Issn 1110 -6352

THE EGYPTIAN JOURNAL OF FERTILITY AND STERILITY

Volume 28 Number 2 Mar.-Apr. 2024

EFSS

The Egyptian Journal Of Fertility And Sterility

The Official Journal of the Egyption Fertility and Sterility Society (**EFSS)**

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

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

2- Books:

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

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

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

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Contents :

Letter from the Editor:

Dear colleagues,

very interesting subjects are included in this edition. Pain during office hysteroscopy affected by main complaints and the difficulty of hysteroscopic procedure in terms of duration and scope introduction also pain increased by increasing anxiety score. However, no correlation was found between pain and age, or parity. Conservative surgery (preservation of the uterus) is a suitable treatment of placenta accrete spectrum especially in communities like Egypt in which women want to preserve fertility and refuse hysterectomy but the woman must be diagnosed during pregnancy and admitted before surgery to tertiary care hospital to be operated under care of multidisciplinary team expert in dealing with this condition with possibility of hysterectomy if needed. Nitrous oxide donor plays no role in the therapy of fetal growth restriction with minor Doppler alterations and maternal side effects. It had a minor positive effect on the umbilical artery Doppler and placental circulation. Caesarean section scar was visible in all women at 6–12 weeks after caesarean section. The prevalence of niches detected by 3D is high after caesarean section (56.6%), and more niches are detected than using TVUS (41.3%), with a larger observed niche size and reduced residual myometrial thickness. The presence of a niche is significantly related to postmenstrual spotting. Twelve hours postpartum magnesium sulphate intake could be beneficial in women with severe preeclampsia as regard prevention of eclampsia with fewer side effects. In women with unexplained infertility undergoing long protocol in assisted reproduction cycles, there were no significant differences between the relative effectiveness and safety of administering progesterone versus progesterone combined with estrogen for luteal phase support regarding biochemical, clinical pregnancy and live birth rates. There are encouraging results from the use of cabergoline, metformin, and clomiphene citrate in patient with mild to moderate endometriosis.

Best regards.

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World Health Organization Quality of Life Questionnaire in Women with Placenta Accreta Spectrum: A Single Center Hospital Based Study

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Abstract

Background: Placenta accreta spectrum (PAS) has serious fetal and maternal outcomes. Short-term morbidities of placenta PAS are well defined, but little is known about long-term outcomes and quality of life (Qol).

Aim: This study aimed to evaluate the World Health Organization Quality of Life Questionnaire (WHOQOL) in women with PAS.

Methods: This is a cross-sectional study. All women with a confirmed diagnosis of PAS were included. The study was conducted in an outpatient maternal clinic, Assiut University Hospital, Assiut, Egypt, between October 2020 and October 2021. All participants underwent detailed clinical and obstetric evaluation. WHOQOL score was measured in those patients at short and long-term postpartum follow-up.

Results: A total of 80 women were eligible for our study. The mean age of recruited women was 30.86 ± 4.68 years. A total of 38 (47.5%) women developed different forms of complications. Both groups with/without complications showed significant improvement in different domains of the score at the 12th month of follow-up. At baseline, women with complications had significantly lower environment domain. Also, baseline social relationships had a significant positive correlation with the frequency of parity and cesarean section (CS).

Conclusion: Pregnant women complicated by PAS had significant improvement in WHOQOL- domains after 1 year of follow-up. Domains of WHOQOL weren't greatly affected by complications of PAS. Future research at several centers is necessary to confirm these findings.

Synopsis:

Keywords: placenta accrete spectrum, quality of life, questionnaire, hysterectomy

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INTRODUCTION

An aberrant placental attachment to the uterus is known as placenta accreta spectrum (PAS). Massive obstetric bleeding, the requirement for an urgent hysterectomy, admission to an intensive care unit, protracted hospitalization, and even maternal mortality are among the severe and frequent short-term morbidities of PAS. (1).

It is a matter of a multidisciplinary team; such cases should be delivered in excellence centers of birth that significantly improve the outcome and decrease the comorbidities. Short-term complications are well discussed in the literature however long-term complications and its effect on the quality of life especially in complicated cases with peripartum hysterectomy, sterility, sexual problems, and posttraumatic stress disorder are less investigated (2).

Long-term complications may be attributed to several factors; extensive surgical dissection with relatively long operative time may lead to extensive adhesions, scