Twenty-three women were excluded during the screening phase. However; 35 women were lost from follow up and 11 women requested ESI removal. So, 254 women finally analyzed **(Figure 1)**.

The mean age of the women was 28.45. About 50% had bleeding days of 2-3 days and a cycle length of 21-28 days. The median of parity was 3. About 44.7% of women delivered before by CS only. The most frequent contraceptive method used before was COCs (24.4%) **(Table 1)**. At 6 months, 27.5 % of women used ESI had amenorrhea, while at 1-year, 38.6% of women used ESI had amenorrhea **(Table 2)**.

There was a statistically significant difference

between the women regards the BMI and uterine artery PI during the first year follow up visits. However; there was a statistically significant difference between the uterine and ovarian volumes from baseline and 12 month and also from 6 month to 12 month. While no a statistical significant difference was noted between baseline and 6 month (p=0.372, p=0.247; respectively) **(Table 3)**. At 6 month; the breast tenderness (12.6%) was the common side effect. While at 12 month; the most common side effect was nausea (15.4) **(Table 4)**.

The multiple logistic regression model confirmed that fewer bleeding days (p=0.020), the shorter cycle (p=0.002), smaller uterine (p=0.000) and ovarian volume (p=0.002), and higher uterine artery PI (p=0.000) were significant predictors for amenorrhea at 12 month of ESI use **(Table 5)**.

A ROC curve analysis included the revealed predictors of amenorrhea at 12 month of ESI use in the predictive model. The analysis demonstrated that the bleeding days ≤ 3 days, cycle length ≤ 28weeks, uterine volume ≤ 44, ovarian volume ≤ 5ml, and uterine artery PI > 2.62 clearly predicted the amenorrhea with a sensitivity (68.37 %, 71.43%, 86.73%, 69.39%, and 65.31%; respectively) **(Table 6) (Figure 2)**.

Discussion

The present work demonstrated that 38.6% of women who were using ESI had amenorrhea at the end of the first year of use. Moreover; our results revealed that the fewer bleeding days, short menstrual cycle, lower uterine and ovarian volume and high uterine PI were risk factors to develop amenorrhea at 1 year use of ESI.

The number of users of POCs of contraception has been increasing progressively because they are effective, safe and the long-acting properties of some of them [18]. The subdermal implants are attractive because they are simple, long-term action, and with relatively little contraindications, with additionally non-contraceptive benefits [19].

Despite abnormal bleeding patterns with the ENG implant may reach up to 78% in a 3-month period, 50% of women will improve with continuous use and 30% of users will be amenorrheic by one year of use [20]. Most implant users will experience a reduction in the frequency of menstrual bleeding with time [21]. The main cause of unscheduled bleeding with ESI is due to the significant endometrial thinning [22]. With sustained use of method, inhibition of ovulation will occur; this lead to a great improvement in the bleeding pattern [23].

In our study; the rate of amenorrhea at 6 month and 12 month after ESI use was 27.5% and 38.6%. Yildizbas B et al reported that the rate of amenorrhea after 3 month of ESI use was 32.1% [24]. Mansour D et al., in their study found that the rate of amenorrhea was 22% after three years of use [17].

In this study; the rate of discontinuation of ESI was 2.2% and 4.3% at 6 and 12 month of ESI use; respectively. All of them were complaining of abnormal uterine bleeding and none of them requested ESI removal due to amenorrhea. The relation between abnormal uterine bleeding and the early removal of the implant is very strong.

Removal rates for bleeding range from less than 1% in Southeast Asia, 22.6% in England and 13.0% in USA [7]. Harvey C et al. study showed that the continuation at 6 months after insertion was 94% of women and 74% continued at 1 year [25]. Again; Moray K.V et al. concluded that the continuation rates were 89% at 6 months, 75% at 1 year [26]. The main cause of the discontinuation was the frequent and/or unpredictable bleeding. So, we are in the same track with these previous studies.

Our results showed that there was a statistically significant increase in BMI from baseline to 12 month. Weight gain is a common side-effect of hormonal contraceptives and is given as an important reason for method discontinuation [27]. Casey PM et al found no

relation between obese women and implant removal for bleeding [28].

A significant decrease in the ovarian volume had been observed in this study. This can be easily explained. ESI suppress FSH and LH with continued use, hence decreasing the follicular activity and lead to decrease in ovarian volume [29].

The uterine volume and uterine artery blood flow decreased significantly at 1-year of ESI use. Prolonged use of POCs associates with a pseudogestational status and hypoestrogenemia which causes significant decrease in blood flow to and inside the uterus [30].

The most common reported side effects of ESI during the follow-up visits were the breast tenderness and nausea. Hidalgo MM et al. found that the ovarian cysts were detected in 7.2%, and 26.7% at 6, and 12 months [31]. We reported a lower figure than he did (5.2% at 6 month and 6.7% at 12 month). The acne developed in 6.3% at 6 month and 5.7 % at 12 month in this study. Funk S et al. reported a figure of 23.8% [32]. While mood changes (17.1%) and acne (26.8%) were the most common side effects of ESI in Yildizbas B et al study [24]. The most commonly reported side effect was headache (15.3%) in Blumenthal PD et al study [33]. In contrast; Olaifa BT et al mentioned that the arm discomfort and weight gain were causes of women dissatisfaction and devise removal [34].

The interesting issue in our study was the trial to explore the potential clinical and ultrasonographic predictors associated with amenorrhea at 1 year use of ESI. Mansour D et al. found in their predictive model that implant users with favorable bleeding in the first few months are likely to continue with favorable bleeding over the next 2 years [11]. Darney PD et al. evaluated the predictors of amenorrhea during the first year after levonorgestrel 52 mg intrauterine system (IUS) placement [35]. They found that the amenorrhea at 12 months is most common among women with shorter baseline duration of menstrual flow. So; we are on the same track with their results.

The small uterine volume was a significant predictor for the development of amenorrhea at 12 month of ESI use. The uterine shrinkage had been observed before after using of progestogens for long time [30]. This effect was secondary to changes in uterine artery blood flow from before to after progestogens use. Also; our predictive model proved that the uterine artery PI was a risk factor for amenorrhea at 12 month of ESI use.

There is only one study pointed to the predictors associated the amenorrhea at 12 month of ESI use. Tsevat D et al. in a retrospective study found that patients with amenorrhea at 12 months had higher baseline BMI and were more likely to be amenorrheic prior to insertion [36]. We did not find these factors in our study.

This study has both strengths and weaknesses. To our knowledge; this is the first study which addressed the clinical, ultrasound and Doppler parameters as predictors for development of the amenorrhea at 1-year of ESI use. Furthermore, the ultrasound assessment was performed by a single investigator to decrease the bias. We were able to recruit our calculated sample size for achieving sufficient power to detect a clinically significant difference according to our primary outcome.

However, the present work had some limitations. Subjective rather than objective evaluation for the bleeding pattern by the menstrual diary was a limitation. We tested only the clinical effect of ESI methods but we did not test any markers like estradiol. Long term follow up (more than 12 month) is essential needed. The studying of predictors associated with other uterine bleeding pattern was not addressed in our study. Moreover, the small sample size that was available for the final analysis at 12 month is 254 patients.

Conclusion

Momentous number of women will have amenorrhea at the end of first year of ESI use. The ESI users are associated with significant increase in the BMI, decreases in the uterine and ovarian volume and the uterine blood flow. The fewer bleeding days, short menstrual cycle, lower uterine and ovarian volume and high uterine PI were significant predictors for development of amenorrhea at 1-year use of ESI.

Acknowledgements

Not applicable.

Authors' contributions

Conception and design of the study: AMK and MHS. Data collection: AMA and AMA. Data analysis and interpretation: MHS. Statistical analysis: AMK. Manuscript preparation: AMK and AMA. Recruitment of patients: AMA. The authors read and approved the final manuscript.

Funding

No funding.

Availability of data and materials

The datasets used and analyzed during the current study are attached as a Supplementary file.

Declarations

Ethics approval and consent to participate

Ethical approval is attached as a Supplementary material document. The institutional review board approved the study protocol (code: IRB17101567) in November 2021, and the authors obtained written informed consent from all patients before inclusion in the study.

Consent for publication

All patients provided written informed consent that the study results would be published.

Competing interests

The authors declare that they have no competing interests.

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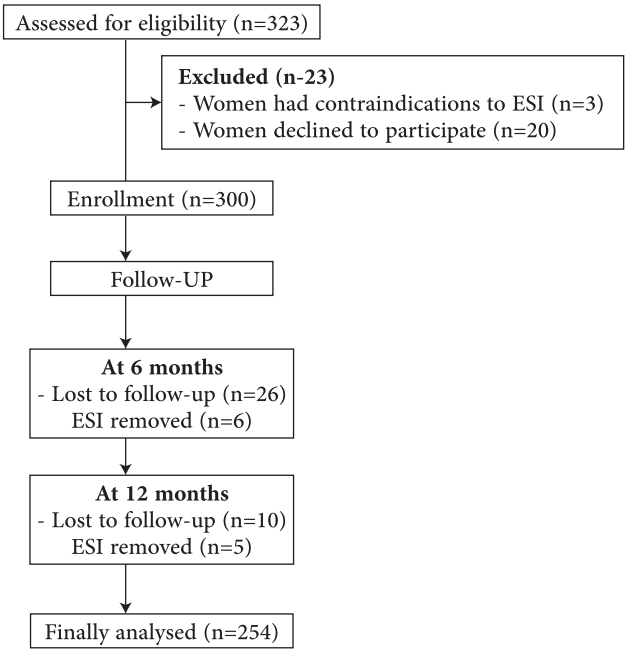

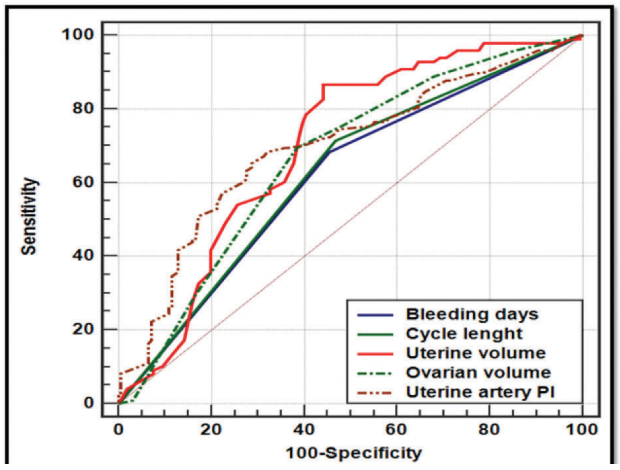

Table 1: Demographic, menstrual, obstetric, contraceptive data of the participants

	No (%) (300)
Demographic data	
Age (years), n (%)	
< 25	106(35.3)
25 - 30	83(27.7)
> 30	111(37.0)
Mean ± SD	28.45 ± 6.83
Residence, n (%)	
Urban	140(46.7)
Rural	160(53.3)
Level of education, n (%)	
Illiterate	54(18.0)
Basic education	133(44.3)
Secondary or more	113(37.7)
Employment, n (%)	151(50.3)
Menstrual data	
Bleeding days, n (%)	
2-3	153(51.0)
> 3	147(49.0)
Cycle length, n (%)	
21-28	160(53.3)
29-35	140(46.7)
Obstetric data	
Parity, Median (Range)	3.0 (1.0-7.0)
Number of living children, Median (Range)	3.0 (1.0-7.0)
Duration from last pregnancy (month), Median (Range)	33.0 (15.0-81.0)
Mode of delivery, n (%)	
VD	124(41.3)
CS	134(44.7)
VD+CS	42(14.0)
History of previous abortion, n (%)	23(7.7)
Contraceptive data, n (%)	
IUD	32(10.7)
ESI	71(23.7)
COCs	73(24.3)
POPs	18(6.0)
DMPA	24(8.0)
CI	15(5.0)
Others	8(2.7)
No	59(19.7)

CI combined injectable, **COCs** combined contraceptive method, **Cs** caesarian section, **DMPA** depot-medroxyprogesterone acetate, **ESI** etonogestrel subdermal implant, **IUD** intrauterine device, **POPs** progesterone only pills, **VD** vaginal delivery

Table 2: The rate and types of uterine bleeding pattern during ESI use at 6 and 12 months

Uterine bleeding pattern	No (%)
At 6 months: (n= 269)	
Amenorrhea	74(27.5)
Spotting	70(26.0)
Hypomenorrhea	66(24.5)
Heavy prolonged bleeding	38(14.2)
Normal menses	21(7.8)
At 1-year: (n= 254)	
Amenorrhea	98(38.6)
Spotting	68(26.8)
Hypomenorrhea	53(20.9)
Heavy prolonged bleeding	29(11.4)
Normal menses	6(2.4)

Table 3: BMI, uterine, ovarian volume and uterine artery PI volume changes during 1st year of ESI use

	Mean ± SD	P-value[1]	P-value[2]	P-value[3]
BMI(kg/m^2)				
Baseline	24.53 ± 2.76			
6 months	26.85 ± 3.12	0.000*	0.000*	0.000*
12 months	29.02 ± 2.83			
Uterine volume (mL)				
Baseline	43.51 ± 13.17	0.372	0.000*	0.000*
6 months	42.33 ± 13.37			
12 months	38.05 ± 13.21			
Ovarian volume(mL)				
Baseline	6.26 ± 1.79	0.247	0.000*	0.000*
6 months	5.97 ± 1.62			
12 months	4.71 ± 1.34			
Uterine artery PI				
Baseline	2.65 ± 0.70	0.000*	0.000*	0.000*
6 months	3.91 ± 0.63			
12 months	4.35 ± 0.60			

BMI body mass index, **mL** milliliter, **PI** Pulsatility index
P-value[1] between baseline and 6 months
P-value[2] between baseline and 12 months
P-value[3] between 6 months and 12 months
* Statistical significant difference ($P < 0.05$)
The data did not include women who lost from follow up or stopped using the method.

Table 4: Reported side effects of ESI method at 6 months and 12 months

Side effects	No.	%
At 6 months: (n= 269)		
Breast tenderness	34	12.6%
Headache	31	11.5%
Nausea	35	13.0%
Ovarian cysts	14	5.2%
Acne	17	6.3%
Stomach cramping	22	8.2%
Dizziness	17	6.3%
No side effects	171	63.6%
At 12 months: (n= 254)		
Breast tenderness	33	13.0%
Headache	32	12.6%
Nausea	39	15.4%
Ovarian cysts	17	6.7%
Acne	16	7.5%
Stomach cramping	19	6.3%
Dizziness	17	6.7%
No side effects	157	61.8%

ESI etonogestrel subdermal implant

Table 5: Multiple logistic regression analysis for risk factors of amenorrhea at 12 months among ESI users

Variables	P-value	OR	95% C.I.	
			Lower	Upper
Bleeding days	**0.020***	2.079	1.121	3.858
Cycle length	**0.002***	2.647	1.421	4.930
Uterine volume baseline	**0.000***	0.949	0.925	0.974
Ovarian volume baseline	**0.002***	0.756	0.633	0.904
Uterine artery PI. baseline	**0.000***	2.544	1.637	3.955

OR Odds ratio, **CI** confidence interval

Table 6: Sensitivity, Specificity, +PV, -PV, accuracy and AUC of the potential predictors for amenorrhea at 1-year among ESI users

Risk factors	Cut-off	Sensitivity	Specificity	+PV	-PV	Accuracy	AUC
Bleeding days	≤ 3	68.37	54.49	48.6	73.3	59.8	0.614
Cycle length	≤ 28	71.43	53.21	49.0	74.8	60.2	0.623
Uterine volume	≤ 44	86.73	55.77	55.2	87.0	67.7	0.699
Ovarian volume	≤ 5	69.39	61.54	53.1	76.2	64.6	0.666
Uterine artery PI	> 2.62	65.31	71.15	58.7	76.6	68.9	0.666

AUC area under the curve, **ESI** etonogestrel subdermal implant, **+PV** positive predictive value, **-PV** negative predictive value

Comparison between Effect of Letrozole plus Misoprostol and Misoprostol Alone in Terminating Non-Viable First Trimester Pregnancies: A Randomized Controlled Trial

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Abstract

BACKGROUND: Abortion is one of the most common complications of pregnancy. One type of abortion; missed abortion, occurs in 15%–20% of clinically diagnosed pregnancies and is the retention of pregnancy products in the uterus for several days or weeks after death of the fetus. Many medications registered had been described to terminate pregnancy replacing the surgical procedure avoiding considerable perioperative complications.

AIM: This study aimed to evaluate the effect of letrozole plus misoprostol to terminate non-viable pregnancies in first trimester compared with the use of misoprostol alone.

METHODS: This study included two groups: Group I, (Misoprostol group) received 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 1st day of enrolment (3 tablets twice, 4 hours apart).Group II, (Letrozole + Misoprostol group) received letrozole 2.5mg (Femara®, Tab. 2.5- mg, Novartis company, Egypt) , one dose 10 mg (4 tablets) on the 1st day of enrolment followed by 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 2nd day of enrolment (3 tablets twice, 4 hours apart). All women underwent detailed history, physical examination including local examination to assess the cervix. Investigations included: Complete blood count, Blood group analysis, Rh typing, Ultrasound.

RESULTS: 90 women were enrolled, divided into 45 women in letrozole + Misoprostol and 45 women in Misoprostol group. Four women from Misoprostol group and 2 women from Letrozole + Misoprostol group were lost to follow-up. Baseline characteristics regarding age, parity, gestational age and BMI revealing non significant difference between studied groups. The mean interval time of start of bleeding, induction to expulsion interval and abortion time were significantly lower in Letrozole + Misoprostol women compared to Misoprostol group. The most common side-effects in both groups were abdominal pain and headache. The incidence of side-effects was comparable for the two groups (P > 0.05),

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also the severity of side-effects was not significantly different between groups (P > 0.05). Complete abortion was observed in 36 subjects in Letrozole +Misoprostol group which was significantly more frequent than 26 subjects in Misoprostol subjects (83.7% and 63.4%, respectively, P < 0.05). No statistical significance was seen regarding Hb levels before and after treatment, while Hct levels showed significant difference before and after treatment concerning women underwent complete abortion only in the 2 studied groups.

CONCLUSION: The use of letrozole in addition to misoprostol was associated with shorter induction to complete expulsion interval, higher complete abortion rate and less curettage rate compared to misoprostol group in patients undergoing induction of first trimesteric missed abortion (less than 14 weeks). Further larger studies are needed to determine the optimum treatment protocol to achieve the highest success rate, and the lowest rate of side effects and the most cost-effective.

Introduction

According to the National Center for Health Statistics, Centers for Disease Control and prevention and the World Health Organization definition, abortion is the termination of a pregnancy before the 20th week of pregnancy or termination of pregnancy before the fetus weighing 500 g [1].

Missed abortions have been managed surgically and medically using a variety of techniques. Vacuum aspiration, dilatation, and curettage are surgical techniques. However, medical methods are typically chosen over surgical methods for abortion because they are more costly and require anesthesia. Medical approaches include prostaglandins, either alone or in conjunction with other medications. Misoprostol, or prostaglandin E1, is one of the prostaglandins that has drawn the most attention due to its high level of safety and potential for outpatient use. Misoprostol is commonly used for curettage, therapeutic abortion, inducing labor in the second trimester, and treating postpartum hemorrhage following term delivery [2].

With a success rate ranging from 65 to 93%, misoprostol is used alone as a medical alternative to surgery in the management of miscarriages. Early in pregnancy is when it works best, and it also has the benefits of being less expensive, less invasive, and preventing surgical complications. To boost the success rate, misoprostol is also used in combination with other drugs like methotrexate and mifepristone [3].

Letrozole is an important aromatase inhibitor that is used to stimulate ovulation in infertile female suffering from ovulatory dysfunctions. It is active when taken orally, has a 45-hour half-life, and inhibits aromatase enzymes in the opposite way. In abortion therapies, letrozole may be useful because it inhibits the synthesis of estrogen, which raises endogenous gonadotropin and stimulates the growth of ovarian follicles. Furthermore, letrozole has reportedly been used to treat estrogen-related breast cancer and has the potential to replace mifepristone, which is costly and unavailable in many countries [4].

Some Studies have shown that adding aromatase inhibitors before taking the main medication, such as mifepristone or misoprostol, to induce a drug abortion improves treatment effectiveness and reduces the need for surgery [5].

Materials and Methods

After ethical committee approval and informed consent from the patients, this randomized controlled trial was performed on 90 pregnant women diagnosed with non-viable first trimester pregnancy (less than 14 weeks based on Last Menstrual Period (LMP) or according to dating scan), recruited from the obstetric outpatient clinic at Ain Shams

University, Maternity hospital between January 2022 and July 2022. Participants included in this study were 20-40 years old pregnant ladies in the first trimester, diagnosed as non-viable first trimester pregnancy. 1. CRL ≥ 7 mm without fetal pulsations. 2. MSD ≥ 25 without fetal pole inside. 3. Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac. 4. Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac [6, 7].Exclusion criteria included patients who need interference and emergency treatment, with history of known allergy to misoprostol or letrozole drugs, pregnancy ≥ 14 weeks of gestation, any maternal diseases such as heart disease, asthma, thromboembolism, cancer, renal failure, and liver diseases, previous attempt to terminate the pregnancy, abnormal uterine lesions such as fibroids or congenital malformations, or pregnancy on top of intrauterine contraceptive device.

All women included are subjected to detailed medical history including the date of the first day of the LMP to calculate gestational age. They also underwent physical examination including local examination to assess the cervix. Obstetric ultrasound was done to all of them to confirm the diagnosis and to exclude the presence of any uterine lesions or congenital malformations in addition to CBC and blood and Rh grouping. 90 eligible women were randomly allocated to one of 2 groups . ▪ Group I (Misoprostol group): received 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 1st day of enrolment, (3 tablets twice, 4 hours apart) [8]▪ Group II (letrozole group): received letrozole 2.5mg (Femara®, Tab. 2.5-mg, Novartis company, Egypt) , one dose 10mg (4 tablets) on the 1st day of enrolment followed by 600 micrograms of misoprostol (Misotac®, Tab. 200 mcg, Sigma company, Egypt) administered sublingual on the 2nd day of enrolment (3 tablets twice, 4 hours apart). Randomisation was conducted using a computer-generated table of random numbers with allocation concealment. Once allocation has been done, it will not be changed. The misoprostol dose was not changed for women with prior CS as there is no recognized protocol to adjust the dose for women with previous CS, and also so as not to affect the study results. All women were told to record the date of the first vaginal bleeding; the date of first passage of tissue pieces; lower abdominal pain of any degree, with pain assessed using a pain visual analog score; vaginal bleeding of any degree; any side effects such as nausea, vomiting, fever and shivering; any return to hospital for severe pain, bleeding or intolerable side effects; and to return to hospital on the 7th day after administration of misoprostol. An ultrasound scan was done on the 7th day after misoprostol administration to ensure complete evacuation of the uterine contents. Surgical evacuation was only performed if there was inevitable or incomplete miscarriage. Primary Outcome Measure was success of medical approach (Full evacuation of the uterine contents without the need for operative intervention). Secondary outcome Measures were 1. Hemoglobin and hematocrit values before and after evacuation. 2.Medication side effects e.g. nausea, vomiting, fever and shivering. 3. Surgical evacuation complications. 4.Dose required to achieve complete evacuation. 5.Hospital stay. 6. Pain using visual analog scale.

Results

One hundred forty two women were assessed for eligiblility and randomly assigned into two intervention groups. During follow up period, 14 women weren't meeting inclusion criteria , 33 declined to participate, 5 were excluded for other reasons. Finally, 90 women were enrolled, divided into 45 women in letrozole + Misoprostol group and 45 women in Misoprostol group. Four

women from Misoprostol group and 2 women from Letrozole + Misoprostol group were lost to follow-up or continuation of pregancy (Figure 1).

Baseline characteristics regarding age, parity, gestational age and BMI were shown in (Table 1) revealing non significant difference between studied groups. The mean interval for time of start of bleeding, induction to expulsion interval and abortion time were significantly lower in Letrozole + Misoprostol women compared to Misoprostol group (P< 0.001) (Table 2). The most common side-effects in both groups were abdominal pain and headache. The incidence of side-effects was comparable for the two groups (P > 0.05), also the severity of side-effects was not significantly different between groups (P > 0.05) (Figure 2). Complete abortion was observed in 36 subjects in Letrozole +Misoprostol group which was significantly more frequent than 26 subjects in Misoprostol subjects (83.7% and 63.4%, respectively, P < 0.05) (Table 3). No statistical significance was seen regarding Hb levels before and after treatment, while Hct levels showed significant difference before and after treatment; concerning women underwent complete abortion only in the 2 studied groups (Figures 3, 4).

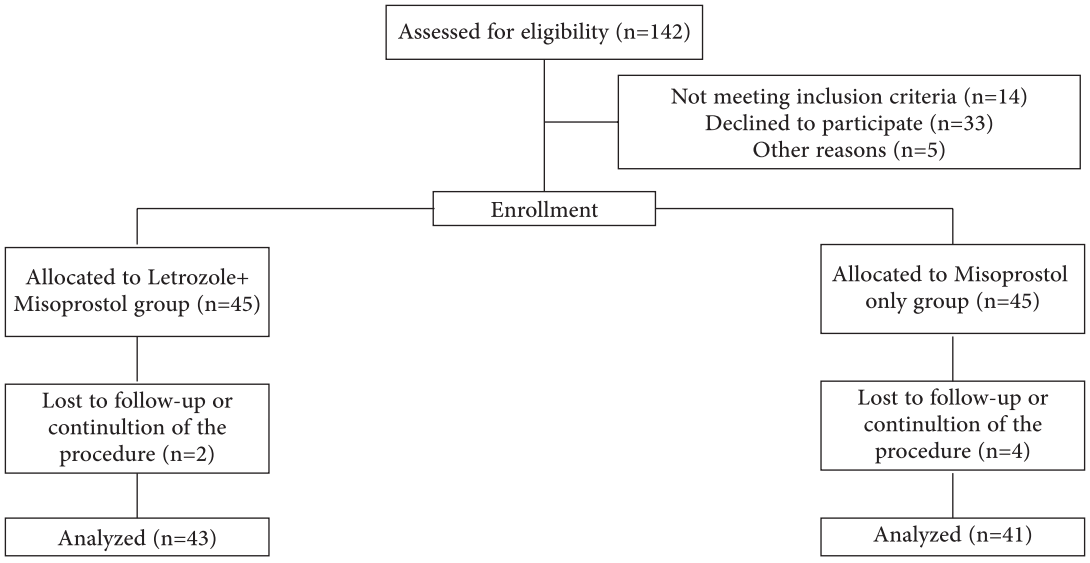

Figure (1): Patients study flow diagram

Table (1): Comparison between Misoprostol and Letrozole Misoprostol group regarding demographic data of the studied patients.

		Misoprostol group	Letrozole+ Misoprostol group	Test value	P-value	S.
		No. =45	No. =45			
Age (years)	Means ± SD Range	29.60 ± 5.84 19 - 45	29.64 ± 6.37 19 - 10	-0.035*	0.973	NS
Parity	PG MP	9 (20.0%) 36 (80.0%)	13 (28.9%) 32 (71.1%)	0.963*	0.327	NS
GA (weeks)	Means ± SD Range	9.13 ± 2.26 6 - 14	8.38 ± 1.66 7 - 13	1.808*	0.074	NS
BMI (Kg/m^2)	Means ± SD Range	29.82 ± 3.91 22 - 37	30.11 ± 4.79 22 - 38	-0.313*	0.755	NS

*S.: Significance. P-alue>0.05: Non significant (NS); Chi-square test; *: independent t-test. No. Number*

Table (2): Comparison between Misoprostol and Letrozole Misoprostol group regarding time of start of bleeding, time of start of expulsion, abortion time in hours of the studied patients.

		Misoprostol group	Letrozole+ Misoprostol group	P-value	S.
		No. =45	No. =45		
Time to start bleeding (hours)	Means ± SD Range	6.4 ± 1.2 4 - 9	4.49 ± 1.5 3 - 8	< 0.001	HS
Time to expulsion (hours)	Means ± SD Range	15.44 ± 2.29 10 - 20	10.44 ±3.12 7 - 18	< 0.001	HS
Abortion time (hours)	Means ± SD Range	23.58 ± 2.43 19 - 28	17.73 ± 4.58 12 - 28	< 0.001	HS

S.: Significance. P-alue>0.05: Significant (S); P-value<0.01: highly significant(HS). No. Number

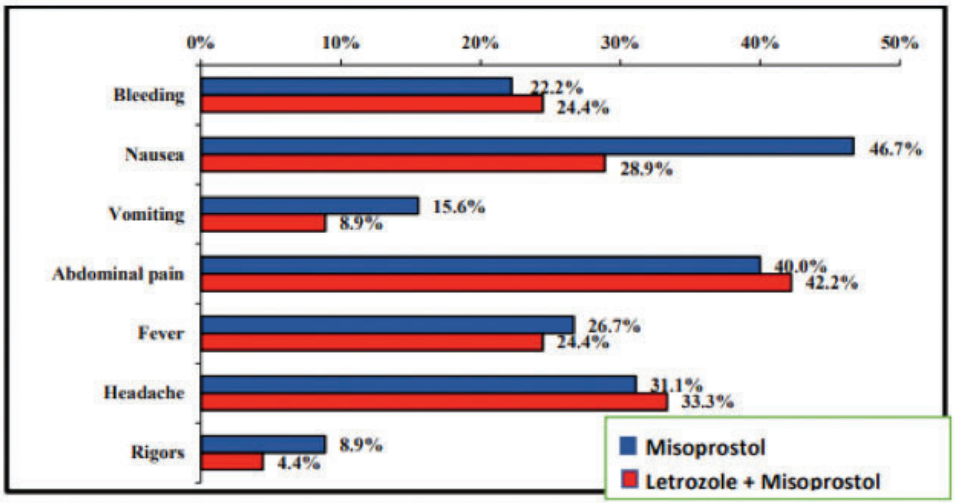

Figure (2): Side effects between the studied groups

Table (3): Complete abortion rate within 24 hours between the studied groups.

		Misoprostol group		Letrozole+ Misoprostol group		P-value	S.
		No.	%	No.	%		
Complete Abortion rate	Yes No	26 15	63.4% 36.6%	36 7	83.7% 16.3%	< 0.05	S

S.: Significance. P-alue>0.05: Significant (S); P-value<0.01: highly significant(HS). No. Number

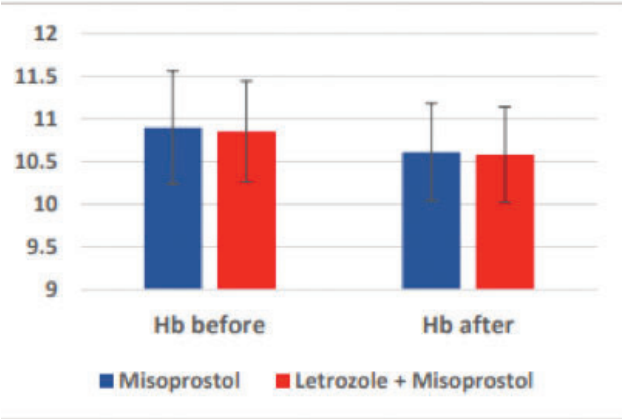

Figure (3): Hb levels before and after treatment in complete abortion only women in the studied groups (gm%).

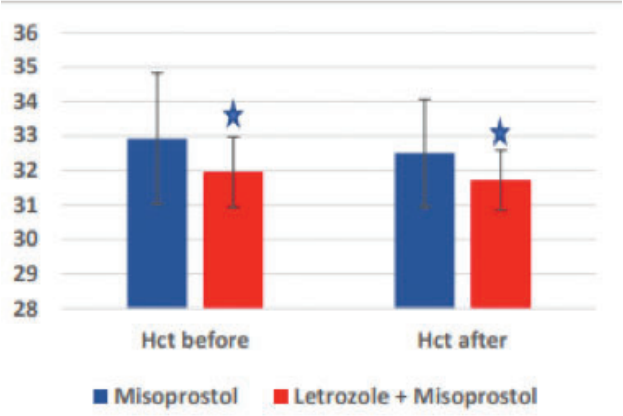

Figure (4): Hct levels before and after treatment in complete abortion only women in the studied groups (%). S: ★

Discussion

The current randomized controlled study that included two matched groups, had compared the effectiveness of misoprostol combined with letrozole versus misoprostol alone for the induction of abortion in the first trimester of pregnancy. It was found that the addition of letrozole for 24 hours prior to the administration of misoprostol has a higher rate of complete abortion in pregnancies less than 14 weeks of gestation in comparison with the administration of misoprostol alone.

This finding is in accordance with most of the studies [3, 4, 7, 9-12] performed in this context although different doses, regimens and routes were used among different studies. The rate had ranged between 76-88% vs 41-56% in the letrozole + misoprostol group vs misoprostol only group respectively; while the rate was as low as 69% vs 30% in Javadi et al. study [1] and as high as 93% vs 69% in Abbasalizadeh et al. study [5] in the two groups respectively.

One of the pilot studies that initiate the use of letrozole as a neoadjuvant to misoprostol was that held by Yeung et al. [9].They conducted this case series in 2012 on 20 women candidate for induction of abortion. They started a long preparatory phase with letrozole for 7 days prior to receiving vaginal misoprostol, which ended in a 95% abortion with no major adverse effects, which was higher than their previous pilot randomized controlled study Lee et al. [13] that showed complete abortion in 89%.

The only study that negated the difference in abortion rate was that held by Allameh et al. [2] who had studied 120 cases with a complete abortion rate of 80% and 75% in the letrozole+misoprostol group and misoprostol only group respectively.

As regard Lee et al [14], the rate of abortion that vary apparently between several studied groups could be attributed to the different doses, the treatment duration of the medication, and to the different 9 9.5 10 10.5 11 11.5 12 Hb before Hb after Misoprostol Letrozole + Misoprostol 28 29 30 31 32 33 34 35 36 Hct before Hct after Misoprostol Letrozole + Misoprostol 9 gestational age range. No one can tell definitely for how long this pregnancy had been in a missed state (i.e. fetal demise); probably longer durations of fetal demise could give fair periods of downregulation.

As regards the dose of letrozole in the current study, we had used a new dose of 10 mg for only 24 hours; in contrary, the other studies used from 7.5 mg once per day Elnashar et al [11] to 10 mg twice daily Afifi et al. [4] while the others used 10 mg once daily Yeung et

al. [9]; Javadi et al. [1]; Naggshineth et al. [7]; Beehrozi-Lak et al. [10]; Abbasalizadel et al. [5]; Torky et al. [3]; and Amer et al. [12], all for three consequetive days. Although different studies used different regimens of Letrozole, the abortion rate was still significantly different between the two groups in theirs and ours.

The dose and the route of misoprostol were different between the current study and the other studies as well as in-between other studies. We opted to use the sublingual route with two doses of 600 mcg 4-hour apart on the next day to letrozole dose. While other studies had used doses ranging from single dose 600 or 800 mcg either sublingually, vaginally or orally for one dose or two doses or even three doses with 4 to 12-hours apart. The difference that had not ultimately affected the significant difference in the rate of abortions among groups.

Actually, many studies had been held to explore the best route for administration of misoprostol for induction of abortion with contradictory results, no single regimen had considered to have best results Zhang et al. [15].

In the current study, we were confined to the 14 week-duration, although other studies had extended the duration to 17 weeks Naggshineh et al. [7] and to 20 weeks Javanmanesh et al. [17], and on the other hand; some studies confined the pregnancy duration to 9 weeks only Chai and Ho [16].

The present study reported that time between induction of abortion to start bleeding was significantly shorter among letrozole+misoprostol group than among misoprostol only group. This was in contrary to the studies of Javadi et al. [1] and Amer et al. [12] who reported no significant difference between the two groups. Other studies had not commented on this duration.

The current study reported that the time between induction of abortion to start of expulsion of pregnancy products was shorter in the letrozole+misoprostol group compared to misoprostol only group. This was in convenience to Torky et al. study in which they reported a time to start passage of products of conception following administration of misoprostol was 2.09 hours in letrozole+ misoprostol group vs 3.05 hours in misoprostol only group Torky et al. [3]; as point of obvious difference the current study reported longer periods for staring the passage of products of conception ((7.8 hours vs 11.2 hours respectively). Torky et al. [3] had investigated 438 women in their huge comparative study that entailed 219 women in each arm. They had used letrozole 10mg orally daily in two divided equal doses for three days followed by 800mcg misoprostol vaginally and the doses were the apparent difference between their study and the current one (viz.letrozole for 24 hours only and the misoprostol given sublingually with two doses of 600 mcg).

The current results showed induction to complete expulsion interval that was significantly shorter in letrozole+misoprostol group than misoprostol only group which is in agreement to 10 other studies. One of them, that was held by Naghshineh et al. on 130 cases who showed figures of 5 and 9 hours between the groups Naghshineh et al. [7], whilst the current study concluded longer durations (although still statistically significant) viz. 17 and 23.5 hours in the two groups. One of the big differences between the current study as well as other studies and between Naghshineh et al. study is that they had administered variable doses of misoprostol changing with gestational age according to the FIGO guidelines (FIGO, 2017), this would be explained by the inclusion of women pregnant up to 17 weeks in their study.

Similar to our study, Behroozi-Lak et al. [10] reported that induction-to-abortion time in letrozole group was significantly shorter than the control group in a randomized trial conducted on 78 women with gestational age less than 14 weeks who received daily

oral dose of 10 mg of letrozole for three days followed by vaginal misoprostol.

Javanmanesh et al. [17] reported shorter induction-abortion intervals in the letrozole group although they held their study on only 46 women with a wide range of gestational age extended to 20 weeks.

Afifi et al. [4] showed an obvious difference in the induction-abortion interval from the current study and the other studies as well; they reported clear prolonged interval that was 61 and 99 hours in the two groups respectively. They had not explained on what basis they had extended the definition of this period in their study.

Letrozole has its appealing action on preparation for induction of abortion. It had been used as an adjuvant to mifepristone prior to misoprostol administration with an abortion rate of 98% Chai and Ho [16]

Recently, the study of Alabiad et al. [18] reported that letrozole in the treatment of ectopic pregnancy had markedly reduced expression of estrogen and progesterone receptors as well as the vascular endothelial growth factor (VEGF) with a significant elevation of the apoptotic index cleaved caspase-3. Letrozole probably cause a decline in the placental estrogen causing decrease in the signals for vascular network with subsequent marked apoptosis.

On the contrary, one decade before, Lee et al. [19] on two separate articles, had shown that letrozole increases the blood flow to the uterus, and it does not downregulate the progesterone receptors or affect the apoptotic factors in the placenta. Moreover, Kallner et al. [20] showed that letrozole did not affect uterine contractility or increase the sensitivity to misoprostol of the uterine myometrium.

Availability wise, letrozole could be easily obtained in the Egyptian market in contrary to mifepristone which is not legalized in Egypt.

The present study reported no significant differences between the study groups regarding adverse effects. This was in accordance with the results of similar studies Chai and Ho [16]; Lee et al. [14]; Javanmanesh et al. [17]; in which there were no significant differences between the study groups regarding side effects.

In contrast to the current study Javadi et al. [1] reported common side effects in 3.8% of cases in the letrozole+misoprostol group and in 19% in the misoprostol alone group; the difference being statistically significant (P= 0.043). No explanation for this result had been attributed to Javadi et al. [1]

Another study Torky et al. [3]showed that more women experienced nausea and vomiting in the letrozole group than in the misoprostol only group, and the result was significant (P= 0.002). There were no significant differences between groups with regard the incidence of fever, abdominal pain and vaginal bleeding that needed surgical management.

Logistically and administratively speaking, the inpatient treatment was disfavored, and the patients were followed up in the outpatient clinic. The hospitalization rate was low, saved for patients with considerable bleeding, pain or cannot readily reach a well occupied medical authority or those who ultimately failed to abort. Again, this was based on the safe, acceptable and effective home-based medical abortion especially during the last three years that witnessed the pandemic of COVID-19 and this was supported by the study conducted by Gambir et al. [21].

A point of strength in this study is the short duration of the pretreatment with letrozole viz. a 24-hour duration that possibly decreases the psychological and financial burden on women needing medical abortion especially if this protocol is generalized in the usual practice.

A limitation point in this study is the lack of estimation of the amount of blood loss, this issue is attributed to the low number of case

hospitalization. Other limitation is the failure to assess the visual analog scale (VAS); it was omitted from the evaluation of the patients in this study as the rate of hospitalization was low in both groups. Generally speaking, Letrozole could be added to the battery of medication used in induction of abortion with appealing good results as regards effectiveness and low adverse outcome.

Conclusion and Recommendations: The use of letrozole in addition to misoprostol was associated with shorter induction to complete expulsion interval, higher complete abortion rate and less curettage rate compared to misoprostol group in patients undergoing induction of first trimesteric missed abortion (less than 14 weeks). Further larger studies are needed to determine the optimum treatment protocol to achieve the highest success rate, and the lowest rate of side effects and the most cost-effective.

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Searching for a Cheap Marker for Placenta Accreta Spectrum in a Low Resource Country: A Prospective Cohort Study

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Abstract

Objective: To assess maternal serum amyloid A (SAA) levels among women with Placenta Accreta spectrum.

Methods: We performed a prospective observational cohort study among women with Placenta Accreta Spectrum at Ain Shams University Maternity Hospital, Cairo, Egypt, between March 2017 and August 2017. The study group included women with a previous CS and diagnosed with placenta previa or accreta (20 patients in each group), while the control group included twenty women with a normally situated placenta. We collected Serum samples to measure SAA levels at the time of admission. The primary outcome was the association between SAA and the Placenta Accreta Spectrum. SAA levels were compared using the ANOVA test. We also performed Receiver Operating Characteristics characteristic analysis for previa/accrete versus normal and previa versus accreta.

Results : Each group contained 20 participants with comparable baseline characteristics. The Maternal serum amyloid-A level was 19.9±5.0 μg/mL, 18.3±5.5 μg/mL in the previa and accreta groups versus 11.4±2.1 μg/mL in the control group (P<0.001). The ROC analysis was significantly lowest among the normal group with no significant difference between the previa and accrete groups. Maternal serum amyloid-A had significantly high diagnostic performance in differentiating previa and/or accreta groups from the normal group and low non-significant diagnostic performance in determining previa from accreta groups.

Conclusion: Maternal SAA levels are increased in women with Placenta Accreta Spectrum.

Keywords: Serum amyloid A, Placenta Accreta Spectrum, Morbid adherent placenta, biochemical marker.

Introduction

Placenta accreta is defined as abnormal trophoblastic invasion of the placenta (either partly or totally) into the myometrium of the pregnant uterus. The Placenta accreta

spectrum was known as morbidly adherent placenta, which refers to the pathologic adherence of the placenta, including placenta accreta (invading the decidual surface of the myometrium), placenta increta (invading more deeply within the myometrium), and placenta percreta (penetrating the uterine serosa and invading the surrounding organs such as the bladder).[1]

Placenta accreta spectrum (PAS) disorders are life-threatening obstetrical problems with a mortality rate of approximately 7.0% and several maternal morbidities, which include obstetric hemorrhage, massive blood transfusion, urinary tract injury, and hysterectomy. The incidence of placenta accreta spectrum disorders is steadily rising in Egypt; it was recorded at 0.91% in a tertiary university hospital in Minya from 2017 to 2018. 2 In 2022 and 2023, it reached 2% in Ain Shams university hospital. This is driving our high rate of CS of 56%. [3]

Several fetal and placental hormones have been found to have different concentrations in the serum of patients with placenta previa accreta compared with those with non-accreta women. At 11–12 weeks of pregnancy, the pregnancy-associated plasma protein A (PAPP-A) is higher in the maternal serum of women with PAS disorders. At 14–22 weeks, serum β-hCG and alpha-fetoprotein (AFP) are above 2.5 multiples of the median higher in the maternal serum of women with PAS disorders. Biomarkers could be used with ultrasound imaging to screen for PAS disorders prenatally. [4]

Serum amyloid A (SAA) is an immunoregulatory protein in the acute-phase reaction.[3] Its functions include immunomodulation, cell differentiation, cell proliferation, migration, and invasion. SAA is synthesized mainly in the liver, other sources, including trophoblasts, have been described. SAA exerts immunoregulation and plays an important role in the trophoblasts' migration, invasion, and differentiation. SAA at low concentrations regulates both trophoblast invasion and metalloprotease activity within the microenvironment of the placenta, which is important for placentation and placental homeostasis. In the presence of high levels of SAA, this sequence is markedly disturbed. 5

The present study aimed to examine the hypothesis that Placenta Accreta Spectrum (PAS) might be associated with high maternal SAA.

Methods

Study Design: We performed a prospective observational cohort study. This study was done on 60 pregnant women attending the outpatient obstetric clinic or who came to the emergency ward and were all admitted to the inpatient ward as high-risk pregnancies with a diagnosis of Morbid adherent Placenta (MAP); The study group included women with a previous CS and diagnosed with placenta previa or accreta (20 patients in each group), while the control group included twenty women with a normally situated placenta. They were recruited through the period of March 2017 and August 2017. The original study is a master thesis that took the approval of the scientific committee of the Obstetrics and Gynecology Department of Ain Shams University Hospital and gained the ethical committee approval of Ain Shams University, Faculty of Medicine (Research Ethics Committee) under the number FMASU MS 26/2017.

Eligibility criteria: We studied women diagnosed with placenta previa or accreta with a history of previous CS. Women had to be more than 18 years, had a history of previous CS, and had a gestational age > 28 weeks. The placenta previa/accreta diagnosis was established by ultrasonography, Doppler, and occasionally by MRI. Women with rupture of membranes, chorioamnionitis, multiple pregnancies, or any medical disorder were excluded from the study. We excluded women with infection and medical

disorders, which could affect serum amyloid assessment 5. The control group was women with a normal placenta and no specific complaint.

The women were allocated consecutively and alienated into three groups by their clinical fate. Women with placenta previa/accreta were included in the cases group (first and second), while women with normal placenta were included in the third group.

All participants had general examinations, including blood pressure, pulse, and respiratory rate. An abdominal examination was performed to assess contractions and electronic fetal monitoring. Pelvic examinations were not done except if the patient was contracting, in which speculum examination was done.

Ultrasound and Doppler were done, and the diagnosis of placenta accreta was based on the loss of the retroplacental sonolucent zone, presence of irregular retroplacental sonolucent zone, thinning or disruption of hyperechoic serosa – bladder interface, presence of focal exophytic masses invading the urinary bladder (presence of focal exophytic mass with the same echogenicity as the placenta beyond the uterine serosa) and abnormal placental lacunae: An irregular vascular space in the placental parenchyma.

After diagnosing Morbid adherent placenta, women were admitted either for conservation or termination if they were presented at term or with significate attacks of antepartum hge. Complete laboratory investigations were performed for all participants, including CBC, coagulation profile, and liver and kidney function tests. Cross-matching of packed RBCs and plasma was done.

A sample of venous blood was taken from each patient participating in the study under aseptic conditions to assess the level of serum aa. Blood samples were centrifuged at 2500 g for 15 minutes at 4°C, separated into serum aliquots, and stored at −80°C until used for the SAA assay. Levels of SAA were assayed simultaneously for all groups using the same microtiter plates provided with the human SAA solid phases and which enzyme-linked immuno- sorbent assay kit (BioSource Europe, Nivelles, Belgium), according to the manufacturer's protocol. The inter-assay and intra-assay coefficients of variation were 7.4% and 6.1%, respectively. The sensitivity had been <0.004 μg/mL.

Participants were either admitted to the emergency room for termination or admitted to high- risk inpatient ward after being assessed by the consultant on duty, who gave the management's final decision.

Sample size justification: At the time of the study, no study used serum amyloid A in its association with the morbidly adherent placenta. So, we assigned 20 patients in each group according to the number of available kits.

Statistical Analysis: The data were analyzed using SPSS version 21.0 (IBM, Armonk, NY, USA). Numerical data were tested for normal distribution using the Shapiro–Wilk test. Normally, distributed data were presented as a mean and standard deviation; differences were assessed using the ANOVA test between groups. Categorical data were presented as numbers and percentages, and differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Correlations were tested using the Spearman rank correlation. ROC curve analysis was used to examine the predictive value of SAA. P values < .05 were considered statistically significant.

Results

Sixty women were included in the study, equally distributed among 3 groups (placenta previa (N=20), placenta accrete (N=20), and a normal control group (N=20). There is no statistically significant difference between the three groups regarding the demographic criteria (Age, BMI, GA, and, Hysterotomy/ CS) (Table 1).

The **Maternal serum amyloid-A level** was significantly lowest among the normal group than the previa and accreta groups (P<0.001), with no significant difference between previa and accrete groups (P = 0.351). The correlation between the maternal SAA and demographic data among the studied groups revealed no statistically significant difference (P>0.05), as shown in Table 2.

Maternal serum amyloid-A had significantly high diagnostic performance in differentiating previa and/or accreta groups from the normal group and low non-significant diagnostic performance in differentiating previa from accreta groups. Maternal serum amyloid-A level ≥15.3 (µg/mL) had high specificity& PPV and moderate sensitivity& NPV in differentiating the previa group from the control group. Maternal serum amyloid-A level ≥15.3 (µg/mL) had high specificity& PPV and low sensitivity& NPV in differentiating the accreta group from the control group. Maternal serum amyloid-A. A level ≥15.3 (µg/mL) had high specificity& PPV and low sensitivity& NPV in differentiating previa/accreta groups from the control group. (Table 3 and Fig 1a-d) .

Table 1 Clinical characteristics of studied groups

Variables	Measures	Previa (N=20)	Accreta (N=20)	Normal (N=20)	P
Age (years)	Mean±SD	27.9±3.0	28.8±2.6	28.4±2.4	**0.605 ***
	Range	23.0–33.0	25.0–33.0	22.0–32.0	
BMI (kg/m^2)	Mean±SD	29.5±1.8	29.1±1.6	29.6±1.4	**0.552***
	Range	26.3–33.0	26.4–31.6	27.4–31.9	
Hystroto my/CS	Mean±SD	2.3±0.6	2.4±0.7	2.6±0.8	**0.383***
	Range	2.0–4.0	2.0–4.0	2.0–4.0	
Gestational Age (GA in weeks)	Mean±SD	32.1±2.2	32.5±2.6	32.3±2.5	**0.873***
	Range	28.0–36.0	27.0–38.0	27.0–37.0	

* ANOVA test - BMI: Body Mass Index

Table (2): Correlation between maternal serum amyloid-A levels in 3 groups

Maternal Serum Amyloid A (µg/mL)	Mean±SD	19.9±5.0	18.3±5.5	11.4±2.1	**<0.001** HS**
	Range	10.3–30.3	9.2–29.3	8.4–16.2	
	HG	**a**	**a**	**b**	

**ANOVA with post hoc test HG: Homogenous groups

Table (3): Correlation between maternal serum amyloid-A level and demographic characteristics among the studied groups

Variable	Previa (N=20)		Accreta (N=20)		Normal (N=20)	
	r	P	r	P	R	P
Age	0.137	0.565	-0.009	0.970	0.129	0.588
BMI	0.277	0.237	-0.403	0.078	0.018	0.940
Hystrotomy	0.093	0.697	-0.222	0.346	-0.075	0.753
GA	-0.280	0.233	-0.180	0.446	-0.018	0.941

Pearson correlation

Table (4): Diagnostic performance of maternal serum amyloid-A in differentiating the studied groups.

	Previa from normal	Accreta from normal	Previa/ Accreta from normal	Previa from Accreta
AUC	0.941	0.869	0.905	0.586
SE	0.038	0.059	0.038	0.091
95% CI	0.500–1.000	0.753–0.985	0.831–0.979	0.500–0.765
p-value	<0.001*	<0.001*	<0.001*	0.351
Cut off	≥15.3	≥15.3	≥15.3	≥18.3
Sensitivity	85.0% (62.1%–96.8%)	70.0% (45.7%–88.1%)	77.5% (61.5%–89.2%)	56.58% (44.90%-65.12%)
Specificity	95.0% (75.1%–99.9%)	95.0% (75.1%–99.9%)	95.0% (75.1%–99.9%)	69.35% (54.82%-72.93%)

AUC: Area under the curve, SE: Standard error, CI: Confidence interval, *Significant

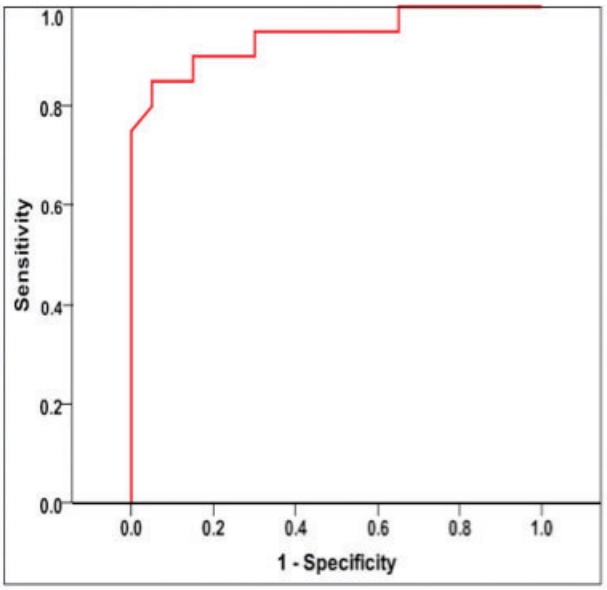

Figure (1a): ROC curve for maternal serum amyloid-A in differentiating the previa group from the normal group.

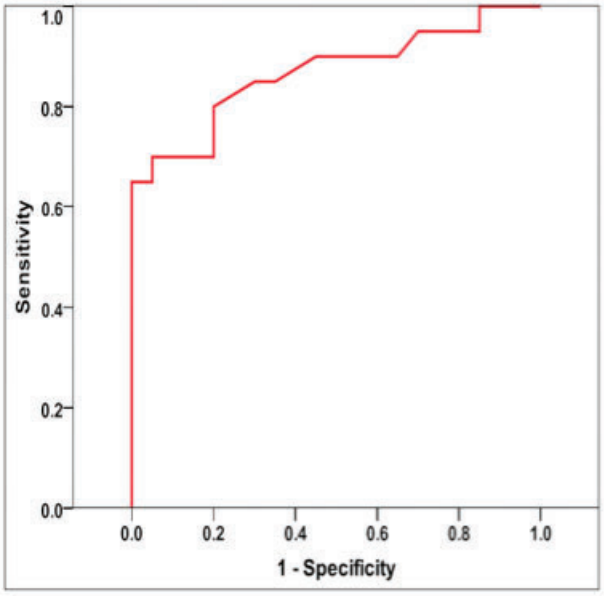

Figure (1b): ROC curve for maternal serum amyloid-A in differentiating the accreta group from the normal group

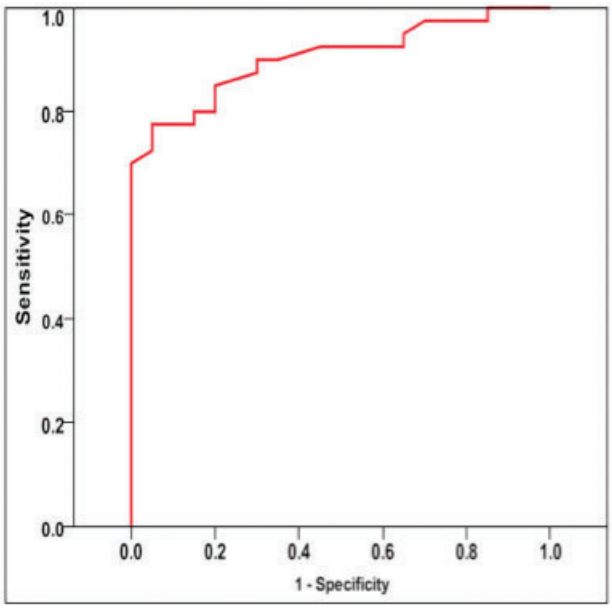

Figure (1c): ROC curve for maternal serum amyloid-A in differentiating the previa/accreta groups from the normal group

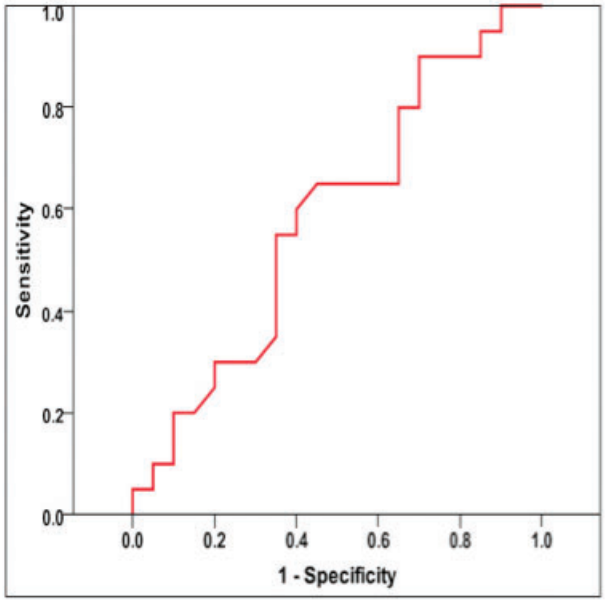

Figure (1d): ROC curve for maternal serum amyloid-A in differentiating the previa group from the accreta group

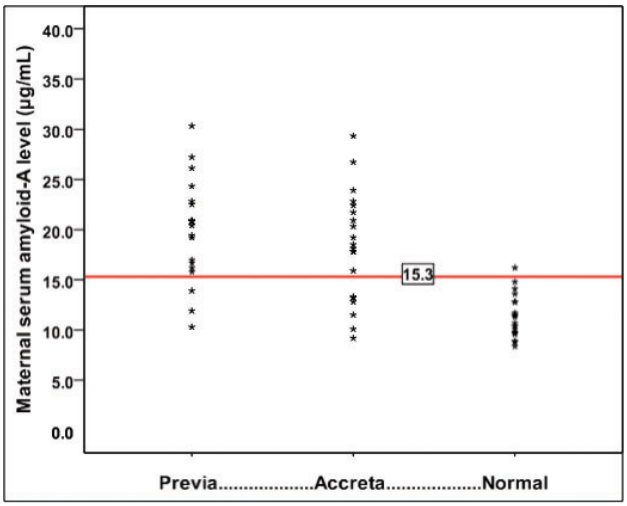

Figure (2): Diagnostic characteristics of maternal serum amyloid-A level ≥15.3 (µg/mL) in differentiating previa and/or accreta groups from the control group.

Discussion

The present study showed that maternal serum amyloid A is significantly elevated in placenta previa and placenta accreta over the normal control group. There was no correlation between levels of m SAA and the demographic criteria of selected patients. Maternal serum amyloid-A had significantly high diagnostic performance in differentiating previa and/or accreta groups from the normal group and low non-significant diagnostic performance in differentiating previa from accreta groups.

Comparison of our results to related studies

Investigators tried to analyze the association between SAA levels and the normal pregnancy and labor process, as well as abnormal pregnancy. Maternal SAA levels were measured during and after pregnancy in healthy pregnant women. SAA levels remained unchanged during normal pregnancy and were elevated only during concurrent infections. Maternal SAA concentrations were normal when measured one day before delivery. On the contrary, labor caused a marked increase in maternal

SAA levels that increased several hundred folds. [6]

SAA regulates trophoblastic invasion into the decidua at physiological levels by activating toll-like receptor 4 (TLR-4). By contrast, the increased levels of SAA are associated with increased trophoblastic invasion and syncytialization. [7]

At physiological levels, SAA regulates trophoblastic invasion into the decidua through the activation of toll-like receptor 4 (TLR-4). By contrast, the increased levels of SAA are associated with increased trophoblastic invasion and syncytialization. [7]

In the study of Sandri et al., they evaluated the role of SAA in placental invasion. SAA was expressed in the syncytiotrophoblasts, extravillous cytotrophoblasts, and decidual cells. They used the extravillous cytotrophoblasts (ECT) and a trophoblast-like human cell line to evaluate the influence of exogenous SAA on trophoblastic migration, invasion, and differentiation. They concluded that, at concentrations of 1 and 10 μg/mL, SAA doubled the invasion of ECT by stimulating the TLR-4 receptor. Also, SAA stimulated the invasion of the trophoblast-like cell line and induced both the gene expression and enzyme activity of metalloprotease (MMP-2 and MMP-9), which are proteases involved in the process of invasiveness of the EVT cells. [8]

SAA has been shown to aid in tumor cell invasion and metastasis by enhancing the Extra-cellular Matrix degradation through the induction of MMP-9 and 11 proteases activity [(9-11)].

SAA levels were also increased in some cases of gynecological cancers. In the study of Kovacevi et al. and Rossmann et al., they showed that first-trimester trophoblasts and malignant trophoblast-like choriocarcinoma cells (JAR and Jeg-3 cells) express SAA transcripts. [12-13]

Cocco et al.'s study reported that SAA gene and protein expression levels were highly expressed in Uterine serous papillary carcinoma. Interestingly, they have shown that high serum SAA levels predict different stages of the disease and could help in staging patients preoperatively. [14-15]

In contrast to the results of our study are the studies concerning increased levels of SAA in Preeclampsia, eclampsia, and Recurrent early pregnancy loss. It has been shown that there was a shallow invasion of the EVT into the endometrium in cases of Preeclampsia and that maternal SAA levels were significantly increased in preeclamptic patients over the controls. Maternal SAA levels were also increased in eclampsia and HELLP syndrome. This was explained by the insufficient blood flow to the placenta due to the shallow invasion of extravillous trophoblasts (EVT) into the endometrium.[15-16]

In the study of Ibrahim et al., serum amyloid levels were significantly higher in patients with recurrent early pregnancy loss than among their controls. They explained that SAA (At physiological levels) modulates the trophoblastic invasion into the decidua via activation of toll-like receptor 4, and maintains a functional balance between the pro-inflammatory and anti-inflammatory cytokines. Their study's increased SAA levels were associated with impaired trophoblastic invasion and syncytialization.

As SAA levels were elevated in different situations of both shallow and excessive invasiveness of Extra Villous cytotrophoblasts, it is assumed that the alteration of SAA levels in maternal blood in pre-eclampsia and Placenta accreta spectrum are the non-specific reflections of the inflammatory and injury states of the diseases. [17]

Clinical implication of our study

This study, among other studies, utilizes different biomarkers that could be used with ultrasound imaging to screen for PAS

disorders prenatally which aids in early referral to higher centers.

Strengths and limitations of the present study

The strength of our present study is that, to our knowledge, it was the first to address the association of the placenta accreta spectrum with the SAA levels. The limitations of the present study included the absence of sample-size justification due to the need for published data (at the time of the study) on SAA levels among women with the placenta accreta spectrum. Indeed, the present study suggested a possible association between SAA level and Placenta accreta spectrum, whether the exact mechanism is to be determined.

Recommendations for further studies

We recommend studying the levels of SAA in patients with the low-lying placenta in the early second trimester and following up to assess the outcome of the occurrence of the placenta accreta spectrum.

Conclusion

Maternal SAA levels are increased in Placenta Accreta Spectrum, and the exact pathophysiology is yet to be determined.

LIST OF ABBREVIATIONS

PAS ……..Placenta Accreta Spectrum

MAP……..Morbid Adherent Placenta

EVT……..Extra-villous cyto-trophoblast

Ethical approval and consent to participate

In accordance with local regulations, the protocol gained Ethical and Research approval from the council of the OB/GYN Department, Ain-Shams University. Furthermore, the study protocol was approved by the Ethics Research Committee, Faculty of Medicine, Ain-Shams University (number: FMASU MS 26 / 2017). Written informed consent was obtained from every candidate after explaining the procedure before enrollment. WE Confirm that All methods were performed in accordance with the relevant guidelines and regulations according to the Declaration of Helsinki.

Consent for publication

NOT APPLICABLE

Availability of data and materials

All Data and ethical committee documents are available from the corresponding author on reasonable request

Competing interests

The authors report there are no competing interests to declare

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Authors' contributions

Ahmed Sherif Abdel Hamid 1, Hazem El Zeneiny 1, Amira El Nahas 1

All authors jointly contributed to the conception and design of the study.

Ahmed Sherif Abdel Hamid: Design of the study, helped in the review of literature, revision of results and data analysis, writing the manuscript,

Hazem El Zeneiny; design of the study, revision of review of literature, and revision of the manuscript

Amira El Nahas: Candidate of the master thesis, design of the study, obtaining ethical committee approval, reviewing the literature, sharing in the collection of Data, revision of results and data analysis, and contributing to writing the manuscript

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Not applicable.

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Comparative between Pregnancy Outcomes in Non- versus Vaccinated Females by Covid-19 Vaccine: A Retrospective Comparative Study

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Abstract

Background: Over two years, the coronavirus disease 2019 (COVID-19) pandemic has impacted a significant number of individuals worldwide, emerging as a major public health concern and compelling medical facilities to reorganize their medical departments, including obstetrical and gynecologic services.

Aim of the Work : to retrospectively explore the maternal, fetal, and neonatal outcomes in COVID-19- vaccinated pregnant women compared with those not receiving COVID-19 vaccine.

Patients and Methods: This was a retrospective cohort study that was conducted at Ain Shams University Maternity Hospital (ASUMH). Pregnant women who attended ASUMH for delivery were divided into two groups: **Group A** consisted of 200 COVID-19 vaccinated women who received at least one vaccine dose six months or more prior to labor (the study group); **Group B** consisted of an age-matched control group of 200 unvaccinated women.

Results: Our study demonstrated the relation between age and two study groups, the mean age of non-vaccinated group was 27.23 ± 4.78, while it was 27.21 ± 4.66 for vaccinated group without statistically significant difference between two study group as P-value was >0.05. Our study illustrated the relation between pre-eclampsia as a complication and two study groups, the number of patients who had PE within non-vaccinated group were 10 (5%), while they were 9 (4.5%) within vaccinated group without statistically significant difference between two study group as P-value was >0.05. Our study showed the relation between NICU admission as a complication and two study groups, the number of patients who admitted to NICU within non-vaccinated group were 39 (19.5%), while they were 28 (14%) within vaccinated group without statistically significant difference between two study group as P-value was >0.05. Our study demonstrated the relation between preterm labour as a complication and two study groups, the number of patients who had preterm labour within non-vaccinated group were 9 (4.5%), while

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they were 13 (6.5%) within vaccinated group without statistically significant difference between two study group as P-value was >0.05.

Conclusion: Given the lack of significant differences in these maternal complications and neonatal outcomes between the vaccinated and unvaccinated groups, our study supports the safety of COVID-19 vaccination during pregnancy in terms of it not leading to increased major poor outcomes for mother or baby. More research is still warranted to further establish the risks versus benefits with larger sample sizes.

Keywords: Non-versus Vaccinated, Covid-19 Vaccine.

INTRODUCTION

COVID-19 is considered a global epidemic of catastrophic proportions. Since the discovery of the first instances of COVID-19 induced by SARS-CoV-2 in December 2019 in Wuhan, China, and the virus has swiftly spread globally. Almost 207 million people have been infected globally, resulting in over 4 million fatalities.[1]

As of August 15, 2021, about 620,000 people have perished from COVID-19 in the USA alone.[2]

Several researches on COVID-19 health issues, including investigations on the mental and physical impacts of COVID-19 for the duration of pregnancy, have been published.[3]

The lower lung capacity associated with fetal development, together with the normal prenatal inhibition of the maternal immune reaction, may result in significant COVID-19 expression in pregnant women.[4]

Vaccine reluctance among pregnant women has been influenced by a number of factors, including the absence of knowledge with mRNA vaccine portals from outside research settings, the exemption of pregnant women from preliminary COVID-19 vaccine trials, and the resulting mutable and uncertain vaccination guidelines from formal bodies, in addition to antivaccine misinformation.[5]

Fears about the safety of vaccines within pregnant women are a continuing barrier to vaccination during pregnancy. Previous investigations on the correlation between maternal COVID-19 immunization and newborn outcomes were restricted by small sample sizes or the absence of an unvaccinated group.[6]

According to statistics from the UK Obstetric Surveillance System (UKOSS), the vast majority of pregnant women who needed medication or intensive care unit (ICU) care for COVID-19 during the delta wave were not vaccinated.[7]

Currently, clinical trials are investigating the unanswered concerns with COVID-19 immunization in pregnancy, such as the ideal dose schedule, the durability and effectiveness of antibodies transmitted transplacentally and via lactation, and the optimal dosing schedule.[8]

Currently, the following three COVID-19 vaccinations are available: Two mRNA vaccines, one from Pfizer-BioNTech (Germany and New York) and another one from Moderna (Cambridge, MA) were tested, and one adenoviral vector vaccination (Johnson & JohnsoneJanssen, Belgium). The CDC stipulates that any of the presently permitted vaccinations may be delivered to women who are pregnant or breastfeeding, regardless of vaccine type.[9]

The Royal College of Obstetricians and Gynecologists in the United Kingdom suggests mRNA immunization for pregnant women because mRNA vaccines have better safety evidence than adenoviral vaccinations. There is an acute need for high-quality, accurate data to assist pregnant women considering COVID-19 vaccination in the absence of fresh updates from large national registries and the outcomes of current studies.[10]

AIM OF THE WORK

To retrospectively explore the maternal, fetal, and neonatal outcomes in COVID-19-vaccinated pregnant women compared with those not receiving COVID-19 vaccine.

PATIENTS AND METHODS

A retrospective cohort study that included all pregnant women who attended Ain Shams University Maternity Hospital for delivery for 3 years (from Jan 2020 till Dec. 2022) at least 200 patients, to measure the effect of COVID-19 vaccination on the pregnancy outcomes.

Ethical and Safety Consideration: The Ethics Committee of the Department of Obstetrics and Gynaecology, Faculty of Medicine, Ain Shams University, gave its clearance before this study could be carried out. A pledge was executed. All information was gathered in confidence. The researcher's own funds served as the foundation for the investigation.

Inclusion criteria: age: 18 - 35 years, gestational age: any gestational age. Gestational age will be confirmed as regard documented 1st day of last menstrual period or 1st trimester ultrasound, singleton viable healthy fetus, uncomplicated pregnancy or labor, vaginal or cesarean deliveries at the period between starting of 2022 until now and COVID vaccinated women - as a study group - with at least one shot of vaccine six months or more before labour and age matched non-vaccinated women – as a control group.

Exclusion criteria: 1- women with incomplete data or unwilling to participate in the study, 2- women with systemic medical disorders before pregnancy, 3- known structural or chromosomal fetal abnormalities and 4- women with risk factors of preterm labour as: multifetal pregnancy, poly- or oligohydramnios, preterm premature rupture of membranes (PPROM), antepartum hemorrhage (placenta Previa or abruption placenta) and cervical incompetence. 5- Women received different types of COVID-19 vaccine.

Sample Size: A retrospective cohort study was conducted to include all pregnant women who attended Ain Shams University Maternity Hospital for delivery for 3 years (from Jan 2020 till Dec. 2022) at least 200 patients, to measure the effect of COVID-19 vaccination on the pregnancy outcomes.

Study procedures and interventions: after approval of study protocol, patient's records were enrolled into the study according to inclusion and exclusion criteria and eligible patients were divided into two groups: **Group A (Vaccinated women):** COVID vaccinated women - as a study group - with at least one shot of vaccine six months or more before labour. **Group B (unvaccinated women):** age matched un vaccinated women – as a control group.

Methodology: **The following data were collected from patient's records:** **History:** Including the following points: **Personal history:** age, maritalstatus, special habits, occupation, address and phone number. **Present history** of her pregnancy as gravidity, parity, gestational age, etc. **Menstrual history** as regularity and date of 1st day of last menstrual period. **Obstetric history:** gravidity, parity, previous abortion, gestational age, associated medical conditions, history of maternal or fetal complications. **Medical history:** of systemic medical disorders. **Surgical history:** of previous cesarean sections ant its maternal and fetal outcomes. **History of COVID-19 vaccination:** type, date, number of doses and associated adverse effects. **Examination:** Complete general, abdominal "obstetric" and local examinations for confirmation of inclusion and exclusion criteria. **Conventional 2D ultrasonography:** for documented basic fatal biometry data. All women were called on their phones to ask about their vaccination certificates and record their pregnancy outcomes.

Outcomes: ***Maternal outcomes:*** preeclampsia (PET) and venous thromboembolism (VTE). ***Neonatal outcomes:*** neonatal intensive care unit (NICU) admission and Preterm labor.

Data Management and Analysis: After revision, coding, tabulation, and introduction to a PC, the gathered data was processed through the Statistical Package for Social Science (SPSS 26). Data were shown, and appropriate analysis was carried out in accordance with the kind of data found for each parameter.

Descriptive statistics: include the mean, range, and standard deviation (± SD) for parametric numerical data, and the median, interquartile range (IQR), frequency, and percentage of non-numerical data for non-parametric numerical data.

Statistics for analysis: The statistical significance of the difference between the means of the two research groups was evaluated using the Student T Test. To investigate the association between two qualitative variables, ***the Chi-Square test*** was employed

P- value: level of significance: P>0.05: Non significant (NS). -P< 0.05: Significant (S).

RESULTS

Table 1: Demographic data for the whole study group.

		Mean / N	SD / %	Median (IQR)	Range
Age "years"		27.22	4.72	27 (23 - 31)	(18 - 38)
Group	**Non-Vaccinated**	200	50.0%		
	Vaccinated	200	50.0%		

This study was conducted on 400 female pregnant patients divided equally into two groups according to the vaccination history of COVID-19, (table 1) shows that the mean age of the study group was 27.22 ± 4.72 and ranged from 18 to 38 years old.

Table 2: Perinatal and postnatal complications for the whole study group.

		N	%
PE	**No**	381	95.3%
	Yes	19	4.8%
VTE	**No**	400	100.0%
	Yes	0	0.0%
NICU	**No**	333	83.3%
	Yes	67	16.8%
Preterm	**No**	378	94.5%
	Yes	22	5.5%

(Table 2) shows the prevalence of perinatal and postnatal complications for the whole study group, the most frequent complication was NICU admission by 67 (16.8%) of patients followed by preterm by 22 (5.5%), then pre-eclampsia by 19 (4.8%), while no one had VTE.

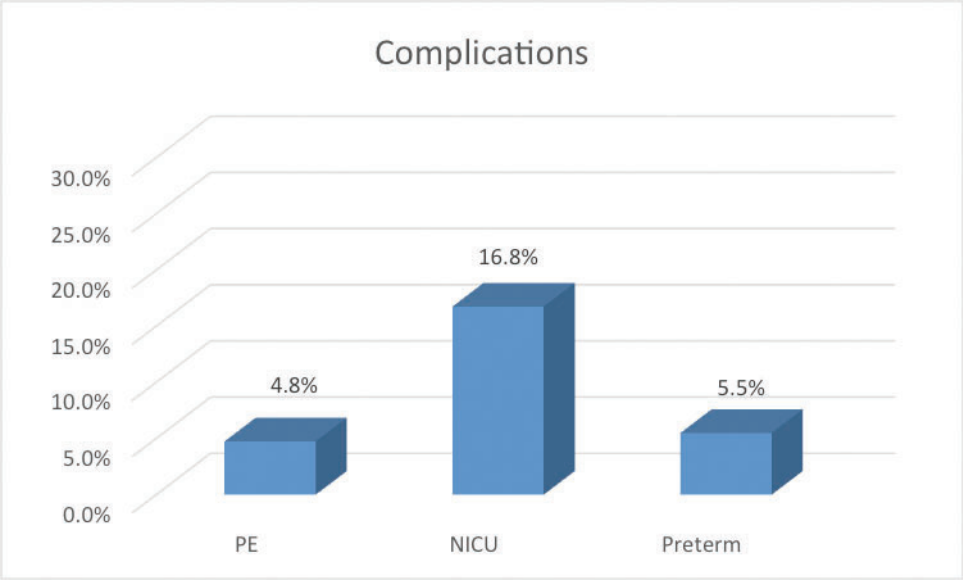

Figure (1): shows perinatal and postnatal complications distribution among the study group.

Table 3: Relation between age and two study groups.

		Group		Student t-test		
		Non-Vaccinated	**Vaccinated**	**t**	**P-Value**	**Sig.**
Age "years"	**Mean ± SD**	27.23 ± 4.78	27.21 ± 4.66	0.042	0.966	NS
	Range	(18 -36)	(18 -38)			

(Table 3) demonstrates the relation between age and two study groups, the mean age of non-vaccinated group was 27.23 ± 4.78, while it was 27.21 ± 4.66 for vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

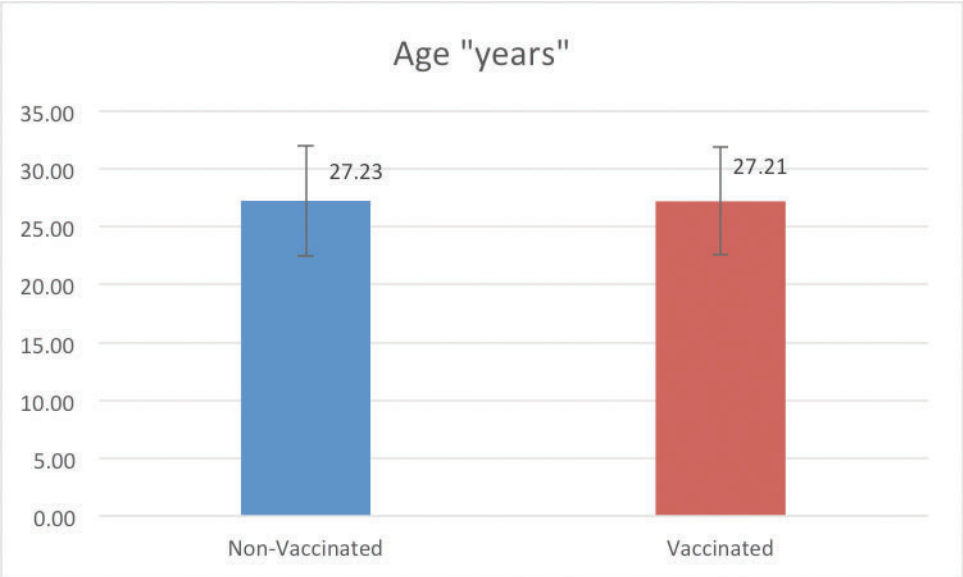

Figure (2): Shows age difference between two the study group.

Table 4: Relation between pre-eclampsia as a complication and two study groups.

		Group		Chi-Square test		
		Non-Vaccinated	Vaccinated			
		N (%)	N (%)	X^2	P-Value	Sig.
PE	No	190 (95%)	191 (95.5%)	0.055	0.814	NS
	Yes	10 (5%)	9 (4.5%)			

(Table 4) illustrates the relation between pre-eclampsia as a complication and two study groups, the number of patients who had PE within non-vaccinated group was 10 (5%), while they were 9 (4.5%) within vaccinated group ***without statistically significant difference*** between two study groups as P-value was >0.05.

Table 5: Relation between neonatal intensive care unit as a complication and two study groups.

		Group		Chi-Square test		
		Non-Vaccinated	Vaccinated			
		N (%)	N (%)	X^2	P-Value	Sig.
NICU	No	161 (80.5%)	172 (86%)	2.169	0.141	NS
	Yes	39 (19.5%)	28 (14%)			

(Table 5) shows the relation between NICU admission as a complication and two study groups, the number of patients admitted to NICU within the non-vaccinated group was 39 (19.5%), while they were 28 (14%) within vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

Table 6: Relation between preterm labor as a complication and two study groups.

		Group		Chi-Square test		
		Non-Vaccinated	Vaccinated			
		N (%)	N (%)	X^2	P-Value	Sig.
Preterm	No	191 (95.5%)	187 (93.5%)	0.77	0.38	NS
	Yes	9 (4.5%)	13 (6.5%)			

(Table 6) demonstrates the relation between preterm labor as a complication and two study groups, the number of patients who had preterm labor within non-vaccinated group were 9 (4.5%), while they were 13 (6.5%) within vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

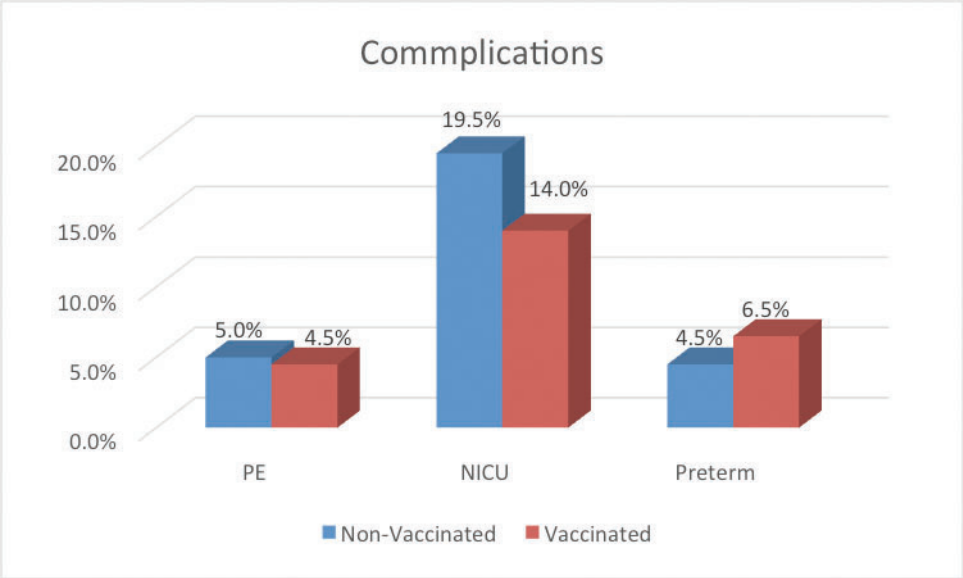

Figure (3): Shows relation between perinatal & postnatal complications and two the study group.

DISCUSSION

Preterm birth, caesarean section, and pre-eclampsia have all been linked to the novel coronavirus disease 2019 (COVID-19), which may cause more severe illness during pregnancy. There is a dearth of information on the safety and effectiveness of the COVID-19 vaccinations in foetuses, newborns, and pregnant women. This is mostly because pregnant women are not allowed to participate in clinical vaccine trials.[11]

the Centers for Disease Control and Prevention (CDC), advises pregnant women to get vaccinated against COVID-19 due to the possible severity of the disease. Nonetheless, despite the paucity of safety information, it was suggested that expectant mothers receive a clear, balanced assessment of their risk of contracting COVID-19 during pregnancy as well as an overview of the possible advantages of COVID-19 vaccinations.[12]

Goldshtein et al. (2021) demonstrated that severe acute respiratory syndrome coronavirus (SARS-CoV-2) messenger RNA (mRNA) vaccination in pregnant women was associated with a significantly lower risk of COVID-19 infection compared with unvaccinated women.[13]

Furthermore, after immunisation, there was reportedly a very low incidence of obstetrical problems, such as preterm rupture of membranes, vaginal bleeding, and uterine contractions. However, due to a lack of information regarding the COVID-19 vaccine's safety during pregnancy, many expectant mothers refuse to receive the shot.[14]

Although the COVID-19 vaccine reduces the risk of being infected with a life-threatening virus, as long as the risks to the fetus are unknown, an informed woman's choice should be honored.[15]

Data regarding perinatal outcomes following the COVID-19 vaccination is still limited. Self-reported pregnancy outcomes among 827 pregnant participants in a vaccination surveillance system were similar to historic controls before the COVID-19 pandemic including preterm birth and small for gestational age 6. Another small cohort study found no significant difference in adverse pregnancy outcomes between 133 women who received at least one vaccine dose and

399 unvaccinated pregnant women.[16]

The current study aimed to retrospectively explore the maternal, fetal, and neonatal outcomes in COVID-19- vaccinated pregnant women compared with those not receiving COVID-19 vaccine.

This was a retrospective cohort study that was conducted at Ain Shams University Maternity Hospital (ASUMH). Pregnant women who attended ASUMH for delivery were divided into two groups: **Group A** consisted of 200 COVID-19 vaccinated women who received at least one vaccine dose six months or more prior to labor (the study group); **Group B** consisted of an age-matched control group of 200 unvaccinated women.

Our study demonstrated the relation between age and two study groups, the mean age of non-vaccinated group was 27.23 ± 4.78, while it was 27.21 ± 4.66 for vaccinated group ***without statistically significant difference*** between two study groups as P-value was >0.05.

In accordance, ***Kugelman et al. (2023)*** found no statistically significant differences in maternal characteristics between vaccinated and unvaccinated pregnant women.[17]

However, ***Theiler et al. (2021)*** found older age to be significantly associated with increased likelihood of vaccination.[18]

Also, ***Carbone et al. (2022)*** aimed to explore perinatal outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-vaccinated pregnant women compared with unvaccinated counterparts. They observed differences among vaccinated and unvaccinated women in relation to age.[19]

Our study illustrated the relation between pre-eclampsia as a complication and two study groups, the number of patients who had PE within non-vaccinated group was 10 (5%), while they were 9 (4.5%) within vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

Accordingly, ***Theiler et al. (2021)*** compared 1862 pregnant women who were not vaccinated with 140 women who received vaccinations in their third trimester of pregnancy (212 of them had contracted COVID-19 during the present pregnancy) in a manuscript that was released online before peer review. When it came to severe composite unfavourable outcomes, which encompassed issues for both the mother and the newborn, as well as particular maternal or delivery outcomes, there was no discernible difference between pregnant women who had received vaccinations and those who had not.[18]

In agreement, ***Wainstock et al. (2021)*** performed a subgroup analysis, observing no differences in the rate of pregnancy-related hypertensive disorders.[20]

According to two recent observational studies conducted in Palestine, there was no significant difference in maternal outcomes between pregnant women who received the mRNA COVID-19 immunisation and those who did not.[21, 22]

Another retrospective cohort study by ***Piekos et al. (2023)*** concluded that, COVID-19 vaccination protects against adverse maternal–fetal outcomes, with booster doses conferring additional protection.[23]

The results of ***Carbone et al. (2022)*** reinforced the idea that receiving the SARS-CoV-2 vaccine during pregnancy is not associated with an increased probability of adverse outcomes for mothers.[19]

Both ***Goldshtein et al. (2021)*** and ***Theiler et al. (2021)*** found that pregnant women who received the BNT162b2 mRNA vaccine during pregnancy had significantly lower risk of COVID-19 infection, further supporting the importance of this vaccination during the COVID-19 epidemic.[13, 18]

Our study showed the relation between NICU admission as a complication and two study groups, the number of patients who

admitted to NICU within non-vaccinated group were 39 (19.5%), while they were 28 (14%) within vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

The results of ***Blakeway et al. (2021)*** are also in agreement with ours, showing similar rates of NICU admissions, when they compared 141 vaccinated pregnant women with 1187 unvaccinated pregnant women. In their study, 86% and 14% were vaccinated in the third and second trimester, respectively.[16]

Accordingly, ***Kugelman et al. (2023)*** showed that the rate of the composite adverse perinatal outcome was similar for pregnant women who had received vaccinations and those who had not; no appreciable differences were observed in the rate of the composite adverse perinatal outcome or the individual adverse perinatal outcomes, such as the rate of NICU admission, when compared to unvaccinated parturient.[17]

Our study demonstrated the relation between preterm labor as a complication and two study groups, the number of patients who had preterm labor within non-vaccinated group was 9 (4.5%), while they were 13 (6.5%) within vaccinated group ***without statistically significant difference*** between two study group as P-value was >0.05.

Similar to our findings, ***Goldshtein et al. (2021)*** reported no notable differences between the vaccinated and unvaccinated groups regarding preterm birth <37 weeks. However, their study design did not provide adequate power to statistically assess differences in adverse events.[13]

In accordance, ***Shimabukuro et al., (2021)*** in a study based on data from the v-safe after vaccination registry, found that adverse neonatal outcomes including preterm birth before 37 weeks, in vaccinated pregnant women were similar to incidences reported in studies involving pregnant women that were conducted before the COVID-19 pandemic.[6]

Neonatal outcomes in a different study, which included digitised questionnaire responses from 57 pregnant women who received vaccinations, were similar to those of the overall pregnant population; however, pregnant women who did not receive vaccinations were not included in the comparison.14 Therefore, all of the studies published thus far show that COVID-19 vaccination during pregnancy did not increase the risk for adverse maternal or neonatal outcomes.

In harmony, ***Kugelman et al. (2023)*** [17] showed that the rate of the composite adverse perinatal outcome was the same for pregnant women who received the vaccination and those who did not; no discernible differences were observed in the rate of the composite adverse perinatal outcome or the individual adverse perinatal outcomes, such as preterm delivery of less than 35 weeks, when compared to unvaccinated parturients.

Similar to our study results, ***Pratam et al. (2021)*** in their meta-analysis and systematic review, found that the administration of mRNA vaccine to pregnant women effectively reduced the incidence of further SARS-CoV-2 infections and also found that the vaccine had no significant effect on neonatal outcomes.[24]

Moreover, ***Goldshtein et al. (2022)*** observed no differences in the rate of preterm delivery, between pregnant women vaccinated during the first trimester and unvaccinated pregnant women.[13]

On the contrary, ***Marchand et al. (2023)*** found that the vaccinated group had significantly lower odds of preterm delivery than the non-infected unvaccinated group. [25]

Ciapponi et al. (2023) discovered that none of the aluminum-based adjuvants or AS03 exposures from mother vaccinations were statistically substantially linked to unfavourable pregnancy outcomes. In certain cases (preterm birth), these vaccinations even shown protective effects linked to particular exposure durations.[26]

A large, multisite, retrospective cohort study in the USA found that receipt of mRNA COVID-19 vaccine during pregnancy was not associated with increased risk for preterm birth. In that study, only 4.2% of pregnant persons received a vector vaccine.[27]

It is possible to speculate that women who received the immunisation also securely self-managed their pregnancies, lowering physical stressors and therefore lowering the chance of different pregnancy problems, including premature birth.[19]

Lipkind et al. (2022) found that pregnant women who received vaccinations had no higher risk of preterm birth than those who did not receive the shots; additionally, they demonstrated that the prevalence of preterm birth was lower following two doses than following one dose, and they found that vaccination in the third trimester had an adjusted OR less than 1.[27]

Dick et al. (2022) showed an increased preterm birth rate and lower overall gestational age at delivery in women vaccinated during the second trimester compared with unvaccinated pregnant women.[28]

INTRODUCTION

Our research confirms the safety of COVID-19 vaccination during pregnancy in terms of its potential to prevent serious adverse outcomes for either the mother or the unborn child, as there were no appreciable differences found in these maternal complications and neonatal outcomes between the vaccinated and unvaccinated groups. To further determine the hazards vs advantages with bigger sample numbers, more research is still necessary.

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Postvoid Residual Urine Measurement in Parous Women with Lower Urinary Tract Symptoms: A Prospective Analytic Study

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Abstract

Background: There are many different bladder complaints that are classified as lower urinary tract symptoms (LUTS). These could be divided into three classes; frequency and nocturia, and storage manifestations of urgency either in presence or absence of urgency urinary incontinence (UUI). Other LUTS include voiding problems like straining, hesitancy, a sense of incomplete emptying, and slow stream. Most of these symptoms are related to vaginal delivery (VD), however bladder dissection during cesarean delivery (CD) may associated with such symptoms.

Objective: To assess the post voiding residual urine and LUT symptoms in parous women with different routes of delivery.

Patients and Methods: We recruited 80 females who were distributed into two groups according to the mode of previous deliveries; group A that included females with previous VD (40 patients) and group B that included females with previous cesarean delivery (40 patients), they were subjected to full history taking (to analyze the presence of different symptoms and other risk factors) and clinical examination (including local examination to assess the state of the pelvic organs). Trans-abdominal ultrasound examination was done to evaluate post-Void Residual (PVR) urine volume was measured in all the cases and correlated with the other symptoms and signs.

Results: There was statistically significantly higher prevalence of positive stress test in the VD group. The mean PVR was statistically significantly elevated in the VD group In comparison with cesarean delivery. There was no statistically significant difference between the two groups in terms of LUTS such as frequency, nocturia, urgency, slow stream, splitting, intermittent stream, hesitancy, straining, and terminal dribbling. The prevalence of incomplete emptying and post micturition dribbling was statistically significantly elevated in the VD group. Degree of prolapse was statistically significantly elevated in the vaginal delivery group.

Conclusion: The current study revealed that; PVR urine

volume was found to be higher in parous women after VD and complaining of pelvic organ prolapse (POP). We recommend using PVR evaluation as a screening approach for all women complaining of LUT symptoms and with history previous vaginal delivery.

Keywords: Lower Urinary Tract Symptoms, Parous Women, Post-Void Residual Urine Volume.

Introduction

Storage, voiding, and manifestations after micturition are three types of LUTS (1). Women can have stress and urge incontinence at the same time, and women voiding dysfunction manifestations are frequently accompanied by manifestations after micturition. (2). The sensation of an incomplete void is said to be more prevalent among postmicturition symptoms in women than post-void dribbling. (3).

It was found that 8.5% of females have experienced the sensation of being empty inside. It is well-known that the prevalence rises at the age of 40 and stays constant at 10% among older people. (4).

PVR measurement appears to be crucial for quality of life (QoL) as it lowers functional bladder capacity and contributes to LUTS. Additionally, it raises the risk of urinary tract infections (UTI). A risk for acute urinary retention only exists if PVR is rising quickly. Urinary infections, bladder stones, and LUTS are frequently linked to urinary retention. Renal failure and hydronephrosis may result from elevated intravenous pressures. (5).

Urinary catheterization and bladder ultrasound are two different techniques used to measure PVR. There are benefits and drawbacks to both methods. Though time-consuming and risky of discomfort, urethral injuries, and UTI, sterile catheterization can give urine samples a more accurate volume. A portable device can be used anywhere to perform bladder ultrasound, that is a quick, noninvasive procedure. (6).

We aimed to evaluate the relationship between LUTS in parous women and PVR urine volume.

Subjects and Methods

This was a prospective cross-sectional study conducted at obstetrics and gynecology department, Mansoura university hospitals, Mansoura, Egypt. The study was conducted for 1 year duration. This study included 80 female patients with LUTS. They were divided into two groups; group (A) comprised 40 cases with previous vaginal delivery (VD) and group (B) comprised 40 patients with previous cesarean delivery. We included females with age ≥40 years old, with history of VD or CD and were complaining of feeling of LUTS included storage symptoms, voiding manifestations and post-voiding symptoms. The study was approved by the institutional review board of the faculty of medicine, Mansoura University.

Entire cases were subjected to history taking that included; personal history (age, residency, educational level, occupation and contact numbers), past medical history (Diabetes mellitus and cardiac diseases), past surgical history (any previous gynecological operations), detailed obstetric history (Gravidity, parity, full term normal delivery, preterm labor, stillbirth, difficult labors, cesarean section, date of last delivery, abortion, previous pregnancies (complicated or not), previous purperia (complicated or not). LUTS included storage manifestations (frequency, nocturia, urgency), voiding manifestations (slow stream, splitting, intermittent stream, hesitancy, straining, terminal dribbling) and post voiding manifestations (incomplete emptying, post-micturition dribbling). Each symptom was analyzed regarding the onset, course, duration, aggravating symptoms and relieving symptoms.

Tin order to detect the frequency of symptoms

associated with pelvic floor diseases, use frequency of LUTS. 10,11 Each of the 11 questions on the FLUTS asks about the frequency (never, 0; occasionally, 1; sometimes, 2; most of the time, 3; always, 4). (7). We considered a prevalence score of at least 2 (at least sometimes) as positive for having the symptom

General examination was concentrated on a general examination of the patient's appearance, body composition, and body mass index (BMI).

Local examination included inspection of vulva, perineum, and during straining for stress incontinence and prolapse. Digital palpation was done while patient was in dorsal position, lubricated index & middle fingers of gloved right hand are introduced through vaginal opening while separating labia with index & thumb of left hand. Palpation included vaginal walls, Vaginal fornices, portio vaginalis of cervix, Levator ani tone, perineal body (pb) thickness and bartholin gland. Bimanual examination was done to assess uterus (position, shape, size, surface, consistency, mobility, tenderness), Adnexa, Douglas pouch and parametrium. Cusco's speculum examination included assessment of portiovaginalis of cervix and lateral vaginal walls.to per form stress test we asked the patients to cough with 1/2 full bladder (with about 200 ml urine in UB). Test was positive if there was escape of urine from urethra limited to period of increased intra-abdominal pressure (if test was negative in lithotomy position we perform it in standing position).

We evaluated POP using POP Quantification (POPQ) System. It consists of 6 points of support around vagina & 3 measurements; points Aa 3 cm above hymenal ring anteriorly, Ap 3cm above hymenal ring posteriorly, Ba Lowest point of prolapse (most dependant point of vaginal wall) anteriorly, Bp Lowest point of prolapse (most dependent point of vaginal wall) posteriorly, C Cervix, D Douglas pouch, Total vaginal length (TVL) Measured at rest, genital hiatus (gh) Measured from middle of urethral meatus anteriorly to hymenal ring posteriorly, and pb. Measured from posterior aspect of gh to mid-anal opening. Hymenal ring was chosen as reference point as it is more precise than introitus. Points are measured in centimeters & are assigned negative (if there is no prolapse) & positive (in prolapse). The Stages included Stage zero shows no prolapse, Stage I where the most proximal portion of the prolapse is greater than one cm above the level of the hymen, Stage II where the most proximal portion of the prolapse is one cm or less proximal or distal to the hymenal plane, Stage III where the most distal portion of the prolapse extends more than one cm below the hymen but no more than two cm less than the TVL and Stage IV where vaginal eversion is essentially complete (procidentia).

Post voidal residual urine estimation was done using trans abdominal ultrasound. The internal volume calculations of the ultrasound device or the mathematical formula are used to determine the bladder's volume. While the patient was lying on his or her back, the suprapubic area was probed. Both the sagittal and transverse planes of the bladder were captured in the images. The largest superior-inferior (height), anterior-posterior (depth), and transverse (width) distances were noted. (8).

Statistical analysis

Collected data was coded, tabulated and introduced to a PC using SPSS (IBM Corp. Released 2017, IBM SPSS Version 25.0, Armonk, NY). Data were presented and suitable analysis was done based on the type of data obtained for all parameters. Kolmogorov-Smirnov test was utilized as a test of normality, in cases when the significance level is more than 0.05, then normality is assumed. Mean±SD was utilized for parametric numerical data, on the other hand median, and range were utilized for nonparametric numerical data. Frequency and %age were utilized for non-numerical

data. Student T, U test, Chi-Square test, Fisher's exact test, and Monte-Carlo test were utilized. With regard to all the previous tests, P-values < 0.05 are considered significant.

Results

The current study comprised 80 females who were distributed into two groups according to the mode of previous deliveries; group A that included females with previous vaginal delivery (VD) (40 patients) and group B that included females with previous cesarean delivery (CD) (40 patients). We found that there was no statistically significant difference between both groups as regards the age (p= 0.271) and BMI (p= 0.080). It demonstrates that there was no statistically significant difference in the presence of comorbidities between both groups. There was no statistically significant difference in the two groups' prior surgical experiences (p = 0.256). There was no statistically significant difference between the two groups regarding the uterine findings (p= 0.062), Table (1).

We found no statistically significant difference between the two groups regarding the LUTS, however, the incidence of incomplete emptying was statistically significantly higher in the vaginal delivery group (60% vs 27.5% in the cesarean delivery group) (P = 0.003). The incidence of postmicturition dribbling was statistically significantly higher in the vaginal delivery group (60% vs 32.5% in the cesarean delivery group) (P = 0.014) , Table (2) .

The degree of POP was statistically significantly higher in the vaginal delivery group (p= 0.048). Also, the prevalence of cystorectocele was statistically significantly higher in the vaginal delivery group (p< 0.001). It shows that there was statistically significantly higher prevalence of positive stress test in the vaginal delivery group (p< 0.001). The mean PVR was statistically significantly higher in the vaginal delivery group in comparison with the cesarean delivery (171.25 ± 78.54 vs 129 ± 48.95 ml respectively) (p= 0.032) ,Table (3).

PVR was higher in the cases who delivered by vaginal delivery with and without the symptoms of LUTS except in cases with and without postmicturition dribbling and the cases without Incomplete emptying where the PVR was higher in the cases with previous cesarean delivery, Table (4).

There was no statistically significant difference in the PVR between the cases with previous vaginal of cesarean delivery according to the degree of prolapse and the results of stress test. However, PVR was higher in the cases who delivered by vaginal delivery with and without Cystorectocele as compared to the cases with cesarean delivery, Table (5) .

Discussion

We conducted a study to detect the correlation between PVR urine volume and LUTS in parous women. Our study included 80 females who were distributed into two groups according to the mode of previous deliveries. In our study the mean PVR was statistically significantly elevated in VD group as compared to cesarean delivery (171.25 ± 78.54 vs 129 ± 48.95 ml respectively) (p= 0.032). Salman et al., conducted a study for 54 women, (37%) underwent an elective cesarean section, and (63%) gave birth vaginally. Pre-labour PVRVs was fund statistically significant higher than postpartum mean PVRVsr (215ml versus 13ml, p.001).Also, abnormal postpartum PVRV was statically significantly higher after VD in comparison with CD (73.5 % vs. 45 %, p 0.05). Mode of delivery had a negative impact on voiding functions. VD is linked to a more voiding dysfunction in comparison to CD. (9).

In a 2014 , Al-Mandeel et al., conducted a study for 236 primiparous women (81 %) gave birth vaginally, and (19 %) underwent a primary elective cesarean section. They

concluded that VD group had a higher postpartum PVRV rate. (8.3 %) of the females who underwent a CD had PPVD, in comparison with (20.2 %) in the VD group (P=0.05) (10).

In our study, the LUTS symptoms were Frequency (27.5%) Nocturia (37.5%) Urgency (25%), Slow stream (35%), Splitting (20%), Hesitancy (25%), Straining to urinate (17.5%), Terminal dribbling (17.5%), Incomplete emptying (27.5%) and Postmicturition dribbling (32.5%) in CD group.

Al-Anbary et al, conducted a study for 187 patients with previous CD. Stress incontinence was found in 35.29 % of patients, while straining and hesitancy to urinate were found in 11.76 %. Frequency was found in 23.5% of patients, urgency in 35.29 % of patients, urge incontinence in this study was accompanied by urgency, nocturia in 14.7% of patients , all of whom complained of frequency and urge incontinence, and dysuria in 26.47 % of patients . There were no reports of weak flow, prolonged voiding, terminal dribbling, or urine retention. (11). The low frequency of these LUTS symptoms was also discovered by Altman et al., similar to this study , they found that 7.6% of people had urinary urgency, and 2.5% had incomplete emptying their bladder. (12).

Women who underwent a single VD or a cesarean section did not have a higher risk of LUTS progression, according to Maserejian et al.,(13). cesarean sections lower incidence against the emergence of LUTS, according to Zhang et al., (14).

The current study demonstrated that; there was no significant difference between both groups with regard to the LUTS including frequency (p=0.805), nocturia (p=0.496), urgency (p=0.228), slow stream (p= 0.469), splitting (p=0.204), intermittent stream, hesitancy (p= 0.152), straining to urinate (p= 0.121) and terminal dribbling (p= 0.075). The incidence of incomplete emptying was found to be statistically significantly higher in the VD group (60% vs 27.5% in the CD group) (P = 0.003). The incidence of postmicturition dribbling was statistically significantly higher in the VD group (60% vs 32.5% in the CD group) (P = 0.014). All symptoms were lower in the CD group. The postal questionnaires were returned by 309 the women who gave birth naturally via vagina and the 208 who chose to have elective cesarean sections, according to Baud et al., Women who underwent elective cesarean sections were significantly less likely to experience urge incontinence and urine leakage while exercising compared to those who gave birth naturally. Contrarily, compared to uncomplicated VD, women who underwent elective cesarean sections were more likely to report lower abdominal pain. Females suffering from one or more symptoms were significantly more frequent after uncomplicated vaginal deliveries than elective cesarean section. (15).

According to Li et al., the VD group was demonstrated to be accompanied by a significant increase in voiding LUTS prevalence. In comparison to the VD group's value of 23.6 %, the incidence of storage LUTS in the CS group was 14.4 % (P 0.001). Urgency was reported as the most frequently encountered symptom in both groups (16.3% in CD versus 9.8% in VD). Urgency (13.9%) and SUI (19.2%) were the two conditions that affected the CS group the most frequently, while UUI (19.2%) and SUI (17.9%) were the two conditions that affected the moderately to severely bothersome LUTS the most frequently after VD. (16).

According to Rortveit et al., CS and VD patients had a 2.3- and 1.5-fold higher risk of urinary incontinence than nulliparae, respectively. When VD and CS were compared together, only stress incontinence was demonstrated to be accompanied by a 2.4 fold increased risk; urge incontinence was unaffected. (17).

Gyhagen et al., examined the data of 5236

Singleton primipare who gave birth between 1985 and 1988 but had no additional children (n = 5236). They also found that the possibility of urinary incontinence increased 1.67 fold after VD in comparison with CS without separating urge incontinence from stress incontinence. (18).

These outcomes may be clarified by the fact that cesarean sections avoid the straining effect of virginal delivery, as well as potential genitourinary tract laceration and instrumental delivery, and have a lower impact on the pelvic floor muscles (PFM) and lower urinary tract. (19,20).

The foetus could induce direct damage to the pelvic floor, anal sphincter, and perineum during the VD as it passes through the soft birth canal. According to studies, the strength of the pelvic organ muscle is the best predictor of SUI in primiparous females six months following VD (21). Women in the CS group have significantly stronger PFMs compared to those in the VD group. (22).

However, 324 females, 378 nulligravida, 473 vaginal births, and 473 cesarean births were included in Khosla et al., study, there were higher odds of nocturia in respondents who had previously delivered vaginally (OR = 1.42, 95 %, p = 0.039) and cesarean section (OR=1.42, p=0.039), although there were no differences between both groups. (23).

The degree of prolapse was a statistically significant increase in the VD group (p= 0.048) in the current study. Furthermore, the prevalence of cystorectocele was statistically significantly higher (p less than0.001) in the VD group. It demonstrates that the VD group had a statistically significantly higher prevalence of positive stress tests (p 0.001). Furthermore, the current study's findings revealed that the VD group had a statistically significantly higher prevalence of positive stress tests (p less than 0.001).

Tsui et al., conducted a retrospective cohort study on 51587 women who had CD and 51,587 females who delivered vaginally (VD). They found that the incidence of SUI and POP was higher in the VD group than in the C/S group (1.6/1000 subject-years and 1.5/1000 subject-years, correspondingly) (0.8 and 0.6 in 1000 subject-years). VD was accompanied by a higher risk of POP and SUI when compared to C/S (hazard ratio (HR): 1.96%, 95% respectively)). (24).

Yang and Sun included 1527 females underwent CSD and 2944 women had a VD. The results showed that there were significant differences in PFM strength, vaginal muscle voltage, maximum urinary flow rate, stress urinary incontinence and POP between the CD group and the VD group. (25).

Hage-Fransen et al., have demonstrated that episiotomy, instrumental VD tears, constipation, and UI during pregnancy are all risk factors for UI at postpartum. Risk factors for postpartum AI include AI during pregnancy, maternal age more than 35, prenatal BMI >30kg/m2, instrumental VD, spontaneous VD, oxytocin augmentations, and newborn > 4000g. (26).

Levator avulsion detachment during VD can happen partially or completely as a result of the foetal head crowning. In other words, the levator hiatus was made larger by the puborectalis muscle avulsion brought on by its insertion on the pelvic sidewall. (27). Forceps delivery may require more space, faster expansion, and stronger force than vacuum or normal VD, increasing the risk of pelvic floor trauma. (28).

The current study is constrained by the small number of cases it included compared to previous studies and by the fact that it only included cases from one center. This might reduce the validity of the results and should be considered in further study.

Conclusion

The current study concluded that; PVR urine volume was found to be higher in parous women after VD and complaining of POP.

We recommend touse PVR evaluation as a screening modality in the context of all women complaining of LUT symptoms and with history previous VD.

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Table (1): Demographic, base line and Ultrasound Findings data of the two studied groups.

	Groups				Test of significance
	Group A (Vaginal delivery) (N=40)		Group B (Cesarean delivery) (N=40)		
Age and Body Mass Index					
Age (years) Mean ± SD	54.48 ± 10.51		56.65 ± 6.61		t = -1.108 p = 0.271
Body Mass Index (Kg/m²)	**31.04 ± 4.17**		**30.56 ± 3.97**		t = 1.784 P= 0.080
Number of previous vaginal deliveries and cesarean deliveries					
Number of previous vaginal delivery	**Median (Range)** 4 (3-12)				
Number of previous cesarean delivery			1 (1-4)		
Medical history and Comorbidities					
Variable	**N**	**%**	**N**	**%**	
Hypertension	10	25 %	10	25 %	$\chi2 = 0$ P = 1
Diabetes	7	17.5 %	8	20 %	$\chi2 = 0.082$ P = 0.775
Epilepsy	0	0 %	1	2.5 %	FET = 1.013 P = 0.314
Cardiac	0	0 %	2	5 %	FET = 2.051 P = 0.152
Stroke	1	2.5 %	0	0 %	FET = 1.013 P = 0.314
Thyroid disorders	2	5 %	0	0 %	FET = 2.051 P = 0.152
Surgical history					
Free	26	65 %	21	52.5 %	$\chi2 = 1.289$ P = 0.256
Positive	14	35 %	19	47.5 %	
Ultrasound Findings					
Uterine findings					
Free	34	85 %	26	65 %	MC = 6.971 P = 0.062
Adenomyosis	0	0 %	2	5 %	
Myoma	3	7.5 %	11	27.5 %	
Polyp	1	2.5 %	0	0 %	
Removed polyps/myoma	2	5 %	1	2.5 %	
Adnexal findings					
Free	39	97.5 %	37	92.5 %	MC = 2.053 P = 0.385
Ovarian cyst	0	0 %	2	5 %	
Removed cyst	1	2.5 %	1	2.5 %	

P: probability. Continuous data are expressed as (mean ± SD) SD: Standard Deviation. T: independent samples t-test. Categorical data expressed as Number (%).
χ2: Chi-Square test, FET= Fischer's exact test, MC: Montecarlo test, Continuous data are expressed as median (range).

Table (2): Analysis of lower urinary tract symptoms (LUTS) in the two studied groups.

	Groups				Test of significance
	Group A (Vaginal delivery) (N=40)		Group B (Cesarean delivery) (N=40)		
	N	%	N	%	
Frequency	12	30 %	11	27.5 %	$\chi2 = 0.061$ P = 0.805
Nocturia	18	45 %	15	37.5 %	$\chi2 = 0.464$ P = 0.496
Urgency	15	37.5 %	10	25 %	$\chi2 = 1.445$ P = 0.228
Slow stream	11	27.5 %	14	35 %	$\chi2 = 0.524$ P = 0.469
Splitting	13	32.5 %	8	20 %	$\chi2 = 1.614$ P = 0.204
Intermittent stream	0	0 %	0	0 %	----------
Hesitancy	16	40 %	10	25 %	$\chi2 = 2.051$ P = 0.152
Straining	13	32.5 %	7	17.5 %	$\chi2 = 2.400$ P = 0.121
Terminal drippling	14	35 %	7	17.5 %	$\chi2 = 3.164$ P = 0.075
Incomplete emptying	24	60 %	11	27.5 %	$\chi2 = 8.584$ **P = 0.003***
Postmicturition drippling	24	60 %	13	32.5 %	$\chi2 = 6.084$ **P = 0.014***

P: probability. Categorical data expressed as Number (%). χ2: Chi-Square test *: statistically significant (p< 0.05).

Table (3): Analysis of prolapse, Cystorectocele, and PVR in the two study groups.

	Groups				Test of significance
	Group A (Vaginal delivery) (N=40)		Group B (Cesarean delivery) (N=40)		
	N	%	N	%	
Degree of prolapse					
Negative	3	7.5 %	8	20 %	MC = 7.808 **P = 0.048***
First degree	13	32.5 %	20	50 %	
Second degree	13	32.5 %	7	17.5 %	
Third degree	11	27.5 %	5	12.5 %	
Cystorectocele					
Absent	5	12.5 %	21	52.5 %	$\chi2$ = 14.587 **P < 0.001***
Present	35	87.5 %	19	47.5 %	
Stress test					
Negative	11	27.5 %	25	62.5 %	MC = 24.889 **P < 0.001***
Present	15	37.5 %	10	25 %	
Present (mixed UI)	13	32.5 %	5	12.5 %	
Complete UI	1	2.5 %	0	0 %	
PVR (ml)					
Mean ± SD	171.25 ± 78.54		129 ± 48.95		z = -2.148 **p = 0.032***
Range	60 - 295		60 – 225		

P: probability. Categorical data expressed as Number (%). $\chi2$: Chi-Square test, MC: Monte-carlo test.

*: statistically significant ($p< 0.05$).

Table (4): PVR according to symptoms in the studied groups.

Symptoms		Group A (VD)	Group B (CD)	P value
Frequency	**Absent**	173.57 ± 82.56	119.48 ± 45.54	**0.003***
	Present	165.83 ± 71.38	154.09 ± 50.83	0.657
Nocturia	**Absent**	150.45 ± 74.29	131.60 ± 51.23	0.312
	Present	196.67 ± 78.05	124.67 ± 46.31	**0.004***
Urgency	**Absent**	163.60 ± 83.80	135 ± 50.15	0.124
	Present	184 ± 69.78	111 ± 42.41	**0.007***
Slow stream	**Absent**	161.55 ± 84.17	127.69 ± 49.52	0.079
	Present	196.82 ± 56.85	131.43 ± 49.63	**0.005***
Splitting	**Absent**	180.74 ± 78.54	132.81 ± 50.96	**0.007***
	Present	151.54 ± 77.85	113.75 ± 38.98	0.220
Intermittent stream	**Absent**	171.25 ± 78.54	129 ± 48.95	**0.005***
	Present	-	-	
Hesitancy	**Absent**	166.88 ± 85.89	122.50 ± 50.77	**0.022***
	Present	177.81 ± 68.19	148.50 ± 38.95	0.229
Straining	**Absent**	180.93 ± 82.35	128.79 ± 49.01	**0.004***
	Present	151.15 ± 68.62	130 ± 52.60	0.488
Terminal drippling	**Absent**	169.81 ± 75.37	132.88 ± 48.48	**0.026***
	Present	173.93 ± 87.01	110.71 ± 50.70	0.094
Incomplete emptying	**Absent**	88.13 ± 20.97	103.10 ± 26.17	0.056
	Present	226.67 ± 46.50	197.27 ± 18.89	0.053
Postmicturition drippling	**Absent**	118.13 ± 60.77	125.74 ± 46.90	0.647
	Present	206.67 ± 69.14	135.77 ± 54.31	**0.003***

P: probability. Continuous data are expressed as (mean ± SD)/ Range. *: statistically significant ($p< 0.05$).

Table (5): PVR according to prolapse, cystorectocele and stress test symptoms in the studied groups.

	Group A (Vaginal delivery)	Group B (Cesarean delivery)	P value
Prolapse			
No prolapse	186.67 ± 67.14	140.63 ± 51.65	0.251
First degree	177.31 ± 71.43	136.25 ± 49.07	0.059
Second degree	176.54 ± 85.69	111.43 ± 58.36	0.091
Third degree	153.64 ± 87.89	106 ± 20.43	0.259
Cystorectocele			
Absent	211 ± 65.33	149.76 ± 48.33	**0,025***
Present	165.57 ± 79.43	106.05 ± 39.21	**0,003***
Stress test			
Negative	139.55 ± 69.33	120.20 ± 45.86	0.328
Present	177.67 ± 88.29	147 ± 54.88	0.339
Present (mixed UI)	196.92 ± 68.63	137 ± 50.94	0.097
Complete UI	90	----------	----------

P: probability. Continuous data are expressed as (mean ± SD)/ Range, statistically significant ($p< 0.05$).

Role of Office Hysteroscopy and Histopathologic Evaluation of Endometrium in Patients with Unexplained Infertility

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Abstract

Background: Infertility affects about 15% of couples. There are several etiologies of infertility, which comprise ovulatory disorders, tubal diseases, and semen abnormalities in males. Hysteroscopy (HS) has been considered as the best approach for uterine assessment, in particular when there is a suspicion of unexplained infertility (UEI). It plays an essential role as regards both taking biopsies and management of pathological conditions in the same diagnostic context.

Aim: To explore the uterine cavity using of office hysteroscopy (oHS) and take endometrial biopsy to evaluate the endometrial pathology in patients with UEI.

Methods: This study was observational cross-sectional study. This study included fifty-three women with UEI with normal ovulation and they had healthy patent tube as revealed by Hysterosalpingography (HSG). Entire cases were divided into two subgroups; primary and secondary, which represented 49.1% and 50.9% of cases respectively. Histopathological biopsy and findings of HS were documented.

Results: There was no statistically significant difference detected between cases with normal and abnormal hysteroscopic findings in terms of other complaints, pathological findings and pregnancy rate. There was statistically significant difference is detected between cases with normal and abnormal pathological findings as regard type of infertility. Every increase in one year in age increases the risk of 2ry infertility by 1.14. Urban residence has increased risk of 2ry infertility by 3.33 times than rural residence, abnormal pathological findings increase risk of 2ry infertility by 3.58 times than normal pathological findings.

Conclusion: Hysteroscopy is considered as a routine step in the fertility work-up program and becomes obligatory before the final diagnosis of UEI. It is an ideal diagnostic approach to several undiagnosed intrauterine pathologies after failure of different routine approaches.

Keywords: Hysteroscopy, Histopathologic examination, Endometrium, Unexplained Infertility.

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INTRODUCTION

The emerging of hysteroscopy (HS) in the gynecological practice presented a real revolution in the management of the intrauterine diseases that mainly interfered with the management of such pathologic situations. By time, recent technical, and technologic developments have made HS much more successful, economic, safe, and helpful. Additionally, several diagnostic and operative hysteroscopy examination might be currently simply conducted in the office base context, with no need for the operating room or anaesthesia [1].

The existence of uterine anomalies might interfere with the reproductive outcomes by increased frequency of miscarriages, preterm labors, and obstetric adverse events [2]. Infertility is the inability of a couple to accomplish pregnancy within a period of one year (among females whose age less than 35 years old) or six months (whose age more than 35 years old) in spite of proper, regular (3-4 times weekly), unprotected sex [3].

Of note, female infertility represents about 48.5 million females globally [4]. The existence of uterine pathologies might harmfully interfere with the implantation process. The prevalence of unsuspected uterine pathologies in asymptomatic women with implantation failure is recorded to be about fifty percent [5]. UEI could be described as the absence of an evident etiology for a couple's infertility and the females' inability to get pregnant after at least twelve cycles of unprotected intercourse or following six cycles in females beyond the age of 35 for whom all the traditional assessments are normal [6].

Hysteroscopy provides precise visual evaluation of the uterine cavity and give a possibility to manage any pathology determined throughout the examination and availability of HS with smaller diameter has made the use of oHS of great importance as a routine examination [7]. Hysteroscopy also has an important role in terms of the establishment of precise diagnosis, in comparison with HSG and even transvaginal sonography (TVS), minor intrauterine disorders that might interfere with fertility. In brief, it is clear why several investigators think that uterine and endometrial integrity must be assessed mostly by HS in the infertile and IVF managed subjects [8, 9].

It has been demonstrated that; infertility due to uterine abnormalities is considered as a causal factor in about 12.5 % of couples seeking treatment. In addition, uterine abnormalities are demonstrated in 34% to 62% of infertile females [10]. Recently, HS has been considered as the best approach for assessing the uterus, and owing to an improvement of endoscopic development, could be carried out in a reliable and safe manner as an office approach [11].

Close assessment of the uterine cavity provides considerable advantages in comparison with the previously used blinded approaches, even though hysterosalpingography (HSG) is to be as precise as HS in the context of diagnosis of uterine abnormalities, the natures of the intrauterine filling defects are more precisely demonstrated by HS [12]. In general, it is conducted as a conclusive diagnostic approach to assess abnormalities on hysterosalpingogram conducted during the evaluation of sub fertile females [13].

Aim of the work

To correlate hysteroscopic findings with endometrial histopathology in patients with UEI.

PATIENTS AND METHODS

This study was observational cross-sectional study. This study included fifty-three women with UEI recruited from the outpatient Clinic of the obstetrics and gynaecology department, Mansoura University hospitals, Egypt, over a period of one year started from March 2021 to March 2022.

Population

Women selected for this study were diagnosed with UEI and had the next criteria; their husbands had normal semen analysis based on WHO 2010, they had normal ovulation (regular menses, confirmed ovulation by using transvaginal sonography (TVS) and the serum progesterone on day 21 of the cycle was more than 3ng/ml indicates ovulation) and they had healthy patent tube determined as evaluated by HSG. But we excluded women with irregular menses, women used hormonal therapy in the past three months, or women with any factor deviating from being UEI as; male factor, tubal blockade, anovulation, previous diagnosis of intrauterine anatomical abnormalities, gynaecological operation in the past six months, and presence of gross uterine pathology.

Methods

Patients with UEI were approached to do hysteroscopy to detect any endometrial pathology. They were invited to take part in the study by the investigator. At first visit, history taking included personal, present, past, family, obstetric and menstrual history, clinical examination included heart rate, blood pressure, temperature, cardiac and abdominal examination. Gynaecological examination included normal HSG that was performed four days after menses. The nature of the study was explained, written consent was obtained. All the participants were assured that the information gathered through the study were kept confidential, being collected anonymously.

Hysteroscopy Procedure

Verbal conversation was done to all patients about the procedure and possible adverse events in an understandable form to her. Informed written consent was taken from all patients before their participation. The examination was done by catheterization and bimanual examination. NSAIDS were given before the procedure. The patient was placed in the dorsal lithotomy position. The patient perineum should be just at the edge of the table. The thighs should be at a 90 angle to the pelvis to form sufficient space for surgeon to conduct the HS. Cleaning of cervix and paracervical block were done. Traction of the cervix with vollsellum was done then office hysteroscope through cervical canal was introduced.

Outcomes

Histopathological biopsy and findings of hysteroscopy (cervical canal-entery-cavity-endometrium-tubal ostia) were reported.

Ethical Considerations

The collected information as regard the conduct, assessment and documentations were planned to confirm that the authors applied the principles of good practice and the ethical principles based on Declaration of Helsinki. This study was presented to Ethical Committee Mansoura University to be approved. Patient approval for registration in this study was documented.

Statistical Analysis

Data were entered and analysed by utilizing IBM-SPSS software (Released 2019, Version 26. Armonk, NY). Qualitative data were expressed as N (%). Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p>0.050$. The existence of significant outliers (extreme values) was assessed for by inspecting boxplots. Quantitative data were expressed as median and range (minimum – maximum). Qualitative data between groups; For 2X2 crosstabulation, the chi-square test was utilized to test the association between two nominal variables. The chi-Square test was used when the expected count in all cells was ≥ 5, otherwise, Fisher's exact test was used. Quantitative data between two group; independent samples t-test was utilized for comparison of normal distribution of quantitative data between 2 groups. The Mann-Whitney U-test was utilized for comparison of non-normal distribution of quantitative data between two groups. The results were considered significant when $p \leq 0.05$.

RESULTS

Table (1) shows that most of the cases of hysteroscopic finding have normal findings by a ratio 56.6%, followed by 13.2% has subseptate uterus, then 11.3 % has endometrial polyp, then 7.5% has partial Asherman Syndrome, 3.8% has partial adhesions of both tubes and finally each of the following; small anterior niche, thick shreddy polypoid endometrium and lateral myoma has the same ratio 1.9%

Table (1): hysteroscopic findings of the studied cases.

	N=53	%
Hysteroscopic Findings		
Normal findings	30	56.6
Subseptate uterus	7	13.2
Endometrial polyp	6	11.3
Small anterior niche	1	1.9
Tubular cavity (partial Asherman syndrome)	4	7.5
Picture of endometriosis	1	1.9
Thick shreddy polypoid endometrium	1	1.9
Partial adhesion both tubes seen	2	3.8
Lateral Myoma	1	1.9

Table (2) shows that there is statistically significant difference is detected between cases with normal and abnormal hysteroscopic results with ratio 21.7% of the cases sof abnormal hysteroscopic finding have parity ≥2 and 80% of the cases of abnormal hysteroscopic findings have abortion ≥2versus 33.3%of the cases with normal hysteroscopic findings

Table (2): Relation between hysteroscopic findings and demographic findings of the studied cases.

	Hysteroscopic findings		**test of significance**
	Normal n=30(%)	**Abnormal n=23(%)**	
Age/years	**28.77±6.47**	**31.87±6.72**	**t=1.70 p=0.095**
Residence			
Urban	**16(53.3)**	**16(69.6)**	**□²=1.43**
Rural	**14(46.7)**	**7(30.4)**	**p=0.231**
Gravidity			
Nulli gravid	**10(33.3)**	**7(30.4)**	
Primi gravida	**9(30)**	**5(21.7)**	**□²=0.761**
≥2	**11(36.7)**	**11(47.8)**	**p=0.684**
Parity			
Nulli para	**17(56.7)**	**10(43.5)**	
Primi para	**13(43.3)**	**8(34.8)**	**□²=7.21**
≥2	**0**	**5(21.7)**	**p=0.027***
Abortion			
1	**10(66.7)**	**2(20)**	**□²=5.23**
≥2	**5(33.3)**	**8(80)**	**p=0.02***
Type of infertility			
1ry	**17(56.7)**	**9(39.1)**	**□²=1.60**
2ndry	**13(43.3)**	**14(60.9)**	**p=0.206**
Infertility duration (years)	**4.74±2.55**	**5.61±3.04**	**t=1.13 p=0.265**

Table (3) shows that there is no statistically significant difference detected between cases with normal and abnormal hysteroscopic findings as regard other complaints, pathological findings and pregnancy rate. Table (4) shows that there was statistically significant difference is detected between cases with normal and abnormal pathological findings as regard type of infertility 62.5% of cases with abnormal pathological findings have secondary infertility versus 33.3% of cases have normal pathological findings. Table (5) shows that there was no statistically significant difference detected between cases with normal and abnormal pathological findings as regard other complaints, hysteroscopic findings and pregnancy rate. Table (6) shows that there was no statistically significant difference detected between cases with normal and abnormal pathological findings as regard hysteroscopic findings and pregnancy rate. Table (7) shows that every increase in 1 year in age increase the risk of 2ry infertility by 1.14. Urban residence has increased risk of 2ry infertility by 3.33 times than rural residence, abnormal pathological findings increase risk of 2ry infertility by 3.58 times than normal pathological findings.

Table (3): Relation between hysteroscopic findings and other complaints, pathological findings and pregnancy rate among the studied cases.

	Hysteroscopic findings		test of significance
	Normal n=30(%)	Abnormal n=23(%)	
Other complaint **Candidiasis** **Secondary amenorrhea** **AUB** **Chronic cervicitis**	 0 2(25) 4(50) 2(25)	 2(40) 0 2(40) 1(20)	MC=4.55 P=0.208
Pathological findings **normal** **abnormal**	 14(46.7) 16(53.3)	 7(30.4) 16(69.6)	□²=1.43 p=0.231
Pregnancy rate **Not pregnant** **Pregnant**	 26(86.7) 4(13.3)	 20(87.0) 3(13.0)	□²=0.001 p=0.975

Table (4): Relation between pathological findings and demographic findings of the studied cases.

	Pathology findings		test of significance
	Normal n=21(%)	Abnormal n=32(%)	
Age/years	28.76±6.13	31±6.99	t=1.19 p=0.238
Residence **Urban** **Rural**	 11(52.4) 10(47.6)	 21(65.6) 11(34.4)	□²=0.930 p=0.335
Gravidity **Nulli gravid** **Primi gravida** **≥2**	 6(28.6) 8(38.1) 7(33.3)	 11(34.4) 6(18.8) 15(46.9)	□²=2.49 p=0.288
Parity **Nulli para** **Primi para** **≥2**	 14(66.7) 6(28.6) 1(4.8)	 13(40.6) 15(46.9) 4(12.5)	□²=3.56 p=0.168

Abortion **1** **≥2**	 6(54.5) 5(45.5)	 6(42.9) 8(57.1)	□²=0.337 p=0.561
Type of infertility **1ry** **2ndry**	 14(66.7) 7(33.3)	 12(37.5) 20(62.5)	□²=4.32 p=0.038*
infertility duration (years)	4.97±2.62	5.22±2.91	t=0.320 p=0.750

Table (5): Relation between pathological findings and other complaints, hysteroscopic findings and pregnancy rate among the studied cases.

	Pathology findings		**test of significance**
	Normal n=21(%)	Abnormal n=32(%)	
Other complaint **Candidiasis** **Secondary amenorrhea** **AUB** **Chronic cervicitis**	 1(16.7) 1(16.7) 3(50) 1(16.7)	 1(14.3) 1(14.3) 3(42.9) 2(28.6)	MC=0.258 p=0.968
Hysteroscopic findings **Normal findings** **Subseptate uterus** **Endometrial polyp** **Small anterior niche** **Tubular cavity (partial Asherman syndrome)** **Picture of endometriosis** **Thick shreddy polypoid endometrium** **Partial adhesion both tubes seen** **Lateral Myoma**	 14(66.7) 4(19) 0 0 1(4.8) 1(4.8) 0 1(4.8) 0	 16(50) 3(9.4) 6(18.8) 1(3.1) 3(9.4) 0 1(3.1) 1(3.1) 1(3.1)	MC=9.38 P=0.310
Pregnancy rate **Not pregnant** **Pregnant**	 18(85.7) 3(14.3)	 28(87.5) 4(12.5)	FET=0.035 P=1.0

Table (6): Relation between pregnancy rate and pathological, hysteroscopic findings of the studied cases.

	Pregnancy rate		**test of significance**
	Not pregnant N=46	Pregnant N=7	
Pathological findings **Normal** **Abnormal**	 18(39.1) 28(60.9)	 3(42.9) 4(57.1)	FET=0.035 p=1.0
Hysteroscopic findings **Normal findings** **Subseptate uterus** **Endometrial polyp** **Small anterior niche** **Tubular cavity (partial Asherman syndrome)** **Picture of endometriosis** **Thick shreddy polypoid endometrium** **Partial adhesion both tubes seen** **Lateral Myoma**	 26(56.5) 5(10.9) 5(10.9) 1(2.2) 4(8.7) 1(2.2) 1(2.2) 2(4.3) 1(2.2)	 4(57.1) 2(28.6) 1(14.3) 0 0 0 0 0 0	MC=3.03 P=0.933

Table (7): Predictors of secondary infertility among studied cases.

	B	p value	Odds ratio (95% CI)
Age/years	0.134	0.008*	1.14 (1.04-1.26)
Residence Urban Rural(R)	1.204	0.04*	3.33(1.05-10.58)
Pathological findings Normal (R) Abnormal	2.01	0.03*	3.58(1.05-10.58)
Overall % predicted =64.2%			

DISCUSSION

Infertility affects about 15% of couples. There are several etiologies of infertility, which comprise ovulatory disorders, tubal diseases, and semen abnormalities in males. Such etiologies represent about seventy-five percent of infertile couples. UEI diagnosis could be established when all routine tests for infertility are negative [14].

HS is considered the best approach for the assessment of uterine cavity, in particular when pathologies are suspected in UEI. It permits close visualization of intrauterine pathologies, exploring their nature, site, shape, size and vascular pattern. In addition, it permits directed biopsy or management of any disorder within the same visit. As a result, in females with UEI, HS might be considered a conclusive diagnostic modality to evaluate any abnormality suspected or couldn't be determined by HSG or TVS in initial assessment of infertile cases [15]. The present study aimed to properly assess the uterus by utilizing office HS and take endometrial biopsy to assess the endometrial pathology among cases with UEI.

This was a cross-sectional study conducted on a total of 53 women with UEI at Mansoura University Fertility Care Unit within the period from March 2021 to March 2022. Entire cases were divided into two subgroups; primary and secondary which represented 49.1% and 50.9% of cases respectively.

Entire cases were divided into two subgroups; primary and secondary which represented 49.1% and 50.9% of cases respectively. In addition, most of the studied cases (60.4%) were living in urban regions, whole only were living in rural regions (39.6%). In the same line, Makled and his colleagues conducted their study on a total of 100 women with UEI women, in which 40 women had primary infertility, whereas 60 women had secondary infertility. The mean infertility duration was 6 years [16]. Also, Matei and his colleagues have demonstrated that; the mean age of subjects was thirty nine years old. Most of cases (88.9%) were living in urban regions; 95.6% of females were in their childbearing period, whereas 4.4% were their menopausal period [17]. On the other hand, Hamada and his colleagues have found that; 70 percent of studied women had primary infertility, while only thirty percent were associated with secondary infertility [18].

The current study demonstrated that; the abnormal hystroscpic findings among the studied cases represented 43.4%. Similarly, Makris and his colleagues conducted HS in cases with previous history of abortion, infertility and repeated IVF failure. They revealed that abnormalities in hysteroscopic outcomes were noticed in 40.5% of cases

where intrauterine adhesions, endometrial hyperplasia and polyps were the commonest findings [19]. Also, Jain and his colleagues conducted an observational study on one hundred women's with UEI who were examined with oHS and demonstrated that abnormal hysteroscopic findings was recorded in 56% [20].

Khalil Abd El-Shafi and his colleagues have demonstrated that; normal hysteroscopic examination were detected among 65% of subjects, while abnormalities were detected in 35% only [21]. Higher incidence was recorded by Mohamed & Elmazzaly who demonstrated that abnormal hysteroscopic examination was detected in 89% of their studied cases [22]. Lower incidence was recorded by Makled and his colleagues who displayed that no hysteroscopic abnormalities were detected in 14% of females with UEI [16].

Regarding hysteroscopic findings, most of the cases of hysteroscopic finding have normal findings by a ratio 56.6% ,followed by 13.2% has subseptate uters , then 11.3 % has endometrial polyp ,then 7.5% has partial Asherann Syndrome , 3.8% has partial adhesions of both tubes and finally each of the following :small anterior niche ,thick shreddy polypoid endometrium and lateral myoma has the same ratio 1.9%. Also, Mohamed & Elmazzaly have displayed that; the percentage of cervicitis, cervical stenosis, cervical polyp, uterine septum, arcuate uterus, uniconuate uterus, bicornuate uterus, endemostritis, intrauterine synchcia, endometrial polyp, submucous myoma and hyperplastic were recorded in 2%, 1%, 4%, 3%, 2%, 2%, 1%, 13%, 8%, 30%, 9%, 14% of cases respectively (22). Also, Ahmed et al. displayed that; according to hysteroscopic results, 22 of cases (18.3%) had polyps, six cases had cervical stenosis (5%), one cases has myoma (0.8%), eight cases had intrauterine adhesions (7%) and 19 cases had congenital anomalies of uterus (16%). Cervicitis was revealed in twelve cases (10%), whereas three cases had endocervical cysts (2.5%), cornu not accessible in four cases (3.3%), while ostia not detected in eight cases (6.6%), three cases had tight isthmus (2.5%) and three cases had polypidal thickness at isthmus (2.5%), while hysteroscopy findings were demonstrated to have no abnormalities in 49 cases (40.8%) [26]. In addition, Hamada and his colleagues have displayed that; among the 100 females studied, 29 % had abnormalities by HS in the uterine cavity and cervical stenosis. Moreover, 71% of studied females had no abnormalities. In addition, 14% were detected to have intrauterine polyps (not detected by both HSG and ultrasonography). Eight females were observed to have submucous fibroids with grades from zero to two and small in size, four women had intrauterine adhesions. A single female had small uterine septum. Failed approach happened in two females with cervical stenosis [18].

Moreover, Makled and his colleagues demonstrated that; according to hysteroscopic results, thirty one cases were finally diagnosed with endometrial polyps; 14 endometritis; 15 endometrial hyperplasia; six submucous myomas; seven intrauterine synechiae; seven congenital uterine anomalies, six cervical stenosis and fourteen females with normal uterus. Assessment of specimens by endometrial suction curette was non-diagnostic in sixteen cases; the commonest endometrial pathologic feature determined by this assessment was endometritis (15%). The prevalence of endometrial hyperplasia was 14%, and 3 patients of endometrial polyps were identified [16].

Concerning predictors of secondary infertility among studied cases, the present study demonstrated that; every increase in 1 year in age increase the risk of 2ry infertility by 1.14 , Urban residence has increase risk of 2ry infertility by 3.33 times than rural residence , abnormal pathological findings increase risk of 2ry infertility by 3.58 times than normal pathological findings. In the same line, Ono and his colleagues

have demonstrated that; age was recognized as an independent predisposing factor for postsurgical secondary infertility. [28].While, Dhont and his colleagues have demonstrated that; predisposing factors in the obstetric history for secondary infertility were absence of prenatal care in the last pregnancy, adverse pregnancy outcomes, stillbirth, postpartum infections and curettage. [29].

The current study demonstrated that hysteroscopic findings have a significant correlation with parity and abortion only. In addition; there was a significant relation between pathological findings and type of infertility only.

With regard validity of hystroscope as compared to pathological findings, the current study demonstrated that; it showed sensitivity 50%, specificity 66.7%, PPV 69.6%, NPV 46.7% and accuracy 66.7 %. Mohamed & Elmazzaly have demonstrated that HS was significant with sensitivity, specificity, PPV, NPV and accuracy of 97.8%, 100%, 100%, 84.6%, 98% respectively [22].

In the same line, Garuti and his colleagues recorded that HS was of great diagnostic accuracy in the context of endometrial polyp diagnosis [30].

In addition, Hauge and his colleagues revealed that the outcomes of HS and TVS were comparable in 90.9% of cases (31). Draz and his colleagues have displayed that HS was of great sensitivity (, but had the same specificity, and was more precise in comparison with saline infusion ultrasonography. Throughout the assessment of subjects with UEI, HS had a better predictive value in comparison with saline infusion ultrasonography [32].

On the other hand, Zargar and his colleagues revealed that the sensitivity of hysterography and sonography were 48.9% and 48%, respectively, on the other hand false negative rates were 51.1% and 52%. Thus, sonography and hysterography were inadequate in the context of uterine cavity evaluation [33].

In addition, Preutthipan & Linasmita carried out a comparative study of HSG and HS in the recognition of intrauterine diseases among infertile females and demonstrated that HSG had a higher sensitivity (98%) and mild specificity (34.6%) [34]. Our study revealed that, HSG had a higher sensitivity and poor specificity in terms of detection of intrauterine pathologies. Thus, although HSG is a useful screening test for intrauterine lesions as it demonstrates the filling defects, which are obtained by HSG (not specific). Only HS has the ability to precisely demonstrate the natures of the intrauterine filling changes. When an HSG demonstrates any uterine abnormalities, HS is suggested to verify their site and extent [34].

CONCLUSION

Planning the HS as a routine step in the fertility work-up program has become obligatory before the conclusive diagnosis of UEI. This approach has been considered a perfect approach to diagnose several intrauterine pathologies undiagnosed with different traditional methods. Of note, the marked improvement in the pregnancy outcomes after the hysteroscopic approach, reinforces the formerly reported suggestions.

Recommendations

Additional researches on large number of cases and different populations are needed to emphasize the current conclusion. There was a need to assess the impact of choice of tubal test on chances of spontaneous conception and therapeutic outcomes in females with UEI. Any patient with UEI must be investigated with hysteroscopy.

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Uterine Rupture in Early Pregnancy - A Tertiary Centre Experience

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Abstract

Background: Rupture uterus is a life-threatening complication, with high maternal and fetal morbidity and mortality. Rupture uterus is more commonly encountered during labour. Rupture uterus during early pregnancy is rarer.

Methodology: Prospective Observational study in a tertiary center collecting data on the rupture of the uterus in early pregnancy (before 28 weeks). Demographic and clinical data were collected from case files to investigate predisposing factors, diagnose, and evaluate the outcome of these cases to obtain learning lessons.

Results: We encountered 17 cases of rupture uterus in early pregnancy. Eleven cases had a previous cesarean delivery. Three cases had a prior history of rupture uterus, 2 cases had a congenital uterine anomaly, and one case had a previous history of laparoscopic resection of corneal ectopic pregnancy.

Conclusion: No trimester is immune from rupture uterus. Careful use of prostaglandins for induction of miscarriage is required in patients with previous cesarean delivery even in early pregnancy. Previous history of rupture uterus requires more attention as the risk of repeat rupture is high and it recurs at an earlier gestation. Diagnosis of the ruptured uterus in early pregnancy can be challenging.

Keywords: Rupture uterus, early pregnancy, previous CS, induction of miscarriage.

INTRODUCTION

Rupture uterus in the early stages of pregnancy is extremely rare however; it is one of the catastrophic events in obstetrics. This could happen spontaneously or on top of preexisting pathology (e.g. uterine scar, uterine anomaly).(1)

Diagnosis of early rupture of the uterus is clinically challenging because its remote potential elevates the threshold of clinical suspicion, vague symptoms in the beginning, especially

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in the scarred wombs, and lack of ultrasound diagnostic consensus.(2)

Clinicians should be vigilant when using ecbolic for induction of miscarriage in the scarred uterus and avoid the false sense of security when using them especially when the repeated dosage is required.(1)

In this work we highlight the predisposing factors, the clinical picture, sonographic finding, and the possible management of pregnant ladies with uterine rupture in the early gestational age aiming to enhance the outcome of such a unique catastrophe.

METHODOLOGY

This was a prospective observational study in which we collected data on cases that had rupture uterus before the age of viability (28 weeks of gestation) over one year in a university hospital from the first of August 2017 till the end of July 2018. Total admission of pregnant cases during this year: 18,666 cases. We collected data on cases that had ruptured uteri in the first and the second trimester and looked for possible risk factors, diagnosis, management, and outcomes of these cases. This study was approved by the Research Scientific and Ethical Committee of the Department of Obstetrics and Gynecology – Cairo University Hospital with ethical approval number (O-170013).

Statistical analysis:

The statistical analysis was done using Microsoft Excel 2016.The data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. All statistical calculations were done using SPSS for IBM (IBM Corp., Armonk, NY, USA).

RESULTS

During the period of the study, we managed 17 cases of ruptured uterus in early pregnancies (before 28 weeks) who were admitted to the Emergency Unit at the Department of Obstetrics and Gynecology at Cairo University Hospital. The mean age of the patients was 30.4 ± 5.3 with a mean BMI of 30.2 ± 3.9. All cases were parous, none were nulliparous. The mean gestational age at which rupture of the uterus occurred was 20.6 ± 5.47 weeks, with ruptures reported as early as 12 weeks. Two cases had rupture uterus near the end of the first trimester, and 15 cases occurred in the second trimester. Table 1, shows the baseline characteristics of women who had ruptured uterus in early pregnancy.

The rupture of the uterus occurred spontaneously in 9 cases and was provoked by induction of miscarriage in 8 cases. Eleven cases had previous CS, three cases had a previous history of ruptured uterus, in 2 of these cases the rupture occurred in the rudimentary horn, and one case had laparoscopic resection of corneal ectopic pregnancy.

Table 1: The baseline characteristics of women who had ruptured uterus in early pregnancy

Variable	Mean ± SD	Range	N	%
Age (years) :	30.4 ± 5.3	25- 46	17	100
• 20-30 • 30-40 • >40			10 6 1	58.8 35.3 5.9
BMI (kg/m²)	30.2 ± 3.9	24.25 - 37.48	17	100
• Normal weight 18.5 to 24.9 • Overweight 25 to 29.9 • Obese (>30) - Class I 30-34.9 - Class II 35-39.9 - Class III >40			3 5 6 3 0	17.6 29.4 53
Gravidity	2.8 ± 1.07	**1 – 5**	17	100
Parity	2.47 ± 0.94	**1 – 4**	17	100
• P1 • P2 • P3 or more			2 8 7	11.8 47.0 41.2
Gestational age (weeks)	20.53 ± 5.32	**12 - 27**		
• **First trimester 2/17** • **Second trimester 15/17**			2 15	11.8 88.2
Associated co-morbidity: • No morbidity • Severe early onset pre-eclampsia • Diabetes Mellitus and hypertension			 15 1 1	 88.2 5.9 5.9
Number of fetuses: • **Singleton** • **Twins**			 16 1	 94.1 5.9
Interpregnancy interval (years)	2.5 ±0.9	1-4		
Mode of previous deliveries: • **NVD** • **CS**			 1 16	 5.9% 94.1%
Mode of ruptured uterus: • **Spontaneous rupture** • **Provoked by Induction of miscarriage**			 9 8	 52.9 47.1
Risk factor for rupture uterus • Rupture rudimentary horn • Previous rupture uterus • Resection of corneal ectopic • Previous Cesarean section			 2 3 1 11	 11.8 17.6 5.9 64.7

We divided patients into four groups according to the main predisposing factor for rupture uterus:

- Cases with a previous cesarean deliveries (11 cases)
- Cases with a previous history of uterine rupture (3 cases)
- Cases with a rudimentary uterine horn (2 cases)

- Case with a previous laparoscopic resection of corneal ectopic pregnancy (one case)
- Cases that had induction of miscarriage (8 cases).

Cases with previous Cesarean deliveries (11 cases)

We encountered 3 cases with one prior CS. In these three cases, the rupture was provoked by the induction of miscarriage. Regarding patients with previous 2 CS, we had 5 cases (three cases had a spontaneous rupture and two cases had rupture provoked by miscarriage induction). There were three cases with previous 3 CS scars one happened spontaneously and the other two had induction of miscarriage. See table 2 for the summary.

Table 2: The characteristics of previous Cesarean delivery cases

number of previous CS	Spontaneous	Provoked (induction of evacuation)
Previous 1CS	none	One case at 14 weeks. Two cases at 22 weeks
Previous 2 CS	One case at 20 weeks One case at 24 weeks One case at 27 weeks	One case at 25 weeks One case at 26 weeks
Previous 3 CS	One case at 24 weeks	One case at 12 weeks. One case at 15 weeks.

Cases with previous ruptured uterus:

Three cases had previous rupture of the uterus. In these cases, rupture of the uterus occurred spontaneously and at a gestational age earlier than the previous incident of rupture of uterus. The first case had a history of previous ruptures of the uterus 3 times at 39, 35 , and 24 weeks respectively, the last one was 2 years ago before subsequent pregnancy. This case had a spontaneous rupture of the uterus at 12 weeks. The second case had a history of a previous rupture uterus at term and had a spontaneous rupture at 14 weeks at subsequent pregnancy. The third one had a previously perforated uterus during surgical evacuation followed by a ruptured uterus at 36 weeks, and this case had spontaneous rupture at 25 weeks gestation.

Cases with a rudimentary uterine horn (2 cases)

The first case had rupture in the rudemintary horn at 18 weeks took induction of miscarriage by PG presented with vaginal bleeding and maternal shock .laparotomy was done the products of conception found outside the horn. The second case had spontaneous rupture at 27 weeks gestation presented to our center by abdominal pain ultrasound picture of the fetal body and placenta outside the contour of the rudimentary horn.

Case with previous laparoscopic management of corneal ectopic

One case was delivered vaginally but had a previous history of laparoscopic management of ectopic pregnancy (corneal). This case had spontaneous rupture at 22 weeks of gestation.

Cases that had induction of miscarriage

The rupture uterus was provoked by induction of miscarriage in eight cases. 7 cases had previous CS. One case had an undiagnosed rudimentary horn. One case had improper dosing of misoprostol outside our tertiary center; however rupture uterus occurred in the remainder despite proper dosage.

Clinical presentation of uterine rupture

Table 3 shows different clinical presentations for cases with a ruptured uterus. The diagnosis was confirmed pre-operatively by ultrasound by seeing the fetus or parts of the products of conception outside the uterus. The diagnosis was established preoperatively in 13 cases by ultrasound finding the fetus/parts of products of the conception outside the uterine cavity. However, in 4 cases, the diagnosis was established intra-operatively.

Table 3: Clinical presentations of ruptured uterus

Symptoms	N	Percentage
Abdominal pain	3	17.6%
Vaginal bleeding	2	11.8%
Abdominal pain and vaginal bleeding	5	29.4%
Failure to progress	2	11.8%
Hypovolemic Shock due to internal hemorrhage	5	29.4 %

Intraoperative findings:

Site of rupture occurred at the site of the previous uterine scar in cases with ruptured uterus, at the site of CS scar in cases with previous CS (Fig.1), at the rudimentary horn (Fig.2) and at the lateral wall in the case with a previous resection of corneal ectopic pregnancy (Fig.3).Pfannenstiel incision was done in 15 cases (88.2%) while midline incision was done in two cases only (11.8%). In cases of pregnancy in a rudimentary horn, the horn was excised. Repair of uterine body was achieved in 13 cases (76.4%). Hysterectomy was done for two cases (11.8%) (Fig.3) as repair was not surgically possible and the patients suffered a major obstetric hemorrhage. See table 4 for details.

Eight ladies (47%) received blood transfusion; five patients (29.4%) had massive transfusion as these cases suffered massive obstetric hemorrhage. Five cases (29.4%) were admitted to postoperative ICU.

Table 4: Outcome of cases with early ruptured uterus:

Outcome	Mean ± SD (Range)	Number	Percentage
Incision: 1. Midline incision 2. Pfannenstiel incision		 2 15	 11.8 88.2
Surgical management • Repair of rupture uterus • Excision of Rudimentary horn • Hysterectomy		 13 2 2	 76.4 11.8 11.8
Estimated blood loss (ml)	1682.4 ± 1597.3 (300 – 6400)		
Blood transfusion		8	47
Massive blood transfusion		5	29.4
ICU admission		5	29.4
Hospital stay (days)	3.3 ± 1.7 (2-7)		
Readmission		0	
Mortality		0	

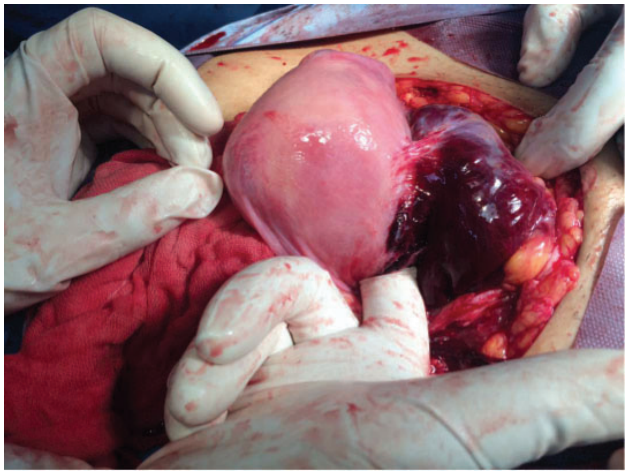

Figure 1: Ruptured uterus at site of previous cesarean scar

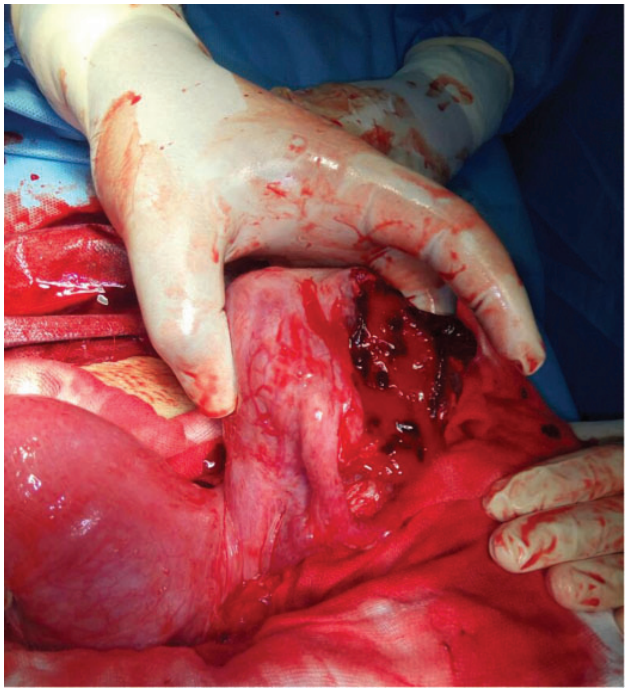

Figure 2: Ruptured uterus in a rudimentary horn (the rudimentary horn enlarges with pregnancy giving the appearance of a bicornuate uterus)

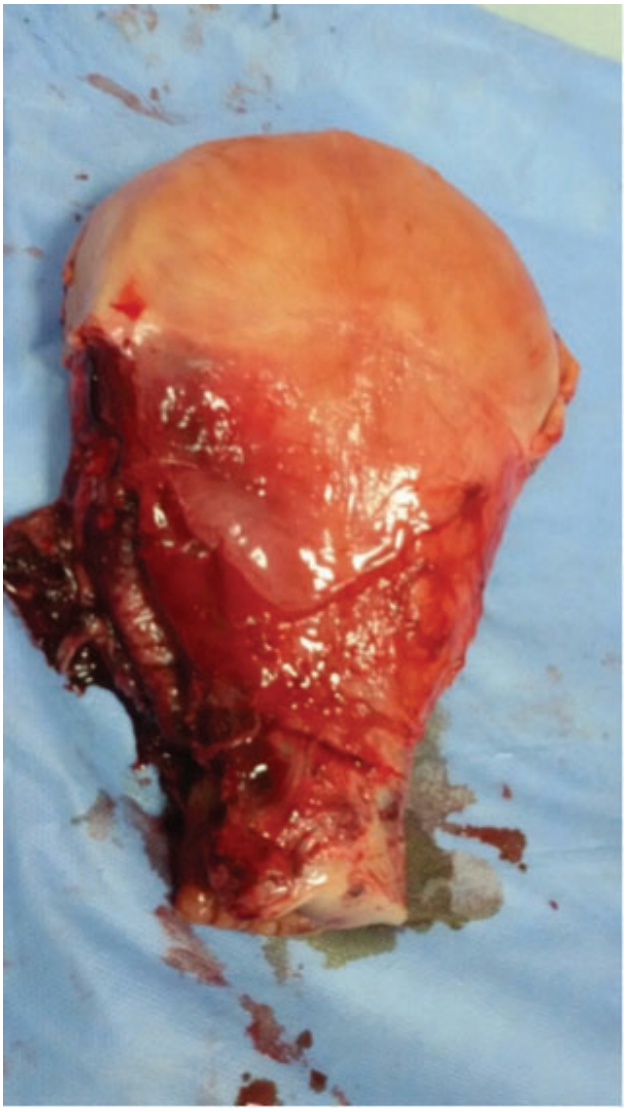

Figure 3: Hysterectomy specimen showing rupture of the lateral wall in a patient who had a previous resection of corneal ectopic pregnancy

DISCUSSION

Rupture uterus is a rare however critical obstetric complication that means interruption of the uterine wall integrity whether partially or completely. It is associated with high maternal and fetal morbidity and mortality.(3)

The incidence of uterine rupture is 5.1/10,000 deliveries in a previously scarred uterus, while in an unscarred uterus it is 1/17,000-20,000.(4, 5)

Uterine rupture is usually observed in association with uterine scarring either in late pregnancy or during labour (6).First and early second-trimester uterine ruptures are very rare, and there are only a few cases in the literature describing first and early second-trimester uterine rupture.(6-9)

According to our study, we encountered 17 cases of ruptured uterus in early pregnancy (before 28 weeks) per 18,666 annual admissions to the Emergency Unit at the Department of Obstetrics and Gynecology at Cairo University Hospital.

Uterine rupture could happen without any prior trauma (8)or could occur on top of underlying risk factors. Previous uterine scars (e.g. CS, myomectomy, and excision of tubal ectopic pregnancy) take the biggest share, followed by uterine malformation, abnormal placentation, improper use of ecbolic and uterine manipulations.(8, 10-13)

Regarding our finding, eleven out of the seventeen cases had prior Caesarean deliveries (3 ladies with prior three Caesarean sections, five with prior two Caesarean sections, and three with a previous one CS). Three cases had prior uterine rupture; their uteri had ruptured during our study at an earlier gestational age than their previous incidents. This raises the alertness that disruption of uterine integrity is not a serious situation of its own but it raises the possibility of recurrence in subsequent pregnancies.

The other risk elements encountered in our work were two cases of rupture in a rudimentary horn at 18 weeks and at 27 weeks, one of which was only discovered intraoperative. The use of prostaglandins is known as a risk factor for uterine disruption, eight out of the eleven cases during the study duration had PG induction of miscarriage. One case had prior normal vaginal delivery but had a history of laparoscopic excision of ectopic tubal pregnancy. Rupture may be attributed to excessive cautery at the uterine cornu.

In the setting of labour, especially after cesarean section, the diagnosis of a rupture uterus can be reached by any of the following: abnormal labour progress, abnormal abdominal pain, vaginal bleeding, and loss of the presenting part, maternal tachycardia, and fetal distress.(14)However, in early pregnancy, especially without the presence of any predisposing risk factors, the diagnosis may occur with latency or may never be detected except intraoperative; leading to life-threatening complications. Furthermore, signs and symptoms of uterine rupture in the early trimester are non-specific and the contour of the small uterus is difficult to be assessed compared to the term uterus. (15-17) .This is because most of the rupture involved a scarred uterus, that scare tissue (ischemic tissue) doesn't elicit a classical picture of pain in uterine rupture.

In our study, the majority of the cases were presented with abnormal abdominal pain or/ and vaginal bleeding (10 cases) with a blood loss range of 300cc up to 6400cc massive hemorrhage. Two were presented by failure of progress of cervical dilatation and five of the seventeen cases had a hypovolemic shock caused by internal bleeding into the peritoneal cavity.

Ultrasound imaging may not fully confirm the diagnosis of uterine rupture especially if incomplete.(18) Eleven of our cases demonstrated definitive ultrasound sign of rupture as the fetal body was seen outside the couture of the uterus. However, in 6 of our cases, the rupture was suspected clinically

but the definite diagnosis was established after the laparotomy was done.

The rate of maternal death due to uterine rupture is 0–1 % in developed nations, but it could be raised to ten folds in developing countries.(19) Owing to early referral to our tertiary Centre, availability of senior obstetricians and availability of blood transfusion facilities, no maternal deaths were encountered in our study. Regarding morbidities, eight cases had received a blood transfusion, five cases had a massive transfusion and five cases were admitted to postoperative ICU.

CONCLUSION

Rupture uterus can occur during any trimester. No trimester is immune. Most important causes include: Previously scarred uterus (CS, and prior rupture), Rudimentary horn pregnancy (which can occur even with a previous history of a normal pregnancy), improper use of ecbolics, and excessive coagulation of cornu at laparoscopic salpingectomy. The commonest presentation is lower abdominal pain but may present with vaginal bleeding only, or both. Ultrasonography is diagnostic when it shows pregnancy outside the uterine cavity. Diagnosis can be established preoperatively however, high clinical suspicion is required. The final confirmation of the diagnosis is usually established intra-operatively. In most cases repair is possible however, hysterectomy can be life-saving. Bleeding is the major morbidity of these cases. Early accessibility to a tertiary facility, availability of a skillful obstetrician and early clinical suspicion improve the maternal outcome. We need further studies to evaluate the reproductive outcome of these cases.

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A randomized clinical trial comparing the cervico-isthmic compression suture versus lower anterior wall uterine resection in cases of the morbidly adherent anteriorly situated placenta

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Abstract

Objective: To evaluate the effectiveness and safety outcome of cervico-isthmic compression suture compared to lower anterior wall uterine resection in preserving fertility and minimizing blood loss in cases of anterior situated morbidly adherent placenta.

Methods: the study was conducted at Mansoura University Hospitals, Mansoura, Egypt during October 2020 to November 2022. A total number of 74 patients with morbidly adherent placenta fulfilled the inclusion criteria and were enrolled and divided into two equal groups. GA, cervico-isthmic compression suture group and GB, lower uterine wall resection group. The main primary outcome measures were intraoperative complications, need for blood or its elements transfusion and emergent hysterectomy, while the secondary outcome measures involved the occurrence of postpartum hemorrhage (PPH) and need for ICU admission as well as neonatal outcome.

Results: the baseline characteristics showed no significance differences between both groups in maternal age, gravidity, parity, fetal gestational age, body mass index, number of previous vaginal or caesarean deliveries, number of previous abortions, ectopic pregnancies, preterm labor or history of gynecological operations as well as preoperative hemoglobin levels, ($p>0.05$). Despite the number is equal in both groups but there is a significant difference as regard the grade of accretion as grade I is found in 9 cases of GA vs 2 only in GB, whilst grade II was diagnosed in 28 cases in GA vs 35 cases in GB, ($p<0.05$). the mean estimated operative time showed no difference between both groups ($p >0.05$) but the mean estimated intraoperative blood loss and the need for packed RBCs transfusion appeared statistically significant between

both groups being lower in GA compared to GB (p 0.001). Sixteen cases of GA were in need of internal iliac artery ligation (IIAL) vs 22 cases in GB, but this did not give any significance. The occurrence of postpartum hemorrhage, endometritis, need for emergent hysterectomy or ICU admission appeared similar in both groups. On the other hand, there is recorded statistical significance as regard bladder injury and mean hospital stay time being lower in GA than GB ($p < 0.05$). The neonatal outcome demonstrated similar results in both groups with no evident of any neonatal complication or need for NICU admission.

Conclusion: The use of cervico-isthmic compression suture appeared more effective and safer than lower uterine wall resection in cases of anteriorly located placenta accreta particularly in terms of intraoperative blood loss, blood transfusion, intraoperative bladder injuries and the postoperative hospital stay.

Keywords: PAS, lower uterine resection, cervical compression sutures.

Introduction

Placenta accreta spectrum [PAS] is an abnormal trophoblastic invasion of part or all of the placenta into the myometrium [1]. It is classified into 3 main subtypes, according to the invasion depth: grade I is abnormally adherent placenta (Creta) when the villi adhere directly to the myometrium without a decidual interface, grade II is an abnormal invasion of placenta (increta) when the villi invade into the myometrium while grade III is abnormal invasion of placenta (percreta) when invasion reaches the peritoneum (3a), surrounding pelvic tissues, vessels, and organs (3b) [2]. PAS prevalence over the last four decades has been continuously increasing and most likely owing to a change in predisposing factors with a notably increased rate of cesarean deliveries [CD] [3-6]. Moreover, when the number of CDs increased the more liability for placenta accreta grades as Marshal et al 2011 [7] proved that the risk increased from 0.3% in females with one preceding CD to 6.74% for females with at least five CDs. Other significant predisposing factors comprise placenta previa even with no prior CD, advanced maternal age, multiparity, assisted reproduction techniques, submucosal leiomyomas or myomectomy, preceding uterine surgeries including curettage or manual placental excision, localized A Sherman syndrome, smoking, and hypertension [8-11].

Despite there is no characteristic clinical data used for the diagnosis of PAS, but this serous obstetric complication should be suspected when one or more of the previous risks are present till assuring the diagnosis by two-D or three-D ultrasound in addition to color Doppler imaging [12-14]. Though magnetic resonance imaging (MRI) also has an important function in the context of PAS diagnosis, with high sensitivity and specificity [15], but US has demonstrated superiority over MRI in this aspect therefore used as a first screening tool [16]. As stated earlier by many researches, the optimal management of such cases should include a standardized procedure with a multidisciplinary care team in a highly specialized tertiary care institutes including a skillful obstetrician and maternal–fetal medicine subspecialists, neonatologist, pelvic surgeon, urologist, interventional radiologist, obstetric anesthesiologist and critical care experts [11, 17].

The main aim of the surgeons during operative management is to minimize operative blood loss, preserve the pelvic organs and to lessen fetal and neonatal complications in addition to intensive hemodynamic supervision in the early postsurgical period in an intensive care unit (ICU). For these benefits, many maneuvers were studied namely, balloon occlusion catheters [11, 18], uterine artery embolization or IIAL [19, 20] all appear to give similar results. Conservative treatment of placenta accreta "leaving the placenta in situ approach" with or without embolization

or vessel ligation was also tried by some studies [21, 22]. In addition, uterine-sparing techniques can be performed via cervico-isthmic compression sutures or tamponade technique [23, 24]. Local uterine resection followed by immediate repair and reconstruction with pelvic devascularization was selected as a line of treatment by Smith D et al., 2016 [25]. Immediate supra-vaginal hysterectomy or planned delayed hysterectomy may be used as a definitive surgical management when extensive invasion of the surrounding structures is proved [26, 27].

Reported maternal complication are many with PAS and may be increased with operative treatment, namely injury to local organs, PPH, internal hemorrhage, amniotic fluid embolism, massive blood transfusion, coagulopathy, electrolyte disturbances, infections, postsurgical thromboembolism, multiple organ failure, hysterectomy or even maternal mortality [28, 29]. Placenta accreta itself appears not directly harmful to the baby or can cause neonatal death but prematurity complications remain threatening for the neonates especially in low resource settings [28, 29]. The aim of the present study was to properly investigate the efficacy and safety of cervico-isthmic compression sutures compared to local myometrial resection in the management of PAS with morbidly adherent anteriorly situated placenta.

Patients and Methods

This was a prospective, randomized controlled parallel-group study conducted within the period from October 2020 to November 2022 in Obstetrics and Gynecology department and high-risk pregnancy unit in Mansoura University Hospitals, Mansoura, Egypt. The study design was approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. MS.20.09.1246) and as a result has been conducted according to the ethical standards of Declaration of Helsinki. During the study period, we selected 91 pregnant females and diagnosed to have placenta accrete grade 1 or 2. All the possible participants were interviewed, received sufficient information about the protocol of the study, and then counseled to be enrolled. The potential participants were then assessed for meeting the inclusion and exclusion criteria.

The main inclusion criterion were those pregnant patients below 40 years, diagnosed as PAS with anterior situated placenta and graded by FIGO as grades, 1 and 2 [2] and welling to preserve fertility. Patient classified as FIGO grade 3, those above the age of 40 years, had having medical disorders as cardiovascular diseases, uncontrolled DM, renal dysfunction, hepatic diseases or those who declined to contribute to the study were excluded. An informed consent was taken from every included patient with the right to withdraw from the study without giving any reason. By this, 74 cases were allocated into either one of the two equal groups using the closed envelope method. Group A: 37 patients underwent Cervico-isthmic compression sutures and Group B: 37 patients underwent anterior wall uterine resection. All patients were subjected to complete history taking, complete general, obstetric but no local examination. Gestational age was calculated depending on the due date of the first day of the last normal menstrual period and transabdominal sonography. Basic laboratory investigations, including CBC, bleeding profile, INR, liver function tests, and kidney function tests were taken from all contributors.

Transabdominal ultrasound using the LOGIQ F6 (GE Healthcare) machine was used for the diagnosis of placenta accreta by the same senior sonographer during the 2nd or 3rd trimester. Absence of normal hypoechoic retroplacental zone, multiple vascular lacunae giving irregular vascular spaces within the placenta, placental tissue bridging, uterine-placental margin, myometrial-bladder interface and retroplacental myometrial

thickness of less than 1 mm [30]. Color Doppler studies were also done for all cases for confirmation of diagnosis and precision of the degree of invasion where lacunar flow patterns and sonolucent vascular lakes with turbulent flow were searched [31]. Transabdominal sonography was also used for fetal data collection primarily fetal number, viability, assessment of amniotic fluid, gestational age, estimation of fetal weight, and presentation.

Preoperatively all patients shaved their pubic hair, took a shower with an antiseptic soap, antibiotic prophylaxis, and a urinary catheter was inserted. All operations were done by the same surgical team and senior obstetrician under spinal anesthesia. After skin sterilization, Pfannenstiel incision was done followed by cutting the subcutaneous fat and rectus sheath and blunt entry into the peritoneum until reaching the uterus. Uterine artery was ligated bilaterally at multiple levels in all involved cases to minimize intraoperative and probably postoperative blood loss followed by a lower segment uterine incision and retroplacental approach for fetal extraction.

In group A, and after delivery of the fetus and placental removal, cervico-isthmic compression sutures was done. First, the bladder was reflected downward to avoid ureteric and bladder injury. A silastic drain was introduced into the internal and across the external os, to drain the uterine cavity and to keep the cervical canal open. Then the surgeon introduced his hand across the uterine incision into the lower uterine segment (LUS) till it touched the cervix. A long Allis forceps passed across the uterine incision and was utilized to grasp the anterior cervical lip pulling the cervix upwards into the uterine cavity. Then the anterior cervical lip was sutured to the posterior surface of the anterior wall of the LUS using continuous locked absorbable stitches (Vicryl no. 2). This aided in compressing the bleeding areas of the placental bed and supported the very thin LUS detected in those patients. The uterus was repaired completely with continuous unlocked suture in two layers using Vicryl 1 suture. The peritoneum was left unsutured while the muscle layer was opposed with Vicryl 0. The rectus sheath was sutured by Vicreyl 1, and the skin was closed with subcutical suture by Proline double zero.

In group B, the same steps were followed till placental delivery then both corners of the uterine incision and the superior and inferior lips were clamped by using four Mayo clamps with blunt dissection of the bladder downwards and uterus peritoneal reflection was performed. The partial anterior wall of the myometrium in which the placenta was deeply adherent was resected together with the invading placenta remnants. It was essential to confirm that enough myometrium above the peritoneal reflection was available for an optimal closure. After that, the remaining placenta tissues were removed as much as possible in piecemeal manner from the uterine incision edge. Clamps and multiple hemostatic sutures were applied quickly on hemorrhagic points on removing the remaining placenta according to the need and the obstetrician's insight. Then, the superior and inferior lips of the uterine incision were sutured to reconstruct a residual uterus and close the abdomen as before. In some cases when bleeding continued, other maneuvers to control bleeding and save patients, including IIAL and compression sutures up to hysterectomy were tried conferring to the consultants' and surgical team opinion.

Measurement of blood loss started following skin incision in every patient. Two trained nurses, one for each group, were responsible for blood and amniotic fluid collection in 2 different suction sets and weighing the surgical towels or gauzes before and after the surgery and depended on the corresponding conversion based on the ratio of 1.05g in weight to one ml in volume. In addition, PPH during the initial 24 hours postoperative was evaluated by

weighing soaked napkins. Presurgical and postoperative data including hemoglobin and hematocrit values 120 minutes before and 24 hours following the operation, the need for whole blood transfusion or packed RBCs, the amount of intra and postoperative blood loss, associated injury to local pelvic organs, ICU admission, hospital stay time, maternal mortality together with neonatal outcome such as; Apgar score, admission to neonatal ICU (NICU), and neonatal mortality were evaluated in the two groups.

Statistical analysis and data interpretation

The sample size was calculated using G*Power version 3.1.9.4 for Windows. Based on intensive literature review, the standard deviation of the mean operative time in the cases underwent uterine wall local resection and reconstruction in the study conducted by Zhao et al. (2018) was found to be 24.5 minutes. At 95% level of significance and power of 80%, the sample size calculated was 37 cases in each group to determine the difference of 1.5 points. Data were gathered, tabulated and analysed by IBM computer using the SPSS (SPSS version 22.0. Armonk, NY: IBM Corp.). Chi- square test was utilized to compare the association between categorical variables between groups and Fisher exact test was used where necessary. Student t-test was utilized to compare means of quantitative variables in parametric data. The differences between two groups were measured by utilizing paired t-test and P value <0.05 was set significant.

Results

A total of 91 patients with morbidly adherent placenta were enrolled in the study, of them 17 were excluded due to failure for fulfilling the inclusion criteria [11] or refutilized to participate [6] (figure 1). The remaining were equally divided into two groups; GA [cervico-isthmic compression suture] and GB "lower uterine wall compression suture". Baseline characteristics are shown in Table (1); there were no significance differences between both groups in maternal age, gravidity, parity, fetal gestational age, body mass index, number of previous vaginal or caesarean deliveries, number of previous abortions, ectopic pregnancies, preterm labor or history of gynecological operations and preoperative hemoglobin levels, $p>0.05$. despite the number is equal in both groups but there is a significant difference as regard the grade of accretion as grade I is found in 9 cases of GA vs 2 in GB, whilst grade II was diagnosed in 28 cases in GA vs 35 cases in GB, $p<0.05$, table (1).

Despite the mean estimated operative time showed no difference between both groups (108.00 ± 16.90 vs 109.43 ± 16.5 , $p > 0.05$) but the mean estimated intraoperative blood loss and the need for packed RBCs transfusion appeared statistically significant between both groups being lower in GA compared to GB (1612 ± 800.85 vs 2633 ± 1153.92 and 2 ± 3.2 vs 4 ± 2.8 respectively, p value 0.001) table (2). Also, in table (2), there was no manifested differences in both groups as regard the intraoperative need for IIAL [16 vs 22 cases], occurrence of postpartum hemorrhage (one case in every group, occurrence of endometritis [no cases in GA vs 1 case in GB). No cases of both groups were subjected to hysterectomy or ICU admission, table (2). On the other hand, a statistical significance regard bladder injury (8.1% in GA vs 16.2 % in GB, p value 0.02) and mean hospital stay time in days (4 ± 2.2 vs 6 ± 5.3 respectively, p value 0.021), table (2). Neonatal outcome showed no statistical differences in both groups as regard APGAR score at 1 and 5 minutes or need for neonatal intensive care unit admission ($p>0.05$), table (2).

Discussion

The primary findings of the study confirmed that cervico-isthmic compression suture appeared better in the mean of intraoperative blood loss, bladder injury and postoperative

hospital stay time when compared to lower anterior uterine wall resection in patients with PAS as fertility sparing surgery.

It has been reported that reduction of blood loss at CD in high risk group, as those having placenta accrete, significantly reduced postoperative maternal morbidity and risks associated with blood transfusions [8, 31]. Conservative management of PAS could be applied to preserve fertility in young women or those with low parity, but the obstetricians should always remember that maternal and neonatal comorbidities and suspected increased mortalities might not appear except during or after treatment. Therefore, many methods were tried including cervico-isthmic compression suture, triple p procedure, uterine artery embolization, local excision of the placental site with involved myometrium and uterine compression sutures (32, 33). None of these studies used comparative maneuvers, so the authors of the current study tried to compare the safety outcome and efficacy of cervico-isthmic compression suture to the anterior wall uterine resection in preserving fertility and minimizing blood loss in such cases.

The technique of cervical inversion and compression was successful in stopping hemorrhage, with a success rate of 90%, and less operative and postoperative blood loss as proved in a study done earlier by Madny et al. 2019 [35]. Despite this comes in accordance with the findings of this study but the previous research [35] demonstrated two cases of interactable bleeding saved by emergent hysterectomy, the measure which is not resorted to for saving any of our cases in both groups.

Some authors demonstrated that patients with PAS treated by local uterine wall resection might be in need of adjoining maneuver as prophylactic abdominal aorta balloon occlusion, uterine or internal iliac tourniquet followed by reconstruction to preserve the uterus [36]. This also supports the current results and proves the superiority of cervico-isthmic compression suture over lower uterine resection as 16 cases only were in need of accompanied IIAL in the first group compared to 22 cases in the later one. In this respect, some stated that the therapeutic effect of IIAL is negligible compared to uterine artery ligation approaches for bleeding management in PAS [37], the point which is not proved by the current study.

In the existing work, no significant difference was reported as regard the mean operative time between both groups of the study but on the other side some international studies confirmed less operative time [36, 38] and others established more time was needed [39] for a comparable maneuver.

As an intraoperative complication, urinary bladder injury occurred less in GA compared to GB and this comes in agreement with findings published before by some authors used lower uterine resection in management of PAS [35, 36].

The intense need for packed RBCs intraoperative infusion in our study appeared less in GA compared to GB and this comes in accordance to results ascertained by Cırpan et al. 2019 [38]. No cases in the current study groups, as mentioned before, had been underwent hysterectomy and this was the same findings reported by recent researches who used uterine preservative surgeries for managing PAS [40]. Postoperatively, the mean hospital stay time in days was shorter in cervico-isthmic compression group compared to lower uterine resection group and this comes supporting results published before [36, 38] and specified longer time when using lower uterine wall resection as fertility preserving surgery in cases of PAS.

In the current study, there was no significant difference in the neonatal outcomes in both groups regarding the maneuver used and this agrees with scientific fact proved recently by Li Q et al., 2023 [41] which state that the pathophysiology of PAS didn't participate in adverse neonatal outcomes and the increase

in incidence of neonatal respiratory or other adverse events will be related to lower gestational age at labor. The mean age in both groups more or less similar and all fetuses were close to maturity [36.19 ± 3.61 vs 35.84 ± 4.11 and P >0.05].

The authors can specify that the primary limitations of this study are lack of double-blind technique and being a single center study instead of multicenter one that will be more informative and the limited number compared to the long study time also.

Conclusion

Cervico-isthmic compression suture and anterior wall uterine resection are apparently safe conservative managements for PAS. However, anterior wall uterine resection is accompanied by more intraoperative blood loss, more hospital stays and more liability for bladder injuries.

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Figure 1. Study flow diagram

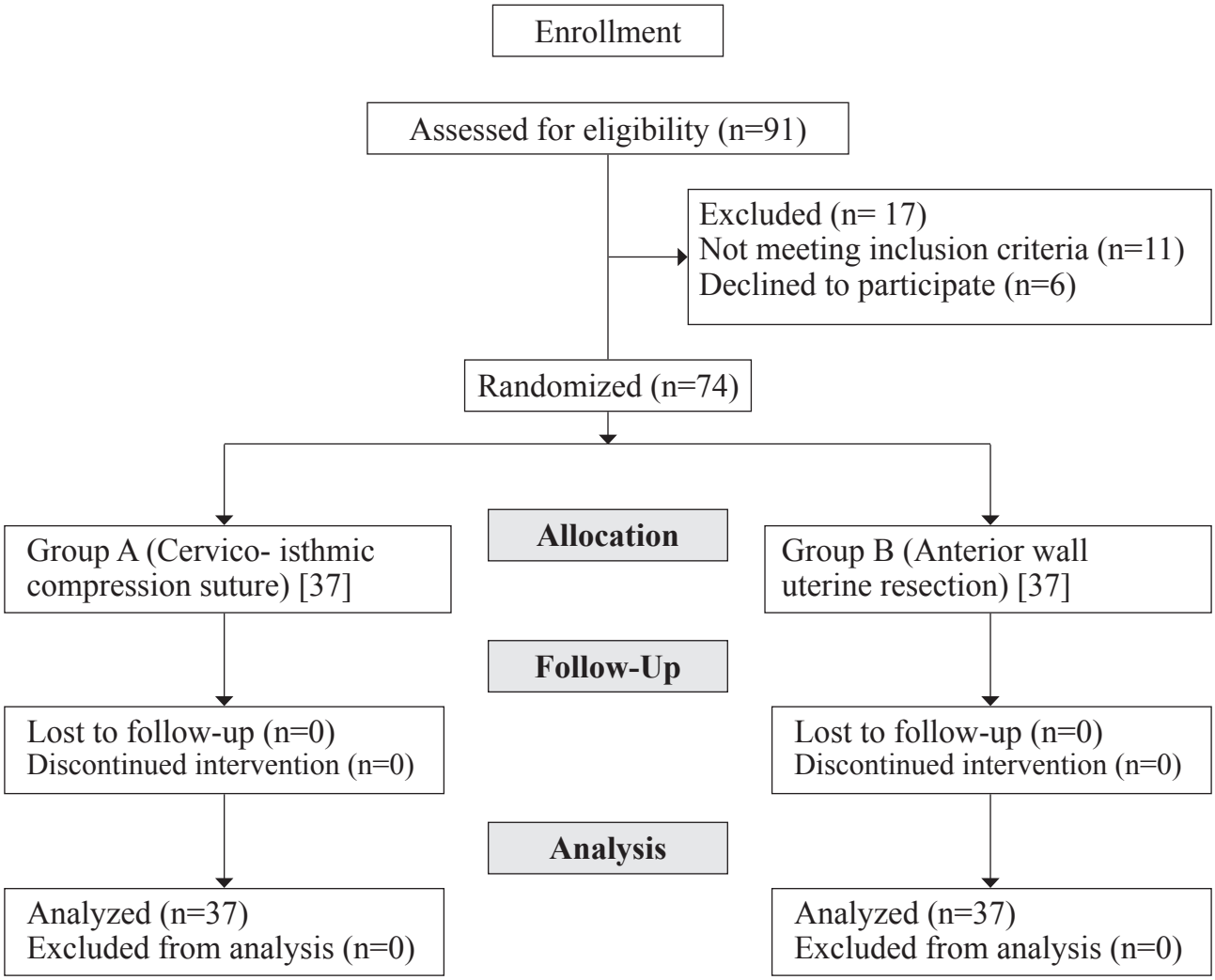

Table (1): Sociodemographic, clinical, and baseline characteristics of the two study groups.

Variable	Group A (n= 37)	Group B (n= 37)	P values
Age (Years) ± SD	31.19 ± 5.24	31.22 ± 4.72	0.981
BMI (Kg/m^2) ± SD	32.91 ± 3.76	32.05 ± 4.62	0.387
Gestational age (Weeks) ± SD	36.19 ± 3.61	35.84 ± 4.11	0.679
Gravidity ± SD	4 ± 2.7	5 ± 2.1	0.130
Parity ± SD	3 ± 1.6	3 ± 1.7	0.803
Previous CD	3 ± 1.2	2 ± 1.4	0.951
Number of previous Abortion	0 (0-3)	0 (0-10)	0.096
Number of previous preterm	0 (0-2)	0 (0-1)	0.184
Previous ectopic pregnancy	0 (0%)	1 (2.7%)	0.314
Preoperative hemoglobin (gm/dl)	10.89 ± 0.88	10.90 ± 0.73	0.943
History of gynecological procedures NO Dilatation and curettage MVA Dilatation and curettage plus MVA	32 (86.5%) 3 (8.1%) 3 (5.4%) 0 (0%)	27 (73%) 5 (13.5%) 3 (8.1%) 2 (5.4%)	0.373
Grading of placenta accreta Grade I Grade II	 9 (24.3%) 28 (75.7%)	 2 (5.4%) 35 (94.6%)	 P= 0.022*

The data is presented as number (%), mean ± (SD), and the p-value is set statistically significant if below 0.05.

Abbreviations: BMI; body mass index, VD; vaginal delivery, CD, cesarean delivery, MVA; manual vacuum aspiration.

Table (2): Operative data and postoperative complications in the two study groups.

Variable	Group A (n= 37)	Group B (n= 37)	P value
Operative time (minutes)	108.00 ± 16.90	109.43 ± 16.5	0.714
Estimated intraoperative blood loss (ml)	1612 ± 800.85	2633 ± 1153.92	0.001
Units of transferred packed RBC units	2 ± 3.2	4 ± 2.8	0.001
Postoperative hemoglobin (gm/dl)	10.94 ± 1.07	10.35 ± 1.03	0.019
Internal iliac artery ligation	16 (43.2%)	22 (59.5%)	0.163
Hysterectomy	0 (0%)	0 (0%)	
APGAR Score	8.92 ± 0.68	8.95 ± 0.78	0.874
Intraoperative and postoperative complications Bladder injury Hospital Stay (Days) Maternal ICU admission Hemorrhage Endometritis NICU admission	 3 (8.1%) 4 ± 2.2 0 (0%) 1 (2.7%) 0 (0%) 0 (0%)	 6 (16.2%) 6 ± 5.3 0 (0%) 1 (2.7%) 1 (2.7%) 0 (0%)	 0.02 0.021 ----

The data is presented as number (%), mean ± (SD), and the p-value is set statistically significant if below 0.05.

Abbreviations: RBC; red blood corpuscles, APGAR, appearance; pulse; grimace; activity; respiration, ICU; intensive care unit, NICU; neonatal intensive care unit.

Prediction of vaginal delivery using Bishop's score, modified Bishop's score, and Levine's score

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Abstract

Background: Induction of labor is a common procedure in obstetrics. Women are anxious about their chances for successful vaginal delivery. Different scoring systems are available for the prediction of vaginal delivery.

Objective: To determine the role of Bishop's score, modified Bishop's score, and Levine's score in the prediction of vaginal delivery.

Study design: This prospective cohort study was conducted at the emergency department of obstetrics and gynecology from June 2022 to February 2023. All healthy, multiparous women with full-term pregnancies were recruited according to predetermined inclusion and exclusion criteria. The cervical length, and cervical assessment to determine the Bishop score were done. The modified bishop score was calculated. Levine's score was calculated using a web-based calculator. Patients were evaluated for a) Duration of the first stage of labor, b) Duration of the second stage of labor, c) total duration of labor, and e) The mode of delivery at the end.

Results: The Levine score correlated significantly with the duration of the first stage of labor, total duration of labor, the dose of Misoprostol, and the mode of delivery (p-value 0.007, 0.008, 0.011, and 0.043, respectively). The dose of misoprostol (50 μg) and fetal head station predicted vaginal delivery significantly (OR 0.055, 95% CI 0.007- 0.408, p-value 0.005) (OD 0.143, 95% CI 0.035- 0.588, p-value 0.007).

Conclusion: The Levine score correlated significantly with the mode of delivery. However, no score predicted vaginal delivery significantly.

Keywords: vaginal delivery; bishop score; modified bishop score; Levine score.

Introduction

Labor induction is a commonly practiced obstetrical procedure with rates reaching 33% (1). The state of the cervix as favorable or unfavorable dramatically influences the success rate of induction (2). It is crucial to present accurate data about the success rate of induction

to laboring women, especially when using cervical ripening agents (3). The first described predictive score was the Bishop's score, 1964. It comprises five parameters retrieved from vaginal examination: cervical dilatation, effacement, position, consistency, and fetal head station. However, it showed a limited predictive value and was applied to multiparous women needing oxytocin-augmentation (4, 5). Multiple modifications were introduced regarding the original bishop score. In 1982, Lang et al used a score including cervical dilatation and effacement and fetal head station. They doubled the score concerning cervical dilatation, and reported better correlation with obstetric outcomes than the original score (6, 7). Then, transvaginal ultrasound was used to determine the cervical length, which replaced cervical effacement in the Bishop score and was called the modified Bishop's score (5). Levine's score was established for women undergoing induction of labor using cervical ripening agents. It included variables that are essential in decreasing the rate of successful induction which are maternal height, parity, and BMI at delivery, gestational age $\geq$ 40, and the modified bishop score (8). External validation of the Levine's score proved its effectiveness in predicting failed induction of labor (3). No studies compared the predictive value of each scoring system for predicting labor among multiparous women. Accordingly, this study was conducted.

Methods

This was a prospective cohort study conducted at the emergency department of obstetrics and gynecology, Suez Canal University, from June 2022 to February 2023. The medical ethical committee approved the study before commencement, and informed consents were obtained from all enrolled patients.

All healthy, multiparous women with full-term pregnancies presenting to the emergency ward were recruited according to predetermined inclusion and exclusion criteria. Inclusion criteria: a) Adult (>18 years) multiparous women, b) gestational age between 40 - 42 weeks, c) Uncomplicated singleton pregnancy with vertex presentation, and d) without ruptured membranes. Exclusion criteria: a) Women with chronic diseases or complicated pregnancy; gestational and pre-gestational (type 1 & 2) diabetes, preeclampsia and\or renal and\or maternal heart diseases, fetal growth restriction, and fetal anomalies, b) obstetric indication for cesarean delivery, c) women refusing to participate in the study, d) women presenting in the active phase of labor, e) history of cervical insufficiency, f) history of previous cervical surgery (cone biopsy, LLETZ), g) previous preterm births, and h) women with intrauterine fetal death.

Eligible women for the study were subjected to the following:

- **History was taken** to obtain their sociodemographic characteristics (age, education, occupation, gravidity, parity, residency, parity, and previous surgeries). Moreover, the gestational age was confirmed based on the last menstrual period and an early ultrasound evaluation.
- **Clinical examination:** Height and weight were measured. BMI was calculated and classified according to WHO classification (9).
- **Ultrasound evaluation:** Transvaginal ultrasound was performed using a Mindray DC- 60 machine with a transvaginal probe V 11-3B. A sagittal view of the cervix with no compression was obtained. The cervical length was measured from the internal to the external os with the cervical canal wholly visualized. Measurements were obtained after enrollment and before the start of induction protocol, with the bladder empty. A senior radiologist did the cervical length measurement for all cases. Three measurements were obtained for the cervical length, and the shortest one was considered in the analysis.

- **Cervical assessment:** to determine the Bishop score. A Bishop score of 8 or greater was considered to be favorable for induction. A score of 6 or less was considered unfavorable for induction with indicated cervical ripening agents (10).
- **Modified bishop score:** was calculated by replacing cervical effacement with cervical length (5).
- **Levine's score:** was calculated using a web-based calculator (8).
- **Induction of labor:** We used Misoprostol (Vagiprost, Adwia, El Oubor, Egypt) with a dose of 25 μg per vaginal every 6 hours (11). Failed induction was managed after patient counseling with a further attempt to induce labor or C.S. delivery (12).

For multiparous women, cervical dilatation of less than 2 cm/4hrs was considered a failure to progress. Delayed progress in the second stage of labor was suspected when no change in fetal head descent or rotation was observed for 1 hour. Every condition was managed according to the NICE clinical guideline (13). The following was reported:

a) The duration of the first stage of labor, including both the latent and active phases. The latent phase was identified with the initiation of painful uterine contractions accompanied by either change in cervical effacement or dilatation up to 4 cm. The duration was reported since admission. The active phase was identified by the occurrence of regular painful uterine contractions accompanied with dilatation of the cervix from 4 cm (13),

b) Duration of the second stage of labor,

c) Total duration of labor, and

e) The mode of delivery eventually.

The primary outcome measure was the predictive role of the three scoring systems in predicting successful induction of labor among multiparous women. Secondary objectives included correlation between the three scoring systems and successful vaginal delivery and factors affecting the duration of labor.

The sample size was calculated at a significance level of 95% and an error level of 10% using a proportion of vaginal delivery among women undergoing induction of labor using bishop score (68.29%), a sensitivity of 60.7% (14), and a drop out of 10%. The minimum number required was 148 pregnant women.

Ethical approval: This study was conducted after the approval of the research ethics committee on 21/6/2022 with a number of 4925#.

Statistical analysis: Data were reported as mean and standard deviation, frequencies, and percentages. P values less than 0.05 were considered statistically significant. All statistical operations were done using the SPSS program (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 23. Pearson correlation coefficient was calculated between parametric quantitative variables, and Spearman was calculated for others. Significance was considered when the p-value was < less than 0.05. Cox regression was done for survival analysis. Analysis was constructed with a vaginal delivery as the outcome measure.

Results

Two hundred and forty-nine women were eligible for the study. Twelve women declined to participate in the study, leaving a total number of 237 women recruited. The mean age of the studied population was 30.219 ± 2.04, with a mean parity of 1.78 ± 0.59. the great majority were from rural areas (126, 53.2%) and middle education (93, 39.2%). The gestational age at admission was 41.01 ± 0.78 (Table 1).

The mean Bishop, modified Bishop, and Levine scores were 4.70 ± 0.88, 5.63 ± 0.99,

and 0.14 ± 0.04, respectively. The probability of C.S. was 14.46 ± 4.05 (Table 2).

Two hundred twenty- nine women delivered vaginally (96.6%). The dose of Misoprostol was 59.6 ± 20.46. the total duration of labor was 474.68 ± 170.6 (min) (Table 3).

The bishop score correlated significantly with the duration of the first stage of labor and the total duration of labor (p-value 0.015 each). The modified bishop score correlated significantly with the dose of Misoprostol (p-value 0.01). The Levine score correlated significantly with the duration of the first stage of labor, total duration of labor, the dose of Misoprostol, and the mode of delivery (p-value 0.007, 0.008, 0.011, and 0.043 respectively) (Table 4).

The modified bishop score and Levine score differed significantly between women who delivered vaginally and those delivered by C.S. (p-value 0.028 and 0.043, respectively) (Table 5).

Multivariate logistic regression, the dose of misoprostol (50 µg) and fetal head station predicted vaginal delivery significantly (OR 0.055, 95% CI 0.007- 0.408, p value 0.005) (OD 0.143, 95% CI 0.035- 0.588, p value 0.007).

Using survival analysis, the dose of Misoprostol (50 µg) contributed significantly to the duration of labor (Figure 1).

Discussion:

The state of the cervix before induction plays a significant role in the possibility of having a successful vaginal delivery (7). The bishop score correlated significantly with the duration of the first stage of labor and the total duration of labor. The modified bishop score correlated significantly with the dose of Misoprostol. The Levine score correlated significantly with the duration of the first stage of labor, total duration of labor, the dose of Misoprostol, and the mode of delivery. In a previous study, the modified bishop score correlated with vaginal delivery (7). This would be rendered to their recruitment of women undergoing a trial of labor after C.S. with a gestational age of 24 weeks to term.

The modified bishop score and Levine score differed significantly between women who delivered vaginally and those delivered by C.S. In an earlier study, the bishop score differed significantly between those with successful and unsuccessful induction of labor. This would be rendered to their recruitment of nulliparous and multiparous women ≥ 37 weeks. Also, the bishop score is a subjective and nominal scale limiting its role (14). Additionally, the method of induction differed between studies (15).

The dose of Misoprostol (50 µg) predicted vaginal delivery and significantly contributed to labor duration. There was no difference in vaginal and cesarean delivery rates (16, 17). This difference would be explained by different primary objectives, target population (different ethnic groups, obese, chronic illness), and induction methods between studies (use of Foley catheter). In an earlier study, vaginal Misoprostol was associated with shorter induction to delivery time. This was rendered to the steady increase of its plasma concentration (70- 80 min) and slow plasma clearance (up to 6 hours) (18). However, another study reported a shorter induction to delivery time; they used a 200µg slow-release Misoprostol vaginal insert (19). Direct comparison is hindered because of heterogeneous preparations, dosages, and methods of administration (20). Accordingly, a previous systematic review reported that successful vaginal delivery was achieved using Misoprostol with doses up to 50 µg in the first six hours of induction (21).

The bishop score, modified bishop score, and Levine score had no predictive role for successful vaginal delivery. Another study reported that cervical dilatation, cervical length, cervical position, and the overall modified bishop score had no predictive role for successful vaginal delivery. However,

this study included nulliparous women with gestational ages ≥ 37weeks (22). Previous studies reported cervical consistency as a significant predictor for vaginal delivery (3, 23). It has been reported that no existing score but for Levine score exclusively predicted successful induction of labor (3). However, another one reported that Levine's score could not predict C.S. rates precisely. This might be related to different demographic criteria of the studied population (24).

A bishop score ≥ 9 was associated with a 96% vaginal delivery rate in a previous review. They reported that a score of 4, 5, or 6 has no predictive role for C.S. (5), limiting its predictive capacity. This would explain the current results regarding the predictive role of the bishop score. In the multivariate model, the modified bishop score significantly predicted cesarean delivery. Additionally, components of the individual score items had no predictive role, especially the cervical dilatation (8), while we reported a significant role for the fetal head station. An earlier study reported a significant role for the head-perineum distance measured by ultrasound in predicting vaginal delivery (25). Contradicting results would be explained by the recruitment of women regardless of their parity and starting with unfavorable cervices (cervical dilatation and bishop score were ≤ 2 and 6, respectively).

Strength and limitations: We recruited a large number of participants. The study was conducted as a prospective cohort study. However; we had some limitations. We recruited multiparous women only, which would limit the generalizability of the results. Also, women were recruited with an unfavorable cervical examination, which is a limitation. We evaluated the predictive role of the three scoring systems for vaginal delivery only. Prediction of CS was not done. We used three scoring systems only. Further studies evaluating the role of other scoring systems are recommended.

Conclusion

The Levine score correlated significantly with the mode of delivery. However, no score predicted vaginal delivery significantly. The dose of Misoprostol and the fetal head station had significant predictive roles.

Conflict of interest: None

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Table 1: Sociodemographic characters of the studied population:

Age (mean ± SD)		30.219 ± 2.04
Parity (mean ± SD)		1.78 ± 0.59
Residence N (%)	Rural	126 (53.2%)
	Urban	111 (46.8%
Education N (%)	None	90 (38%)
	Middle	93 (39.2%)
	High	54 (22.8%)
Gestational age (mean ± SD)		41.01 ± 0.78
BMI (mean ± SD)		29.09 ± 2.23

Table 2: Obstetric data of the studied population

Cervical dilatation (cm) (mean ± SD)		2.08 ± 1.23
Effacement (%) (mean ± SD)		35.15 ± 5.41
Consistency	Soft	71 (30%)
	Firm	102 (43%)
	Hard	64 (27%)
Position	Anterior	18 (7.6%)
	Midway	131 (55.3%)
	Posterior	88 (37.1%)
Station		-1.35 ± 0.7
Cervical length (mm) (mean ± SD)		39.3 ± 7.3
Bishop score (mean ± SD)		4.70 ± 0.88
Modified bishop score (mean ± SD)		5.63 ± 0.99
Levine score (mean ± SD)		0.14 ± 0.04

Table 3: Obstetric outcomes after induction of labor

Mode of delivery N (%)	Vaginal	229 (96.6%)
	C.S.	8 (3.4%)
Dose of Misoprostol (μg) (mean ± SD)		59.6 ± 20.46
Duration of first stage (min) (mean ± SD)		455.49 ± 164.71
Duration of second stage (min) (mean ± SD)		20.96 ± 5.42
Total duration of labor (min) (mean ± SD)		474.68 ± 170.6
Fetal birth weight (gm) (mean ± SD)		3238.33 ± 272.34

Table 4: Correlation between different scores and patient characters

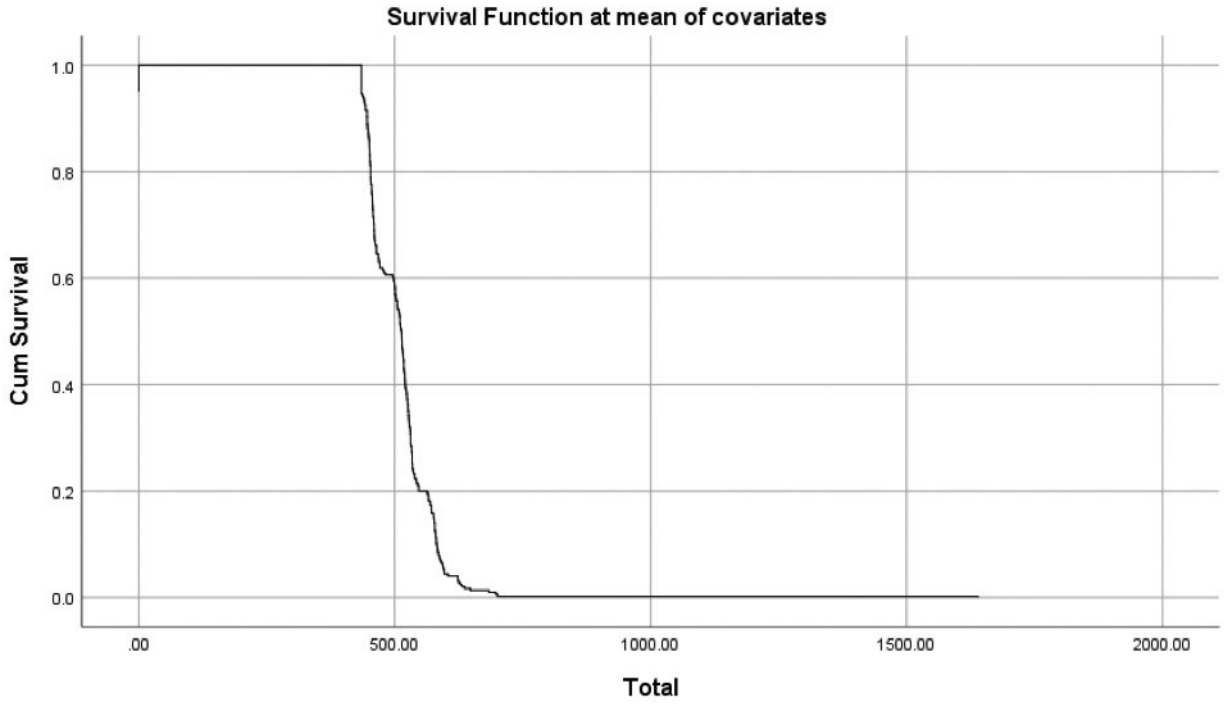
Variable	Bishop score		Modified bishop score		Levine score	
	Cor. coeff	P-value	Cor. coeff	P-value	Cor. coeff	P-value
Age	-0.044	0.501	0.075	0.251	-0.036	0.584
GA	0.048	0.459	-0.048	0.461	-0.023	0.726
Parity	-0.046	0.483	0.007	0.915	0.074	0.255
Dose of Misoprostol	-0.124	0.056	-0.167	0.010	0.165	0.011
Mode of delivery	-0.097	0.138	-0.127	0.05	0.132	0.043
Duration of first stage	0.159	0.015	0.076	0.243	-0.176	0.007
Duration of second stage	-0.017	0.805	-0.072	0.292	0.052	0.447
Total duration	0.157	0.015	0.068	0.300	0.172	0.008

Correlation is significant at the 0.05 level

Table 5: Bishop score, modified Bishop score, Levine score, and the mode of delivery:

	Bishop score	Modified Bishop	Levin score
Normal vaginal	4.72 ± 0.86	5.66 ± 0.98	0.143 ± 0.034
CS	4.25 ± 1.28	2.88 ± 1.13	0.173 ± 0.05
P value	0.138	0.028	0.043

Figure 1: The Cox regression model for women who had vaginal delivery.



Total = Total duration of labor

The effect of maternal fundal height and abdominal circumference on maternal blood pressure during cesarean delivery

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Abstract

Background: cesarean delivery is the most common surgical procedure practiced in obstetrics. It is associated with hypotension that has maternal and fetal effects.

Objective: This study aimed to determine the correlation between maternal and fetal measures (abdominal circumference, symphyseal fundal height, estimated fetal weight, and amniotic fluid volume) and intraoperative hypotension during cesarean delivery.

Study design: This cross-sectional study was conducted at the Suez Canal University hospital operating theatre from May 2021 to January 2023. We recruited women undergoing elective or emergency cesarean delivery. Maternal and fetal measures were recorded, including abdominal circumference, symphyseal fundal height, fetal weight and amniotic fluid index. Baseline maternal blood pressure and heart rate were determined and repeated measures were done at 1, 5, 10, and 15 minutes of the spinal anesthesia. The dose of ephedrine and the occurrence of nausea/vomiting were recorded.

Results: There was a marked decrease in the systolic, diastolic, and mean arterial BP at 5 minutes (P value < 0.001). Hypotension occurred in 69.4% participants. The abdominal circumference was significantly larger among women who developed hypotension (116.7± 12.5 vs 111.4 ± 10.5, P value 0.007). There was a positive correlation between the abdominal girth and the Ephedrine dose required at 5 minutes only (r= 0.246, P value 0.001).

Conclusion: Maternal abdominal circumference was significantly larger with hypotensive patients and correlated with the ephedrine dose at 5 minutes only.

Keywords: Abdominal circumference; Amniotic fluid index; Cesarean delivery; Fetal weight; Hypotension; Symphyseal fundal height.

Introduction:

Cesarean section (CS) is a commonly practiced obstetrical surgery under spinal anesthesia (1). Spinal

anesthesia is a safe procedure preferred over general anesthesia, which is associated with failed intubation, risk of desaturation and aspiration, and neonatal depression (2). However, spinal anesthesia is associated with nausea, vomiting, and hypotension, even in well-hydrated pregnant women (1). Other complications include total spinal block, post-dural puncture headache, and failed technique (2). Hypotension occurs in 15-33% of cases (3), but increased rates are reported among pregnant women (20- 100%) (4). This would lead to severe consequences such as neonatal hypoxia and acidosis (4). It was explained by the aortocaval compression and cranial spread of the anesthesia exerted by the gravid uterus (5). The latter was noted predominantly in twin pregnancies rather than singleton (6). A large uterus was associated with increased congestion of the epidural veins with a resultant decrease in cerebrospinal fluid (CSF) volume. This plays a crucial role in sensory block level (7), affecting maternal blood pressure (8). The fetal weight and amniotic fluid volume influence the uterine size, which increases the abdominal circumference and symphysial fundal height (9). Other factors contributing to spinal-induced hypotension are maternal age (≥ 35), body mass index (BMI) of more than 25kg/m2, level of spinal injection, the anesthetic dose, and fetal weight (1). Accordingly, we hypothesized that enlarged uterus may cause hypotension during cesarean delivery. This study aimed to evaluate the association between maternal abdominal girth and symphysial fundal height (influenced by fetal weight and amniotic fluid volume) and blood pressure among women undergoing cesarean section.

Methods

This cross-sectional study was conducted at the Suez Canal university hospital operating theatre from May 2021 to January 2023. The study included pregnant women undergoing CS who fulfilled the following inclusion and exclusion criteria: **Inclusion criteria:** a) women aged 18-45 years, b) singleton pregnancy, c) gestational age from 37-41 weeks, d) elective or emergency CS, and e) either booked or unbooked women for antenatal care. **Exclusion criteria:** a) prelabor rupture of membranes, b) gestational hypertensive disorder in the current pregnancy, c) chronic hypertension, d) history of cardiac or renal disease, e) fetal death, f) excessive intraoperative bleeding, g) need for additional oxytocin doses, h) failed spinal block and need for general anesthesia, and i) antepartum hemorrhage.

Eligible patients signed informed written consent before recruitment. They had preoperative evaluation including personal data (age, weight, height, BMI, occupation, level of education), obstetric history (parity, mode of delivery), and any chronic illness. The indication for cesarean delivery was reported. Routine preoperative laboratory investigations were withdrawn (complete blood count, coagulation profile, and group and save).

Abdominal ultrasound was done for all participants to determine fetal biometry, estimated fetal weight (EFW), and amniotic fluid index (AFI). The scan was performed at 38 weeks gestation for booked patients while unbooked patients had their scans on the day of delivery. All participants undergoing elective CS have kept nothing per oral for 8 hours before delivery. The fundal height was measured from the symphysis pubis's upper border to the uterus's upper border while the patient was lying supine in bed. The abdominal circumference (AC) was measured at the lower border of the umbilicus. These measurements were reported in the labor and delivery ward before shifting the patient to the operating theatre. The same obstetrician and anesthesia team that obtained these measurements was blinded to the results.

In the operating theatre, patient monitoring included pulse oximetry, non-invasive blood pressure, and electrocardiogram.

An 18-gauge cannula was inserted, and a preoperative infusion of ringer lactate 10ml/kg was started 15 minutes before spinal anesthesia. Primary heart rate, systolic, and diastolic blood pressure (BP), and mean arterial pressure (MAP) were recorded.

The patients were asked to sit, and sterilization of the back was done. Dural puncture was done using a 25-gauge spinal needle by a paramedian approach at the level of L4-5. Hyperbaric bupivacaine (2 ml) and 20 µg fentanyl were injected after ensuring cerebrospinal fluid flow. The patient was turned supine with a slight left lateral tilt (15◦) immediately after completing spinal anesthesia.

The sensory level was evaluated in the midline at 1, 5, 10, and 15 minutes after completing spinal anesthesia. Regular intravenous fluids were administered at a rate of 100 ml/10 minutes. The patients were monitored for heart rate, systolic and diastolic blood pressure, and mean arterial pressure at the same intervals mentioned above. Oxytocin (5 units) was administered following fetal delivery.

The occurrence of hypotension, nausea, and vomiting was recorded. Hypotension was defined as > 20% decrease in systolic BP from the primary record and was managed by injection of ephedrine 6 mg IV (10). This would be repeated with persistent hypotension after 2 minutes. The total dose of ephedrine was recorded.

The primary outcome measure was the association between abdominal girth, symphyseal fundal height, and maternal hypotension after spinal anesthesia. Secondary outcome measures included the incidence of hypotension, the maximum level of sensory block, the ephedrine dose, and the incidence of nausea and vomiting.

The sample size was calculated at a significance level of 95%and an error level of 20% with a correlation coefficient between abdominal girth and systolic blood pressure of 0.47 (11). A drop-out proportion of 10% was added to the raw result giving a final count of 180 women.

Ethical approval: This study was conducted after approval of the research ethics committee of the faculty of medicine, Suez Canal University, on 26/4/2021, with a reference number of 4538#.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. For continuous data, they were tested for normality by the **Kolmogorov-Smirnov test**. Quantitative data were expressed as a range (minimum and maximum), mean, standard deviation, and median. **Student t-test** was used to compare two groups for normally distributed quantitative variables while **One way ANOVA** test was used for comparing the different studied categories and followed by **Post Hoc test (Tukey)** for pairwise comparison. **Pearson coefficient was used** to correlate between two normally distributed quantitative variables. The significance of the obtained results was judged at the 5% level. P value was considered significant when < 0.05.

Results

One-hundred eighty- five women were eligible for the study. Two women refused to participate in the study, while the other three were excluded because of failed spinal anesthesia and received general anesthesia.

The mean age of the studied population was 28.8 ± 5.5. The mean parity and number of previous CS were 1.8 ± 1.5 and 1.4 ± 1.3, respectively. Almost half of the recruited women had middle education (48.3%), and many were housewives (90%). The mean BMI was 31.7 ± 5.3 (Table 1).

The preoperative measures included SFH,

abdominal circumference, AFI, and EFW, with reported means of 37.6 ± 5.1, 115.1 ± 12.1, 10.2 ± 3.3, and 3328.9 ± 447, respectively. Eighty-five (47.2%) and 95 (52.8%) patients had emergency and elective CS, respectively (Table 2).

There was a marked decrease in the systolic, diastolic, and mean arterial BP at 5 minutes (P value < 0.001). The greatest ephedrine dose was given at 5 minutes also (4.8 ± 6.1) (Table 3).

The median level of sensory block was at T6 (range 4-12) at 1 minute and T4 thereafter.

One hundred twenty-five (69.4%) developed hypotension. The abdominal circumference was significantly larger among women who developed hypotension (116.7± 12.5 vs 111.4 ± 10.5, P value 0.007) (Table 4).

There was a positive correlation between the abdominal girth and the Ephedrine dose required at 5 minutes only (r= 0.246, P value 0.001). There was no significant correlation between abdominal girth and the level of sensory block. The symphyseal fundal height, fetal weight, and AFI showed non-significant correlations with either the ephedrine dose or the level of spinal sensory block (Table 5).

Nausea occurred in 26 (14.4%) patients, while vomiting occurred in 9 (5%). There was a significant difference in the abdominal circumference among women who had vomited than those who did not (112.9 ± 15.1 and 114.7 ± 11.9, respectively, with a p-value of 0.049) (Table 6).

Discussion

There was a marked decrease in the systolic, diastolic, and mean arterial BP, with a greater ephedrine dose at 5 minutes. Hypotension occurred in 69.4% ff the studied population. the abdominal circumference was significantly larger among those who had hypotension. Variable incidences of hypotension at CS were reported as 25% (12) and 52% (13). An earlier study failed to demonstrate a correlation between AC and hypotension after spinal anesthesia (7). This would be explained by different AC measurements between studies (115.1 ± 12.1 vs. 98.4 ± 6.8 cm). Another study reported no correlation between the AC in women with singleton and twin pregnancies and hypotension during CS, despite increased AC in twin gestations (6). Contradicting results were reported where there was no difference in hypotension between maternal AC (7, 14). However, the decline in MAP was prominent in those with large AC (14).

Other factors that affected the maternal hemodynamic state included dehydration, capacity and tone of the peripheral vasculature, blood volume, cardiac output, level of sensory block, the addition of fentanyl to bupivacaine, and the extent of aortocaval compression (15, 16). Additionally, different definitions of hypotension between studies and rapid treatment of hypotension by the anesthesiologist to avoid fetal harm explain these different results (17).

The abdominal circumference correlated significantly with the ephedrine dose given at 5 minutes. However, there was no significant correlation between it and the level of sensory block. A previous study reported a significant correlation between the maternal abdominal circumference and the level of sensory block, especially at 5 minutes while no correlation was reported with the ephedrine dose or the maximum sensory block (7). Another one reported an increased level of spinal block in women with large AC (15). Measuring the AC in the supine position revealed a significant correlation with the level of sensory block at 5, 10, and 15 minutes after spinal anesthesia (13); however, we measured the AC in the standing position.

The AC reflects the intraabdominal pressure exerted by the gravid uterus. Greater AC increased pressure on the inferior vena cava (IVC) and decreased CSF volume in the lumbosacral region (7). Failure to demonstrate a correlation between the

AC and the sensory block level would be rendered to the dose of bupivacaine used. The bupivacaine commonly pools in the lower part of the thoracic curvature. Higher levels of spinal block could be achieved when using increased doses of bupivacaine to reach the upper thoracic region (19). The reported level of sensory block was at T6 at 1 minute and was recorded at T4 for further measurements. Additional factors that might play a role include the dose of the anesthetic, volume, level of its injection, needle type, patients' age and weight, anatomy of the spine, and intra-abdominal pressure (20). However, these factors contribute a little to the level of sensory block. Also, they have unpredictable and out-of-control effects (21). It has been mentioned that the level of sensory block is significantly affected by the baricity of the injected bupivacaine and the patients' position after injection (19). We adopted the same technique for spinal anesthesia and the same dose of bupivacaine to avoid bias.

The symphyseal fundal height as a reflection of the uterine size, fetal weight, and AFI showed non-significant correlations with hypotension, the ephedrine dose, or the level of spinal sensory block. This agreed with previous results where the symphyseal fundal height (SFH) did not correlate with the level of sensory block (22, 23). However, a significant correlation was noted between the SFH and fetal weight and the ephedrine dose (22). Another study reported increased fetal weight associated with hypotension during CS (24). This was explained by increased aortocaval compression and hypotension needing ephedrine with higher SFH (22). The lack of correlation between EFW and intraoperative hypotension was rendered to the fact that the uterine size would be affected by other factors such as uterine anomaly, AFI, or uterine fibroids other than the fetus alone. This makes the effect imparted by the fetus tiny (22).

Nausea/vomiting occurred in 35/180 (19.4%) patients. An earlier study reported a higher rate (20/40, 50%) (7). The abdominal circumference was significantly lower among women who had vomited than those who had not. Nausea and vomiting would be explained by the consequences of hypotension as cerebral ischemia, vagal stimulation, and intraoperative visceral traction (22).

Strength and limitations: The anesthetic team was blinded to the preoperative measures. We used a fixed dose of bupivacaine, which might cause hypotension. The study was carried out as a prospective study. We recruited a relatively large sample.

Conclusion

Maternal AC influenced the level of sensory block at 5 minutes. There was no correlation between the other measurements and the level of sensory block or ephedrine dose.

Conflict of interest: None

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Table (1): Distribution of the studied cases according to demographic data (n = 180)

Age (Mean ± SD)		28.8 ± 5.5
Parity (Mean ± SD)		1.8 ± 1.5
Education	**None**	37 (20.6%)
	Middle	87 (48.3%)
	High	56 (31.1%)
Occupation	**Housewife**	162 (90%)
	Worker	3 (1.7%)
	Employee	15 (8.3%)
Weight (Mean ± SD)		84.3 ± 14.4
Height (Mean ± SD)		162.6 ± 5.6
BMI (Mean ± SD)		31.7 ± 5.3
Number of previous CS (Mean ± SD)		1.4 ± 1.3

BMI: body mass index; CS: cesarean delivery

Table (2): Preoperative evaluation of the studied population: (n = 180)

AC (Mean ± SD)		115.1 ± 12.1
SFH (Mean ± SD)		37.6 ± 5.1
AFI (Mean ± SD)		10.2 ± 3.3
EFW (Mean ± SD)		3328.9 ± 447
Indications for CS	**Emergency**	85 (47.2%)
	Elective	95 (52.8%)

SFH: symphyseal fundal height; AFI: amniotic fluid index; EFW: estimated fetal weight; CS: cesarean section

Table (3): Descriptive analysis of the studied cases according to different parameters (n = 180)

	Preoperative	**1min**	**5min**	**10min**	**15min**	**p**
Systolic Mean ± SD.	124 ± 15.8	112.8 ± 20	101.4 ± 21.5	107.7 ± 16.9	107.5 ± 14.6	<0.001 *F
Diastolic Mean ± SD.	76.6 ± 11.6	65.3 ± 15.1	58 ± 14.6	61.2 ± 11.9	59.2 ± 11.8	<0.001 *F
HR Mean ± SD.	98.6 ± 13.6	104.6 ± 20.8	94.8 ± 20.3	95.8 ± 16.6	96.4 ± 14.7	<0.001 *F
Mean blood pressure Mean ± SD.	92.2 ± 12.1	78.4 ± 14.4	70.8 ± 15.5	75.5 ± 12.3	73.8 ± 10.5	<0.001 *F
Ephidren dose Mean ± SD.	–	3 ± 5.6	4.8 ± 6.1	1.6 ± 3.8	1.5 ± 3.4	

HR: heart rate, MAP: mean arterial blood pressure, SD: **Standard deviation, F: F test (ANOVA) with repeated measures**, Sig. bet. periods was done using **Post Hoc Test (Bonferroni)**

Table (4): Relation between hypotension and maternal and fetal parameters

	Hypotension		P value
	Yes (125)	No (55)	
AC	116.7 ± 12.5	111.4 ± 10.5	0.007*t
SFH	37.5 ± 5.5	37.8 ± 4.1	0.779t
EFW	3333.5 ± 401.1	3318.3 ± 541.1	0.852t
AFI	10.2 ± 3.2	10.4 ± 3.7	0.680t

AC: abdominal circumference, SFH: symphyseal-fundal height, EFW: estimated fetal weight, AFI: amniotic fluid index, t: Student T test.

Table (5): Correlation between AC, SFH, EFW, and AFI with Ephedrine dose and spinal sensory block (n = 180)

	AC		SFH		EFW		AFI	
	r	P	R	P	r	P	r	P
Ephedrine dose								
1 min	0.065	0.383	0.012	0.872	0.005	0.944	-0.021	0.775
5 min	0.246*	0.001*	0.044	0.557	0.115	0.124	0.105	0.162
10 min	0.028	0.709	-0.057	0.450	-0.059	0.432	0.029	0.695
15 min	0.081	0.281	-0.003	0.965	0.047	0.529	-0.003	0.969
Spinal sensory block								
1 min	0.024	0.753	-0.007	0.924	0.049	0.514	0.018	0.812
5 min	-0.086	0.250	0.001	0.989	-0.002	0.975	-0.053	0.476
10 min	-0.077	0.308	-0.046	0.544	-0.014	0.854	-0.056	0.453
15 min	-0.144	0.054	-0.118	0.114	-0.099	0.188	-0.142	0.056

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

Table 6: Distribution of nausea and vomiting according to study parameters:

	Nausea (26, 14.4%)		P value	Vomiting (9, 5%)		P value
	Yes	No		Yes	No	
AC	116.1 ± 12.1	115 ± 12.2	0.653t	112.9 ± 15.1	114.7 ± 11.9	0.049*t
SFH	37.2 ± 4.8	37.7 ± 5.2	0.675t	39 ± 5.3	37.5 ± 5.1	0.396t
EFW	3379.6 ± 517.8	3320.3 ± 435.3	0.533t	3582.2 ± 280.7	3315.5 ± 450.7	0.081t
AFI	10.8 ± 3.7	10.1 ± 3.2	0.385t	11.4 ± 3.5	10.2 ± 3.3	0.258t

t: student T-test

The effect of advanced maternal age on pregnancy outcomes: A prospective study

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Abstract

Background: Women who are 35 years of age or older at the anticipated date of delivery are considered to have advanced maternal age (AMA). This cutoff age was chosen in light of decreasing fertility data and growing concerns about the increased likelihood of genetic defects in the progeny of pregnant women over 35. An increased risk of perinatal deaths, spontaneous abortions, pregnancy complications like diabetes mellitus (DM) and hypertension (HTN), interventions like cesarean deliveries (CS), and foetal adverse events like preterm birth (PTB), low birth weights (LBW), congenital anomalies, and NICU admission is linked to older mothers.

Objective: Evaluation of the impact of advanced maternal age on maternal, obstetric, fetal, and perinatal outcomes was the main objective of the study.

Patients and methods: This study was a prospective cohort study at the Obstetrics and Gynecology Department at Mansoura University Hospitals. This study was conducted on a total of 82 primigravida women who were divided into 2 groups. The study group included 41 women aged 35 years or more. The control group included 41 women aged 20 years to 34 years.

Results: there was a significant difference between both groups about cesarean (CS) deliveries, preterm birth, high mean arterial pressure, and high Rate Pressure Product.

Conclusion: advanced maternal age is accompanied by a higher rate of preterm birth, cesarean delivery, high mean arterial pressure, and rate pressure product more than younger age women.

Keywords: advanced maternal age, obstetric, maternal, fetal, perinatal outcomes, cesarean delivery, preterm birth.

Introduction

A woman is deemed to have an advanced maternal age (AMA) if she is 35 years of age or older at the beginning of her pregnancy or at the time of delivery. There's a tendency in rich countries where older primigravida women decide not to have children out of choice or due to underlying

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infertility, but multiparous women are also choosing to continue having children [1].

Very AMA (VAMA) could be described as women over 40, while extremely AMA (EAMA) is utilized to characterize females over 45. These subcategories of advanced maternal age have also been established [2]. The selection of this age threshold was motivated by dwindling fertility data and growing apprehension over the likelihood of genetic defects in children born to pregnant mothers over 35 [3].

In wealthy countries, ladies in their advanced maternal age are probably primiparous. Unlike underdeveloped nations, where poverty, the cultural predilection for large kids, and inefficient family planning measures make childbirth at AMA the most likely among multiparous women [4].

Preeclampsia (PE), stillbirth, and foetal growth restriction (FGR) are among the pregnancy complications linked to advanced maternal age. These complications can be caused by endothelial damage, which ages with the mother, decreased maternal hemodynamic adaptation during pregnancy, and decreased uterine blood vessel compliance [5].

The older the mother, the higher the chance of premature delivery. Placental pathology explains this and might also explain why preeclampsia is more common in AMA. This adds to the list of iatrogenic factors contributing to premature labor induction [6]. Age significantly raises the risk for CD, whether it is an emergency or elective procedure. Fetal malposition, anomalies during delivery, underlying medical co-morbidities, and even mother requests are some of the factors that explain this [7].

As a mother's age rises, there is a greater chance of spontaneous abortion during the first 14 weeks of pregnancy [8]. Pregnancy at an advanced mother age is strongly linked to unfavorable newborn outcomes, which include preterm delivery, early infant mortality, LBW, and admission to the neonatal intensive care unit (NICU) [9]. The unfavorable consequences stem from insufficient cardiovascular adaptation during gestation, impeding the hemodynamic adjustments necessary to sustain the fetus [10].

Aim of the work

Analyzing the effects of advanced mother age on perinatal, obstetric, fetal, and maternal outcomes throughout pregnancy was the aim of this study.

Study design

This study was a prospective cohort study conducted at Obstetrics and Gynecology Department at Mansoura University Hospitals, from June 2021 to June 2022.

This study included primigravida women aged 20 years or more after the exclusion of the patients who refused to be included in this study, patients aged less than 20 years, and patients with medical disorders such as (pre-existing DM, chronic HTN, or autoimmune diseases).

Study population

The studies cases consisted of 82 primigravida women who were divided into 2 groups. The study group consisted of 41 pregnant women aged 35 years or more. Forty-one pregnant women, ages 20 to 34, made up the control group.

Additionally, the research group was partitioned into two subgroups: the very advanced age group, which included those older than 40, and the advanced age group, which included those between 35 and 40.

Methods

- After getting written consent from all participants. We documented personal, menstrual, obstetric, and history of surgical operation.

- Every prenatal appointment included a general examination to rule out chronic hypertension, monitor blood pressure to diagnose hypertensive diseases of pregnancy after 20 weeks of gestation and assess the mother's body mass index to identify obesity. When necessary, local and abdominal exams were performed.
- Between 24 and 28 weeks of gestation, all pregnant females were evaluated for gestational DM (GDM) using an oral glucose challenge test weighing 50 grams. A three-hour oral glucose tolerance test with a 100g oral glucose load was administered to females who had abnormal glucose challenge test results (140 mg/dL). When blood glucose levels are above 95 mg/dL during fasting, 130–140mg/dL one hour after eating, and 120mg/dL two hours after eating, GDM is diagnosed.
- Pregnancy-induced hypertension, gestational diabetes mellitus (GDM), preeclampsia, early pregnancy bleeding, antepartum hemorrhage, oligohydramnios or polyhydramnios, ICU hospitalization, sepsis, and postpartum hemorrhage were among the obstetric outcomes that were documented.
- Premature rupture of membranes, miscarriage, PTB, and CS or vaginal delivery were among the maternal outcomes that were documented.
- Congenital defects, intrauterine growth limitation, intrauterine fetal mortality, and stillbirth were among the fetal outcomes that were documented.
- The NICU hospitalization, early neonatal mortality, LBW (less than 2500g), very LBW (less than 1500g), and macrosomia (more than 4000g) are the categories into which perinatal outcomes were categorized.

Outcomes

The primary outcome was to detect the difference between the advanced age group and the younger age group about maternal, obstetric, fetal, and perinatal outcomes. The secondary outcome was to detect the difference between the advanced age group and the very advanced age group concerning maternal, obstetric, fetal, and perinatal outcomes.

Ethical consideration

The study protocol was approved by the Institutional Review Board (IRB), code no MS.21.06.1542, Date: 07/07/2021, Faculty of Medicine, Mansoura University.

Every patient received an explanation of the procedure's specifics. At every stage of the study, participants gave their informed written agreement regarding confidentiality and personal privacy. The current study was the only use of the data that was gathered.

Statistical Analysis

IBM Corp., 2020 provided the IBM-SPSS software, which was used for data entry and analysis. Armonk, NY: for Windows, Version 27.0.

The notation for qualitative data was N (%). Shapiro-Wilk's test was first used to determine if quantitative data was regularly distributed. If $p>0.050$, the data was considered normally distributed. Boxplots were examined to see whether any significant outliers (extreme values) were present. The interquartile range (Q1, or 25th percentile, to Q3, or 75th percentile) and median for quantitative data were reported as non-normally distributed.

To compare qualitative data between groups, the chi-square, Fisher's exact, or Fisher-Freeman-Halton exact tests were utilized. The quantitative data between the two groups was compared by utilizing the non-parametric Mann-Whitney U-test. The impact of predictor factors on the probability of an event, such as a mother or newborn being admitted to the ICU or NICU, was

determined using binary logistic regression.

If the p-value is less than 0.050, the results of any test that is employed will be deemed statistically significant.

Results

This study had 82 primigravida and was divided into two groups; study group (A) included 41 pregnant women aged 35 years or more. Control group (B) included 41 pregnant women aged 20 years to 34 years.

No statistically significant difference was detected between both groups concerning residence, educational level, type of conception, abnormal OGTT, DBP, Heart Rate (HR), Hemoglobin level, and platelet count. There was a statistically significant difference in previous relevant surgery such (p =.043), systolic blood pressure (SBP) (p=.019), mean arterial pressure (p=.033), Rate Pressure Product (RPP) = (SBP × heart rate) (p=.018), and body mass index (<.001) (Table 1).

Table (1): Comparisons of baseline characteristics of older age (A) vs. younger age groups (B).

Characteristic	Group A		Group B		Total		p-value
Categorical	N	%	N	%	N	%	
Residence Rural Urban	 28 13	 68.3 31.7	 28 13	 68.3 31.7	 56 26	 68.3 31.7	1.00
Education level Low Middle High	 4 25 12	 9.8 61 29.3	 2 17 22	 4.9 41.5 53.7	 6 42 34	 7.3 51.2 41.5	.076
Type of conception ART Natural	 5 36	 12.2 87.8	 4 37	 9.8 90.2	 9 73	 11 89	1.00
Previous relevant surgery	8	19.5	2	4.9	10	12.2	**.043**
Abnormal OGTT	4/37	10.8	1/38	2.6	5/75	6.7	.200
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
SBP (mmHg)	120	115-150	110	110-140	120	110-140	**.019**
DBP (mmHg)	80	75-90	80	70-90	80	70-90	.072
MAP (mmHg)	93.3	88.3-113.3	90	83.3-106.7	93.3	83.3-107.5	**.033**
Heart rate (beats/ minute)	88	80-90	84	80-90	87	80-90	.824
RPP	10920	9350-13350	9680	8800-11760	10480	9000-12390	**.018**
BMI (kg/m^2)	30	28-32.5	25	22-30	29.5	24-31.3	**<.001**
Hemoglobin level (g/dl)	10.9	10.4-11.6	10.6	9.6-11.1	10.9	10-11.3	.099
Platelet count $\times 10^9/L$	280	187-300	240	192-294.5	273	189.8-300	.192

There was a significant difference between the studied groups regarding delivery by cesarean section either elective or urgent (p=.028) being significantly higher in the advanced age group as compared to the younger age group (89.2% vs. 68.4%, respectively) and preterm birth (p=.001) being significantly higher at advanced age group as compared to younger age group (29.3% vs. 2.4%, respectively) and there was not a statistically significant difference as regards to the risk of miscarriage and PROM (Table 2).

Table (2): Comparisons of maternal outcomes in older age group (A) vs. younger age group (B).

	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Maternal outcomes							
Mode of delivery Vaginal delivery CS [elective, urgent]	4 33 [12, 21]	10.8 89.2	12 26 [7,19]	31.6 68.4	16 59 [19, 40]	21.3 78.7	**.028**
Miscarriage	4	9.8	3	7.3	7	8.5	1.00
PROM	3	7.3	6	14.6	9	11	.482
Preterm birth	12	29.3	1	2.4	13	15.9	**.001**

There was no statistically significant difference between both groups concerning obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 3).

Table (3): Comparisons of obstetric outcomes in older age group (A) vs. younger age group (B).

Obstetric outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
Bleeding APH PPH Bleeding of early pregnancy	8 2 2 4	19.5 4.9 4.9 9.8	8 1 4 3	19.5 2.4 9.8 7.3	16 3 6 7	19.5 3.7 7.3 8.5	1.00 1.00 .678 1.00
Sepsis	1	2.4	0	0	1	1.2	1.00
Oligohydramnios	4	9.8	7	17.1	11	13.4	.331
Polyhydramnios	3	7.3	1	2.4	4	4.9	.616
GDM	4	9.8	1	2.4	5	6.1	.359
PET	10	24.4	8	19.5	18	22	.594
HELLP syndrome	2	4.9	1	2.4	3	3.7	1.00
PIH	5	12.2	3	7.3	8	9.8	.712
ICU admission	6	14.6	2	4.9	8	9.8	.264

There was no statistically significant difference between the studied groups about fetal and perinatal outcomes (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 4).

Table (4): Comparisons of fetal and perinatal outcomes in older age group (A) vs. younger age group (B).

Fetal and perinatal outcomes	Group A		Group B		Total		p-value
	N	%	N	%	N	%	
$^{\$\$\$}$Birth weight Very low Low Normal	38 3 7 28	 7.9 18.4 73.7	37 4 3 30	 10.8 8.1 81.1	75 7 10 58	 9.3 13.3 77.3	.666
NICU admission	15	38.5	10	24.4	25	31.3	.175
IUGR	3	7.3	4	9.8	7	8.5	1.00
Early neonatal death	4	9.8	1	2.4	5	6.1	.359
Congenital anomaly	3	7.3	1	2.4	4	4.9	.616
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
*Birth weight (g)	3200	2300-3500	3500	2800-3500	3500	2500-3500	.388

There was no statistically significant difference between the advanced age group and very advanced age group concerning type of conception, or mode of delivery "although 100% of cases in the very advanced age group were delivered by cesarean section but with no statistical difference due to decreased number of cases at this group", miscarriage, PROM, and preterm birth (Table 5).

Table (5): Comparisons of maternal outcomes in advanced vs. very advanced age groups.

Maternal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Type of conception ART Natural	 5 28	 15.2 84.8	 0 8	 0 100	 5 36	 12.2 87.8	.563
Mode of delivery vaginal delivery cesarean delivery [elective, urgent]	 4 25 [9,16]	 13.8 86.2	 0 8 [3,5]	 0 100	 4 33 [12,21]	 10.8 89.2	.556
Miscarriage	4	12.1	0	0	4	9.8	.569
PROM	3	9.1	0	0	3	7.3	1.00
Preterm birth	9	27.3	3	37.5	12	29.3	.672

There was no statistically significant difference between the advanced age group and the very advanced age group about obstetric outcomes including (all types of bleeding, sepsis, oligohydramnios, polyhydramnios, GDM, PET, HELLP syndrome, PIH, and ICU admission) (Table 6).

Table (6): Comparisons of obstetric outcomes in advanced vs. very advanced age groups.

Obstetric outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Bleeding	8	24.2	0	0	8	19.5	.318
Placenta previa	2	6.1	0	0	2	4.9	1.00
PPH	2	6.1	0	0	2	4.9	1.00
Bleeding of early pregnancy	4	12.1	0	0	4	9.8	.569
Sepsis	1	3	0	0	1	2.4	1.00
Oligohydramnios	4	12.1	0	0	4	9.8	.569
Polyhydramnios	3	9.1	0	0	3	7.3	1.00
GDM	4	12.1	0	0	4	9.8	.569
PET	7	21.2	3	37.5	10	24.4	.672
HELLP syndrome	2	6.1	0	0	2	4.9	1.00
PIH	5	15.2	0	0	5	12.2	.563
ICU admission	5	15.2	1	12.5	6	14.6	1.00

There was no statistically significant difference between the advanced age group and the very advanced age group regarding fetal and perinatal outcomes including (low/ very low birth weight, IUGR, NICU admission, early neonatal death, and congenital anomaly) (Table 7).

Table (7): Comparisons of fetal and perinatal outcomes in advanced vs. very advanced age groups.

Fetal and perinatal outcomes	Advanced		Very advanced		Total		p-value
	N	%	N	%	N	%	
Birth weight	30		8		38		.088
Very low	1	3.3	2	25	3	7.9	
Low	5	16.7	2	25	70	18.4	
Normal	24	80	4	50	28	73.7	
NICU admission	12	38.7	3	37.5	15	38.5	1.00
IUGR	2	6.1	1	12.5	3	7.3	.488
Early neonatal death	2	6.1	2	25	4	9.8	.165
Congenital anomaly	3	9.1	0	0	3	7.3	1.00
Numerical	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p-value**
Birth weight (g)	3400	2500-3500	2650	1125-3500	3200	2300-3500	.170

Discussion

Pregnancies in females who are 35 years of age or older at the time of conception or birth are classified as AMA. It is becoming very common in affluent nations, mostly observed in older primigravida women who choose to put off having children out of a desire to live a longer life or because of underlying infertility, however, multiparous women are also doing so (1).

It is crucial to assess if and how AMA influences pregnancy outcomes and the maternal and foetal health, given the notable increase in the proportion of older moms. While the majority of research revealed a significant correlation between age and the outcome of pregnancy, other studies yielded inconsistent findings (11).

According to our study, there was no statistically significant difference between

the studied groups' baseline characteristics—such as place of residence, level of education, and mode of conception.

Our investigation revealed a statistically significant difference in the mean arterial pressure (P=.033), systolic blood pressure (P=.019), and rate pressure product (RPP) (p=.018) between the groups under consideration.

More and more people are using the double (rate-pressure) product (DP) as a proxy for cardiac activity and myocardial oxygen demand. It is calculated by multiplying HR by SBP. The robust correlation between left ventricular mass and DP has revealed its role in predicting the risk of acute myocardial infarction (AMI) and cardiovascular disease in hypertensive individuals (12).

In our study, the AMA group's mean RPP was 10920, whereas the younger age group's mean was 9680. This finding was consistent with research that indicated older women were predicted to have a higher incidence of AMI (13). RPP can be used to predict cardiovascular risk in women with AMA.

In terms of delivery mode, our study revealed that there was a statistically significant difference (p=0.028) between the groups under investigation; among the older group, 89.2% had an urgent or elective cesarean section, compared to 68.4% who were younger.

Although, 100% of the cases of the VAMA group were delivered by CD in comparison with 86.1% of the AMA group but with no statistically significant differences.

In accordance with the findings of Rydahi and associates, who revealed that older females had a greater possibility of CD at AMA (aOR=2.18) and VAMA (aOR=3.64). (15). The high risk of CD at AMA is explained by atherosclerosis of the uterine arteries, a decline in oxytocin receptors with age, and inadequate myometrium contractility, which results from the aged uterus's decreased ability to produce uterine contractions (14).

In our study, Preterm delivery showed statistically significantly higher incidence among older age than younger age group (29.3% versus 2.4%) (p=0.001).

Also, preterm delivery was 37.5 in the VAMA group versus 27.1% in the AMA group but of no statistically significant differences.

A significant retrospective analysis supported Waldenstrom et al.'s findings, showing that AMA and VAMA raised the odds of preterm delivery regardless of parity, both spontaneously occurring and when medically recommended. From 35 to 39 years old, age-related relationships were statistically significant but less strong across all parity groups (15).

However, even after accounting for confounding variables, a major retrospective study from Canada by Fuchs et al. and his colleagues indicated that in comparison with pregnancy at 30-34 years of age, pregnancy at a VAMA increased the risk of PTB by 1.2. Moreover, the age-group distribution of premature labor was found to be "U" shaped, indicating that young mother age is a predisposing factor for preterm labor in addition to AMA (16).

The risk of GDM in the AMA group was 9.8% group versus 2.4% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

However, in comparison to women under 35, the GDM incidence at AMA and VAMA is 1.62 (P<0.001) and 2.1 (P<0.001) higher, respectively, according to the retrospective study conducted by Khalil et al. and colleagues (17). Increasing obesity rates in older adults, which are associated with lower insulin sensitivity, might help to explain this (18).

In our study, the risk of PET in the AMA group was 24.4% group versus 19.5% in the younger age group and 21.2% in the AMA

group versus 37.5% in the VAMA group with no statistically significant difference.

The univariate analysis of the retrospective study by Nieto and his colleagues which compared women under 30 in the AMA, VAMA, and EAMA groups to a control group, only revealed a higher risk for PET at EAMA (OR=3.32). When confounding factors (obesity, utilization of ART, tobacco smoking, chronic HTN, and parity) were adjusted for using a multivariable logistic regression, age and PET did not, however, substantially correlate (19).

Regarding the comparison of fetal and perinatal outcomes, our study revealed that; there was no significant difference between studied groups as regards birth weight, congenital anomalies, NICU admission, and early neonatal death.

The risk of miscarriage was 9.8% in the AMA group versus 7.3% in the younger age group and 12.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

Magnus et al., in contrast, discovered that there was a considerable variation in the probability of miscarriage with mother age. Women between the ages of 25 and 29 had the lowest miscarriage risk (9.8%), while women over the age of 45 had the greatest risk (53.6%). The absolute lowest risk was at age 27 (9.5%). The risk was 15.8% for moms under the age of twenty (8).

The risk of congenital anomalies in our study was 7.3 in the AMA group versus 2.4% in the younger group and 9.1% in the AMA group versus 0% in the VAMA group with no statistically significant difference.

In line with Goetzinger et al.'s retrospective analysis of congenital anomaly prevalence in AMA pregnancies with euploid babies, they discovered that AMA was protective against congenital malformations (aOR 0.59, 95% CI 0.52–0.66). The "all or none" theory, which postulates that anatomically normal foetuses have a better survival rate at advanced oocyte age, can explain this phenomenon (20).

Nevertheless, it was shown that the rate of foetal chromosomal aberrations in spontaneous miscarriages at VAMA was substantially more than in women of a younger age (60.6% versus 33.5% in women 30-34). This Chinese study examined the connection between 497 pregnancies' spontaneous miscarriages, AMA, and chromosomal abnormalities (21).

The results of our study regarding the risk of NICU admission were 38.5% in the AMA group VS. at 24.4% in the younger group and 38.7% in the AMA group VS. 37.5% in the VAMA group with no statistically significant difference.

The AMA and VAMA groups, on the other hand, had higher rates of NICU admission; their respective AORs were 1.68 (95% CI 1.42–2.15, $P < 0.01$) and 1.52 (95% CI 1.21–1.92, $P < 0.01$) were higher. Kahveci and his colleagues assessed the effects of advanced maternal age on the perinatal and neonatal results of nulliparous singleton pregnancies in Turkey (3).

The risk of FGR in our study was 7.3% in the AMA group vs. 9.8% in the younger age group and 6.1% in the AMA group vs. 12.5% in the VAMA group with no statistically significant difference.

However, FGR was described as birth weight below the 5th percentile. Lean et al. found in a major study that women with AMA had a 1.23 (95% CI 1.01–1.52) higher risk of FGR; among women over 40, the risk increases by 1.53 (95% CI 1.07−2.20) This might be explained by incorrect placentation, which causes FGR but is unrelated to a decline in oocyte fitness (22).

The limitation of our study included the small sample size in the studied group and larger future studies are needed.

Conclusion

Advanced maternal age is accompanied by a higher rate of preterm birth, Cesarean delivery, high mean arterial pressure, and high Rate Pressure Product than younger age women.

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Combined Insulin Sensitizers as Double-Weapon to detonate PCOS-induced Vicious Circle

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Abstract

Objectives : assessment of the outcomes of women had polycystic ovary syndrome (PCOS) received 6-month therapy of metformin (Met) or combination of myoinositol (MI)/D-chiro-inositol (DCI) or both.

Patients & Methods : 210 PCOS women underwent clinical, US and laboratory work-up to determine baseline T0-data and were divided into 3-equal groups: Met group received met 500 mg tab three times daily, MI-group received MI/DCI combination in 40:1 ratio twice daily and MM-group received both Met and MI therapy and at the end of 6-m (T6) therapy, all patients were re-evaluated to assess gynecological outcomes including resumption of regular menstrual pattern (RMP) and getting pregnant for PCOS-infertile women wishing for pregnancy and metabolic and endocrinal outcomes including impact on body mass index (BMI), glucose tolerance (GT), homeostasis model assessment of insulin resistance (HOMA-IR) index, and hyperandrogenemia.

Results: At T6, 126 women resumed RMP and 15.8% of women got pregnant. T6-BMI was significantly decreased in all women with improved GT and only 15 of 67 insulin resistant women were still resistant. The frequency of women had serum total testosterone (TT) >0.8 ng/ml was decreased from 35.2% to 13.3% with significantly lower levels of TT at T6-samples than T0-samples. The percentages of change in the studied parameters were higher with MM-therapy than either Met or MI-therapy. The rate of resumption of RMP and percentages of change of BMI, HOMA-IR and serum TT were positively correlated but showed negative relation to the use of insulin sensitizer monotherapy. The Receiver Operating Characteristic (ROC) curve analysis defined high percentage of decrease of HOMA-IR index as positive and the use of monotherapy as negative predictor for getting RMP.

Conclusion: Insulin sensitizers' therapy is effective and safe for control PCOS-associated endocrinal, metabolic and gynecological deregulations. Inositol is a synergistic additive to metformin and this combination results in favorable outcomes than monotherapy.

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Introduction

Polycystic ovary syndrome (PCOS) is a common and complex disease affecting women of reproductive age [1] and is characterized by its complex pathological symptoms and mechanisms resulting in endocrine and metabolic dysfunction [2]. Ovulatory dysfunction, increased ovarian volume and/or polycystic ovary morphology with concomitant menstrual abnormalities, chronic anovulation, and decreased fertility or infertility are the characteristic gynecological manifestations of PCOS [3].

PCOS is highly associated with various metabolic and endocrinal disorders, because of the shared common risk factors; PCOS and metabolic-associated fatty liver disease (MAFLD) are concomitant and at the time of PCOS diagnosis, screening for MAFLD is mandatory because it is mostly asymptomatic [4]. The relation between PCOS and epithelial ovarian tumors is biologically plausible because obesity, hyperandrogenemia and fertility disorders, which are inherent to PCOS, are also risk factors for hormone-sensitive tumors [5].

Despite the high prevalence of PCOS, medical treatment is a dilemma because no available pharmacological option can tackle the entire spectrum of PCOS manifestations [6]. Metformin (Met) has pleiotropic actions, but is mainly, used for its glucose-lowering effects for treatment and prevention of type-2 diabetes mellitus (DM), gestational DM and PCOS [7]. Met through decreasing food intake and body weight, and improving lipid profile can influence multiple cardiovascular risk markers, improve MAFLD, modulate inflammatory markers, and possibly reduce cancer risks [8]. Met is widely used because of its positive glycemic control, safety profile, and low costs, but is not well accepted by all patients due to its common gastrointestinal adverse effect [9].

Myo-inositol (MI) is biosynthesized from all MI-containing compounds, by cyclic synthesis and through hydrolysis of phosphatidylinositol [10]. MI protects against MAFLD through reduction of hepatic accumulation of triglycerides [11] and decreases left ventricular stiffness through removal of cholesterol from the myocardium and increasing cardiac function [12]. Hyperglycemia, hypertriglyceridemia and insulin resistance (IR) induces inositol imbalance with deficiency of D-chiro-inositol (DCI) and higher MI levels and DCI administration might improve this imbalance and IR [13].

Objectives

This prospective study compared the effects of MI/DCI combination alone or in conjunction with Met on PCOS-associated endocrinal and metabolic disturbances.

Patients & Methods

All women presented to Gynecology outpatient clinic or Infertility clinic, Zagazig University Hospital with manifestations suggestive of PCOS were clinically evaluated for the presence of at least two of the Rotterdam criteria for diagnosis of PCOS (14, 15) and women had these criteria were evaluated.

Baseline clinical data collection

Collection of clinical data included age, residence, level of education, type of work, marital and fertility statuses, and if infertility was the main complaint. History taking included inquires about the presence of risk factors as sedentary lifestyle, emotional stress and family history of PCOS, obesity-related medical disorders especially DM or MAFLD, history of previous treatment for PCOS and its outcomes. Menstrual pattern such as infrequent menstrual periods with interval between menstrual periods of ≥35 days or amenorrhea which is defined as absence of vaginal bleeding for at least 90 days was discussed

Exclusion criteria

Women had other manifestations of metabolic

syndrome, cardiac manifestations of PCOS, maintained on other therapies or prepared for /received laparoscopic intervention for PCOS, receiving scheduled exercise, lipid-lowering therapies, or maintained on diabetogenic drugs for any other indications were excluded from the study. Also, women had morbid obesity with body mass index (BMI) >35 kg/m2, causes other than PCOS for infertility, manifest DM, hepatic or pancreatic diseases, refused to participate in the study or missed during follow-up were excluded from the study.

Inclusion criteria

Women with diagnostic criteria of PCOS and free of exclusion criteria, accepted to participate in the study and signed the written fully informed consents were included in the study

Study Protocol

The enrolled women were randomly allocated into three groups according to the scheduled therapy for each group. Women were evaluated at time of enrolment (T0) and at the end of 6-m duration of therapy (T6) for:

1. Metabolic disturbances including

- Obesity as judged by BMI which is determined using the equation of weight divided by square height in meter (16).
- Deregulated glucose tolerance as determined using the 75-oral glucose tolerance test (OGTT) that entails estimation of fasting blood glucose (FBG) and postprandial blood glucose (PPBG) at 1-h and 2-h in response to taking 75-g oral glucose and interpreting the results according to the recommendations of the International association of diabetes and pregnancy study groups (IADPSG) (17) as follows: FBG ≥92 mg/dl, 1-h PPBG ≥180 mg/dl and 2-h PPBG ≥153 mg/dl indicates glucose intolerance.
- Insulin resistance was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR) (18) with index ≥2 was indicated IR (19).

2. Clinical hyperandrogenemia was evaluated as

- The presence and severity of hirsutism according to the modified Ferriman-Gallwey (FG) map (20) that divided the body into 9 areas, each area was evaluated using 5-point scale with higher score indicating more extensive hair growth and a score of ≥8 indicates hyperandrogenemia.
- Acne scoring was determined as previously by Adityan et al. (21) as comedones, occasional papules (Grade 1), papules, comedones, few pustules (Grade 2), predominant pustules, nodules, abscesses (Grade 3) and mainly cysts, abscesses, widespread scarring (Grade 4).

3. Ovarian morphology was assessed using either transabdomial or transvaginal ultrasonography (TAU, TVU) for ovarian volume and number of ovarian follicles; ovarian volume >10ml per ovary and/or detection of >12 follicles of 2-9 mm are diagnostic of PCOS.
4. Laboratory evaluations: blood samples were obtained for estimation of FBG & PPBG, fasting serum insulin (FSI), total testosterone (TT) and dehydro-epiandrosterone (DHEA); serum level of TT >0.8 ng/ml indicates biochemical hyperandrogenemia.

Treatment protocol

Patients were divided into three treatment groups; Met-group received metformin hydrochloride (Cidophage tab, Chemical Industrial Development, Cairo Egypt) 500 mg three times daily, MI-group received tablets containing MI/DCI combination in dose of myoinositol 550 mg and DCI 13.8 mg in a 40:1 ratio with 0.2 mg folic acid (Viocyst

tab, Viomix Pharmaceutical Industries, Egypt) twice daily and MM-group received combination of the treatment received by patients of groups Met and MI. Treatment for all groups was continued for six months with no lifestyle changes, dieting regimens or exercise protocols.

Ethical considerations

The study protocol was approved by the departmental committee and discussed freely with women who had PCOS, and those accepted to participate in the study, receive the assigned therapy and attend for follow-up after 6-m had signed a written fully informed consent to undergo the preliminary clinical examination and US and lab evaluations. At the end of 6-m drug therapy and defining the study outcomes, the final approval by the Local Ethical Committee was obtained (ZU-IRB #11195-5/11-23 and the study was registered at Clinical trial.com: NCT06170463. As a reference for lab findings, 16 women who are free of gynecological problems, accepted to give blood samples and meet exclusion criteria were chosen from those attending the family planning clinic.

Randomization & Blindness

Randomization of the enrolled women was conveyed by an assistant who was blinded about the study protocol by computer sequencing system with 1:1:1 sequence and even-numbers dropping to provide the sequence of cases for each group. Patients' sequence was transformed to group title; Met, MI and MM and women were asked to choose an envelope that contained the drug regimen to be followed and scheduled follow-up visit for each woman. The author was blinded about the sequencing process and patients' distribution and drug regimen used. At the 6-m visit and after patients' evaluation, patients' sequence was declared and outcomes were interpreted.

Statistical analysis

One-way ANOVA test and Chi-square test (X2 test) were used to assess the significance of the results. Evaluation of predictability was conducted using the Receiver characteristic curve. The significance of the area under ROC curve (AUC) was assessed in relation to area under the reference curve using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). Significance of the results was determined using a P-value at cutoff point of 0.05.

Results

Evaluation process excluded 27 women; 8 women were maintained on PCOS treatment regimens, 4 women had manifest DM, 5 women had bariatric surgery for obesity and eight women had concomitant causes for infertility, while two women refused to participate in the study. Another 15 women did not attend the follow-up visit and 18 women at follow-up assured receiving therapy intermittently and these 34 women were also excluded from the study. At 6-m visit, 70 women per group were evaluated and revision of their enrolment data showed insignificant differences between the three groups (Table 1, Fig. 1).

Table 1: Patients' enrolment data

		Met	MI	MM	P
Age (years)		27.8±4	28.2±4.7	27.5±4.3	0.636
Residence	Urban	38 (54.3%)	31 (44.3%)	43 (61.4%)	0.124
	Rural	32 (45.7%)	39 (55.7%)	27 (38.5%)	
Education	Illiterate	19 (27.1%)	22 (31.4%)	14 (20%)	0.299
	Literate	51 (72.9%)	48 (68.6%)	56 (80%)	

Work	Housewives	26 (37.1%)	18 (25.7%)	24 (34.3%)	0.714
	Officers	17 (24.3%)	22 (31.4%)	19 (27.1%)	
	Workers	15 (21.5%)	19 (27.2%)	14 (20%)	
	Farmers	12 (17.1%)	11(15.7%)	13 (18.6%)	
Menstrual pattern	Infrequent cycles	57 (81.4%)	53 (75.7%)	55 (78.6%)	0.712
	Amenorrhea	13 (18.6%)	17 (24.3%)	15 (21.4%)	
Marital status	Single	16 (22.9%)	10 (14.3%)	12 (17.1%)	0.407
	Married	54 (77.1%)	60 (85.7%)	58 (82.9%)	
Infertility as the main complaint among married women	Yes	32 (45.7%)	28 (40%)	35 (50%)	0.161
	No	22 (31.4%)	32 (45.7%)	20 (28.6%)	

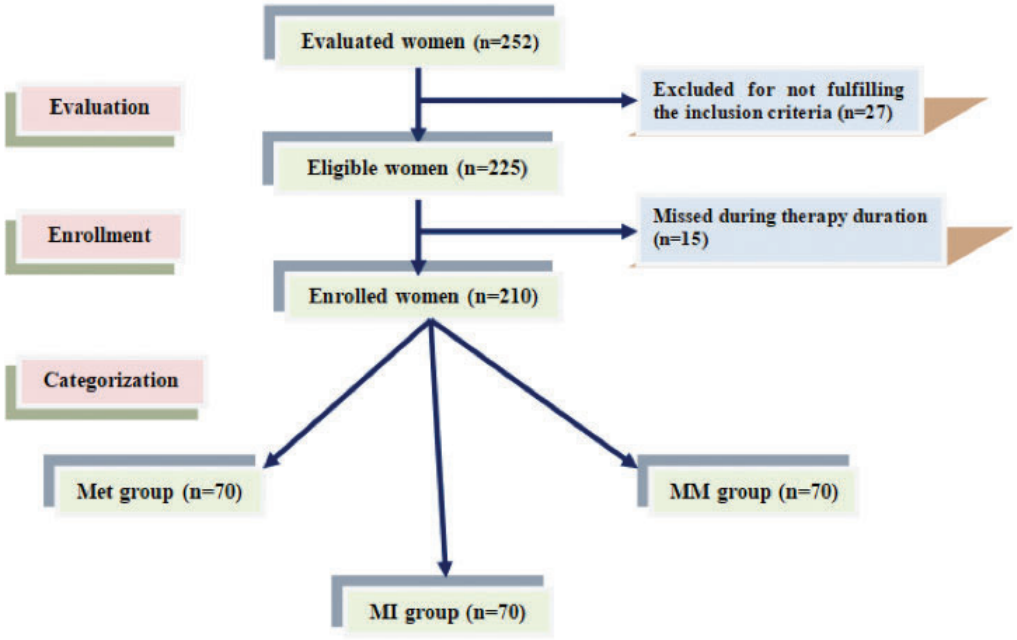


Figure 1: Study Flow Chart

At the end of 6-m therapy (T6), 126 women (60%) resumed regular menstrual cycles and 67 women (31.9%) had infrequent cycles, while 17 women (8.1%) were still had amenorrhea with significantly (P<0.001) reduced deregulated pattern among women of all groups. The frequency of women resumed regular cycles was significantly higher with MM therapy compared to that reported with Met (P=0.041) and MI (P=0.0007) therapies with non-significantly higher frequency with Met therapy (Table 2, Fig. 2).

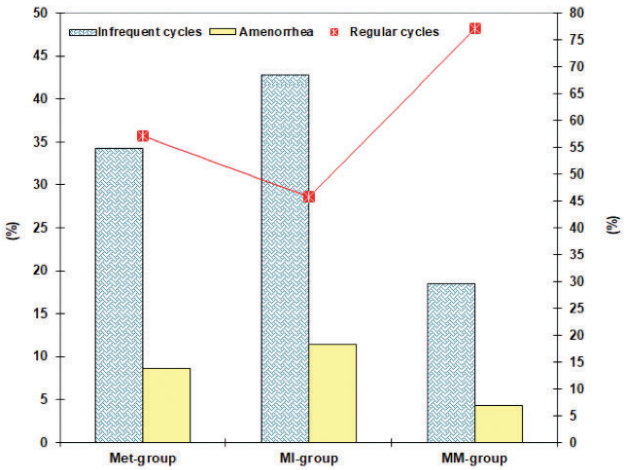


Fig. (2): Patients' distribution according to menstrual outcomes at the end of 6-m therapy

Among women presented with infertility as the main complaint (n=95), 15 women got pregnant for a pregnancy rate of 15.8% that showed insignificant differences between the three groups despite being highest among MM-group (Table 2).

Table 2: Gynecological outcomes

			Met	MI	MM	Total
Menstrual pattern	T0	Regular	0	0	0	0
		Infrequent	55 (78.6%)	53 (75.7%)	57 (81.4%)	165 (78.6%)
		Amenorrhea	15 (21.4%)	17 (24.3%)	13 (18.6%)	45 (21.4%)
	P1			0.687	0.673	
	P2				0.410	
	T6	Regular	40 (57.1%)	32 (45.7%)	54 (77.1%)	126 (60%)
		Infrequent	24 (34.3%)	30 (42.9%)	13 (18.6%)	67 (31.9%)
		Amenorrhea	6 (8.6%)	8 (11.4%)	3 (4.3%)	17 (8.1%)
	P1			0.398	**0.041**	
	P2				**0.0007**	
Pregnancy outcome at T0 for women seeking for pregnancy		Pregnant	5 (15.6%)	3 (10.7%)	7 (20%)	15 (15.8%)
		Not pregnant	27 (84.4%)	25 (89.3%)	28 (80%)	80 (84.2%)
		Total	32 (100%)	28 (100%)	35 (100%)	95 (100%)
		P1		0.577	0.641	
		P2			0.316	

The used therapies significantly (P<0.001) reduced women's BMI at T6 in relation to T0-BMI with non-significant difference between the studied groups both at T0 (P=0.264) and T6 (P=0.209). The percentage of decrease in T6-BMI in relation to T0-BMI was significantly (P<0.001) higher in women of Met and MM groups compared to that of women of MI-group with significantly (P=0.0001) higher in women of MM-group than in women of Met-women (Fig. 3).

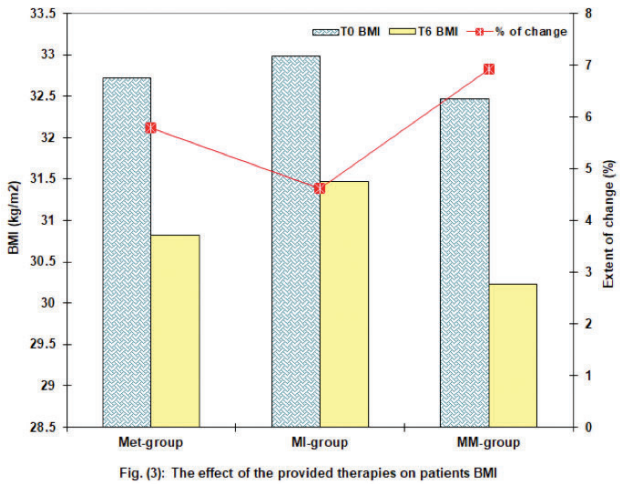


Fig. (3): The effect of the provided therapies on patients BMI

The BG levels estimated at T0 and T6 showed non-significant intergroup differences, apart from FBG that showed significant (P=0.0035) intergroup difference. The estimated BG levels at T6 decreased significantly (P<0.001) in all patients in relation to levels estimated at T0. The percentage of decrease in FBG levels estimated in T6 samples in relation to its T0 levels showed significant (P<0.001, respectively) variance between women of the three groups and was significantly higher with Met- and MM-therapies than MI-therapy (P=0.0009 & <0.001, respectively) with insignificantly (P=0.231) higher percentage of decrease with MM than Met therapies. Despite the significantly lower 1-h and 2-h PPBG levels estimated in T6 than T0 samples of all patients, the intergroup differences were insignificant regarding both the levels and the percentage of decrease.

The results of 75-OGTT conveyed at T0 detected glucose intolerance (GI) of all

women as evidenced by BG levels higher than the diagnostic limits of the IADPSG in all T0 samples; fasting and 1-h and 2-h PP. However, at T6 estimations, 167 patients (79.5%) still had fasting GI, 189 patients (90%) had 1-h GI and 111 patients (52.9%) had 2-h GI with insignificant distribution between the three groups regarding the frequency of women showed FBG level of ≥92 mg/dl or 1-h PPBG level of ≥180 mg/dl. On contrary, the frequency of GI women on 2-h PPBG estimations was significantly lower in MM-group than in MI-group with insignificant difference in distribution of GI women of Met-group and other groups.

Estimated serum insulin levels decreased in all women in T6 samples, but the differences between levels estimated in T0 and T6 samples were insignificant with insignificant intergroup differences both in T0 and T6 samples. However, the percentage of decrease in T6 serum insulin showed significant variance between the three groups and was significantly (P<0.001) higher with MM therapy than Met and MI therapies and significant (P=0.0016) difference in favor of MI therapy. At T0 time, 67 women and at T6 time only 15 women were insulin resistant with HOMA-IR ≥2 with insignificant differences between the distributions of IR women among the three groups. The T6-IR frequency was significantly lower than T0 frequency in the three groups but was lowest with MM therapy. Despite of the insignificant intergroup differences regarding the HOMA-IR index, it was decreased in all patients and the extent of decrease showed significant (P<0.001) intergroup difference and was significantly higher in group MM compared to groups Met (P=0.0004) and MI (P<0.001) with significantly (P=0.027) higher extent of decrease with Met than MI (Table 3, Fig. 4).

Table 3: Metabolic outcomes

Variates Groups			Met	MI	MM	P
BMI (kg/m^2)		T0	32.7±1.8	33±2.5	32.5±1.5	0.264
		T6	30.8±1.6	31.5±2.5	30.2±1.5	0.209
		P1	<0.001	<0.001	<0.001	<0.001
		% of change	5.8±1.6	4.62±1.07	6.93±1.65	
		P2		<0.001	0.0001	
		P3			<0.001	
75-OGTT	FBG (mg/dl)	T0	123.7±7.5	125±9.4	124.4±10.6	0.707
		T6	110±12.8	116.2±14.3	109.1±13.2	0.0035
		P1	<0.001	<0.001	<0.001	
		% of change	11.25±7.12	7.27±6.79	12.5±5	<0.001
		P2		0.0009	0.231	
		P3			<0.001	
	1-h PPBG (mg/dl)	T0	187.5±4.6	187.2±5	188.7±5.4	0.177
		T6	166.5±8.8	167.6±8.7	168.58.3	0.389
		P1	<0.001	<0.001	<0.001	
		% of change	11.2±3.9	10.4±4.7	10.7±4.7	0.576
		P2		0.294	0.452	
		P3			0.788	
	2-h PPBG (mg/dl)	T0	165±7	162.6±6.3	164.5±5.1	0.056
		T6	154.9±9.3	151.7±8.9	152.6±7.8	0.083
		P1	<0.001	<0.001	<0.001	
		% of change	6.1±4.1	6.7±3.3	7.2±4.1	0.242
		P2		0.326	0.115	
		P3			0.451	

Glucose intolerance	Parameter	FBG			1-h PPBG			2-h PPBG		
	Group	Met	Met	MM	Met	Met	MM	Met	Met	MM
	Intolerant	56 (80%)	59 (84.3%)	52 (74.3%)	63 (90%)	61 (87.1%)	65 (92.9%)	43 (61.4%)	38 (54.3%)	30 (42.9%)
	Tolerant	14 (20%)	11 (15.7%)	18 (25.7%)	7 (10%)	9 (12.9%)	5 (7.1%)	27 (38.6%)	32 (45.7%)	40 (57.1%)
	P1		0.508	0.421		0.591	0.543		0.392	**0.028**
	P2			0.144			0.255			0.176
HOMA-IR index	Serum fasting insulin levels	T0		5±1.65		4.83±1.7		5.05±1.68		0.737
		T6		4.83±1.63		4.64±1.6		4.74±1.6		0.858
		P1		0.499		0.472		0.265		
		% of change		3.66±1		4.25±1.18		6.26±2		<0.001
		P2				0.0016		<0.001		
		P3						<0.001		
	IR incidence	T0		22 (31.4%)		22 (31.4%)		23 (32.9%)		0.978
		T6		10 (14.3%)		8 (11.4%)		7 (10%)		0.727
		P1		0.016		0.004		0.001		
	Mean index	T0		1.52±0.52		1.5±0.56		1.57±0.59		0.713
		T6		1.31±0.47		1.34±0.51		1.29±0.5		0.886
		P1		0.013		0.075		0.003		
		% of change		14.06±7.64		11.1±6.88		18±4.84		<0.001
		P2				0.017		0.0004		
		P3						<0.001		

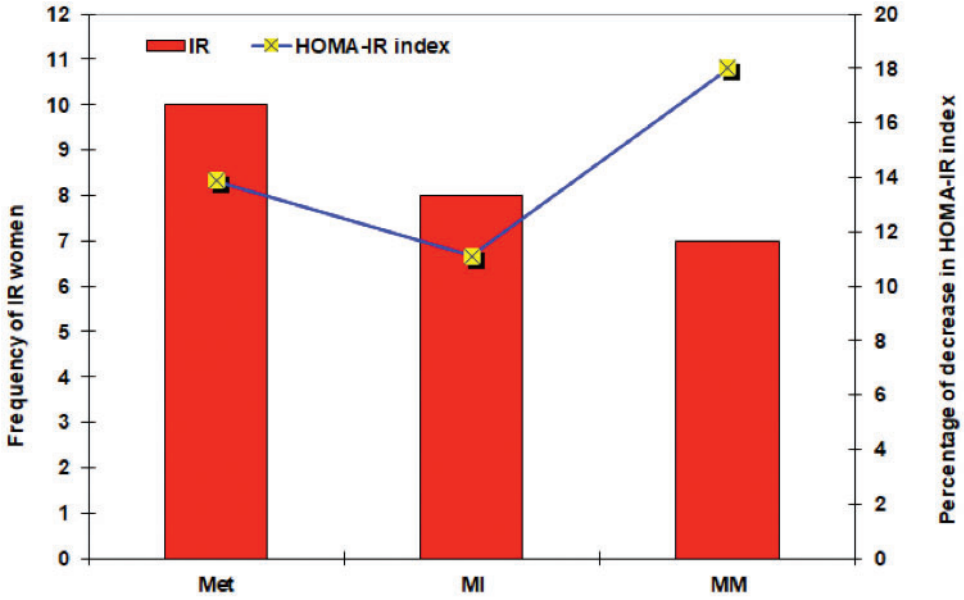


Fig. (4): The frequency of insulin resistant women at T6 evaluation and the percentage of change in HOMA-IR index at T6 in relation to T0

The frequency of women had biochemical hyperandrogenemia, defined as serum TT of ≥0.8 ng/ml, was 35.2% at T0 and was decreased at T6 to 13.3% with significantly lower frequency at T6 than at T0 in all groups. However, the extent of decrease in the frequency of women had hyperandrogenemia showed insignificant differences between the studied groups both at T0 and T6. Moreover, estimated serum TT and DHEA levels were significantly decreased in women of the three groups at T6 in comparison to levels estimated at T0. The inter-group difference was insignificant at T0 for both TT and DHEA, while at T6 the difference was insignificant (P=0.209) in case of TT and was significant (P=0.030) for DHEA levels. The percentage of decrease of serum TT was significantly (P=0.00002) higher in women of MM-group compared to women of other groups, while the percentage of decrease of serum DHEA was significantly higher (P=0.0096) in women of MM-group than in women of Met-group and was insignificantly higher (P=0.151) than in women of MI-group (Table 4).

Clinical hyperandrogenemia manifested as hirsutism was detected in 45 women who showed FG score ≥8 with non-significant distribution among the women of the three groups. Treatment did not improve hirsutism significantly as shown by the insignificant difference in the frequency of women had FG score ≥8 before (21.4%) and after (16.7%) treatment and the non-significant difference between the studied groups. Despite the insignificant differences of mean FG score determined at T0 and T6 between the studied groups, the mean intergroup difference between T0 and T6 FG scores were significant in the three groups (Table 4).

Acne as another manifestation for clinical hyperandrogenemia was frequent among the studied women (68.1%), but unfortunately improved insignificantly with the used therapies and at the end of treatment, the frequency was 61.4%. Regarding the mean acne score, it was decreased insignificantly in patients of groups Met (P=0.205) and MI (0.214) in comparison to mean value of their T0 score, while the difference was significant (P=0.0029) with MM therapy. Further patients' distribution according to the differential items of acne score at T6 showed insignificant difference than that determined at T0 in groups Met and MI (P=0.655 & 0.562, respectively), but the difference was significant (P=0.029) in case of group-MM (Table 4).

Table 4: Endocrinal outcomes

Variates Groups			Met	MI	MM	P
BMI (kg/m²)		T0	25 (35.7%)	22 (31.4%)	27 (38.6%)	0.673
		T6	13 (18.6%)	7 (10%)	8 (11.4%)	0.279
		P1	0.023	0.0018	0.0002	
Hormonal assay	Serum testosterone (ng/ml)	T0	0.77±0.1	0.75±0.09	0.76±0.09	0.264
		T6	0.71±0.09	0.68±0.08	0.69±0.09	0.209
		P1	0.0001	0.0003	<0.001	
		% of change	8.28±2.83	8.42±2.13	10.24±2.46	
		P2		0.739	0.00002	
		P3			0.00002	
	Serum DHEA	T0	296.2±38.8	282.5±29.5	286±38.9	0.066
		T6	273.9±34.5	260.4±28.3	261.5±36.3	0.030
		P1	0.0005	0.00001	0.00018	
		% of change	7.44±2.3	7.82±3.3	8.57±2.75	0.058
		P2		0.425	0.0096	
		P3			0.151	

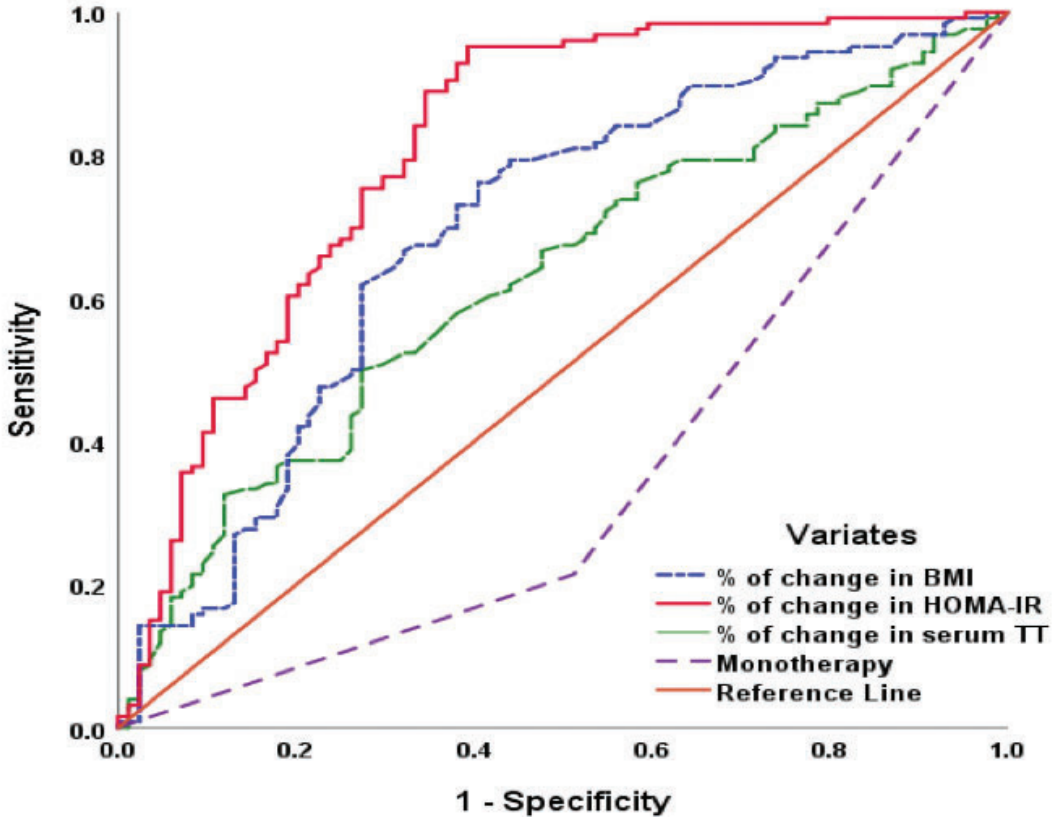
Hirsutism (FG score)	**Incidence (FG score ≥8)**	T0	19 (27.1%)	13 (18.6%)	13 (18.6%)	0.361
		T6	15 (21.4%)	11 (15.7%)	9 (12.9%)	0.383
		P2	0.403	0.654	0.353	
	Mean FG score	T0	7±1.62	6.9±2.09	6.8±1.16	0.777
		T6	5.7±1.8	6±2	6±1.34	0.494
		P2	0.0001	0.001	0.0002	
Acne score	**Incidence**	T0	43 (61.4%)	47 (67.1%)	53 (75.7%)	0.189
		T6	39 (55.7%)	45 (64.3%)	45 (64.3%)	0.485
		P2	0.674	0.722	0.140	
	Mean score	T0	1.71±0.8	1.79±1	1.85±0.93	0.761
		T6	1.49±0.68	1.56±0.78	1.4±0.54	0.552
		P2	0.205	0.214	0.0052	

Score items	Time	T0			T6		
	Group	Met	MI	MM	Met	MI	MM
	0	29 (41.4%)	23 (32.9%)	17 (24.3%)	31 (44.3%)	25 (35.7%)	25 (35.7%)
	1	20 (28.6%)	24 (34.3%)	23 (32.9%)	23 (32.9%)	26 (37%)	28 (40%)
	2	15 (21.4%)	13 (18.6%)	19 (27.1%)	14 (20%)	15 (21.4%)	16 (22.9%)
	3	4 (5.7%)	6 (8.6%)	7 (10%)	1 (1.4%)	2 (2.9%)	1 (1.4%)
	4	2 (2.8%)	4 (5.7%)	4 (5.7%)	1 (1.4%)	2 (2.9%)	0
P1		0.609			0.856		
P2					0.655	0.562	0.029

The reported resumption of regular menstrual pattern and percentages of change of BMI, HOMA-IR and serum TT showed negative relation to the use of insulin sensitizer monotherapy. The resumption of regular menstrual pattern was positively related to the percentage of change of HOMA-IR index, BMI and serum TT levels. Also, the percentage of decrease of serum testosterone was positively related to that of HOMAI-IR index and BMI. ROC curve analysis for the predictors for getting regular menstrual pattern showed that the more the control of IR with high percentage of decrease of HOMA-IR index the higher the possibility for getting regular menstrual pattern and defined the use of monotherapy as a negative predictor for such outcome (Table 5, Fig. 5).

Table 5: Statistical analysis for the relation between the study outcomes

	Mono-therapy		Regular menstrual pattern		% of change in serum TT	
	"r"	P	"r"	P	"r"	P
Regular menstrual pattern	-0.309	<0.001	-	-	0.178	0.010
% of change of BMI	-0.474	<0.001	0.295	<0.001	0.145	0.036
% of change of HOMA-IR index	-0.327	<0.001	0.443	<0.001	0.216	0.002
% of change of TT	-0.151	0.029	0.178	0.010		
The Receiver Operating Characteristic (ROC) Curve						
	AUC	**SE**	**P**	**95% CI**		
Monotherapy	0.351	0.040	<0.001	0.274-0.429		
% of change of BMI	0.693	0.038	<0.001	0.618-0.768		
% of change of HOMA-IR index	0.811	0.032	<0.001	0.747-0.874		
% of change of TT	0.626	0.039	0.002	0.550-0.702		



Discussion

Gynecological outcomes of this trial showed that 60% of women resumed regular menstrual pattern and among infertile women wishing to get pregnant a pregnancy rate of 13.7% was reported. Further, resumption of menstrual regularity showed positive relation to the percentage of change in IR-index, BMI and serum androgens. These findings spotlight on the vicious circle of obesity, IR and hyperandrogenemia that deleteriously affects the ovarian function with subsequent menstrual disturbances and subfertility or infertility.

Moreover, the adjustment of menstrual pattern and its underlying pathogenesis factors; obesity, IR and hyperandrogenemia, was significantly higher with combined metformin/inositol combination therapy than with either Met or MI as monotherapy that showed insignificant differences. Also, the ROC curve defined the use of insulin sensitizer monotherapy as a negative predictor for the possibility of resumption of regular menstrual pattern; a finding that illustrated the ability of the applied regimens to detonate this cycle and that better outcomes were obtained with the use of combination therapy as double-weapon to get such improvement.

The reported effects of the used drug regimens on BMI and IR and the relation between resumption of regular menstrual pattern with the extent of decrease in BMI and HOMA-IR assured the assumption that obesity is a hyperinsulinemic state and the relation between IR and ovarian functions. Such relation between IR and hyperandrogenemia was attributed to decreased levels of sex-hormone binding globulin (SHBG) secondary to obesity and IR with subsequently higher levels of free testosterone and free androgen index as evidenced by resumption of serum SHBG levels with reduction of serum free testosterone and decreased free androgen index using various modalities for weight reduction in PCOS obese women including dietary regimens (22), pharmacological interventions (23) or bariatric surgery (24).

Further the comparable effects of both inositol and metformin indicated their efficiency as insulin sensitizers and metabolic adjusting drugs. Similarly, Soldat-Stanković et al. (25) showed comparable effects of MET and MI on BMI, body composition, hormonal profile, metabolism of glucose and insulin, and adiponectin level and concluded that MET and MI, were useful in reducing BMI and improving body composition in PCOS women without significant differences.

Furthermore, the significant differences between women who received combination therapy in comparison to those received monotherapy illustrated the synergism between the effects of each drug to improve outcomes. Similarly, a recent study compared the efficacy of Met as monotherapy versus Met with MI as combination therapy and detected significantly greater improvement of menstrual regularity with combination, but pregnancy rates were comparable and concluded that addition of MI to Met improved menstrual cycle regularity, and QOL in PCOS-women (26).

The reported comparable outcomes of women used Met or MI as monotherapy, go in hand with Rajasekaran et al. (27) who reported comparable effect of MI and Met on ovarian hyperstimulation syndrome in PCOS women prepared to IVF but MI therapy was associated with significantly higher fertilization and cleavage rates and number of good grade embryos and with a systemic review for randomized controlled trials that assured the non-inferiority of inositol compared to metformin regarding effects on BMI, androgen hormonal profile, and insulin action with a risk ratio for getting regular menstrual cycle of 1.79 higher with inositol than placebo (28). Also, Bodepudi et al. (29) detected the comparable effects of Met and MI on clinical, hormonal, and biochemical profiles of PCOS women and documented that the better safety profile and tolerance of MI, due to its minimal side effects, prevents

discontinuation of therapy till getting the desirable effects.

In support of the efficacy of MI as additive to other drugs used for PCOS treatment, Kachhawa et al. (30) compared the effect of using myoinositol and D-chiro-inositol in 3.6:1 ratio versus combined hormonal contraceptive in a series of PCOS women and reported resumed spontaneous menses in about 85% of women, reduction of mean cycle length and these outcomes were continued for three months after stoppage of treatment and concluded that the used inositol combination is effective in regularizing menstrual cycles. Thereafter, Guarano et al. (31) found the addition of MI to alpha-lipoic acid creates synergistic effect that was manifested as improved IR, menstrual regularity and ovulation rhythm of PCOS women especially in obese/overweight patients with T2DM familiarity. Also, Hassan et al. (32) compared resveratrol and MI versus Met and pioglitazone combinations for treatment of PCOS women and reported significant reduction in serum TT, LH and FSH levels with a marked reduction in the ovarian volume with MI combination and significantly higher frequency of menstrual regularity and concluded that combined resveratrol and MI is more effectively ameliorated the altered endocrine, metabolic indices and stress burden especially in high risk group of obese, oligo-anovulatory married PCOS affected women.

The reported beneficial effects of inositol could be attributed to its variant mechanisms of action; experimentally, Bizzarri et al. (33) shown that MI and its epimer D-chiro-inositol (DCI) permits transduction of insulin and improves the complete breakdown of glucose through the citric acid cycle, especially in glucose-greedy tissues, such as the ovary. Also, DCI inhibits generation of reactive oxygen species secondary to the action of NAPH oxidase and improves mitochondrial disruption, (34), MI through inositol triphosphate (IP3) signaling pathway induces calcium ion (Ca2+) release from the endoplasmic reticulum leading to rising of cytosolic Ca2+ levels which in turn activates many enzymes and proteins (35).

Conclusion

Insulin sensitizers' therapy is effective, safe, cheap and in-hand of all PCOS women to control PCOS-associated endocrinal, metabolic and gynecological deregulations. Inositol is a synergistic additive to metformin and this combination results in favorable outcomes than monotherapy. Lack of inositol side effects allowed patients to continue the therapy duration despite of the unpleasant side effects of metformin.

Limitations

The use of minimal acceptable dose of metformin with higher dose of MI/DCO to minimize side effects need to be evaluated. Follow-up after cessation of therapy to detect recurrence of manifestations was mandatory to adjust duration of therapy

Recommendations

Comparative study of the used drug combination versus other treatment regimens for PCOS was required to define the best of which.

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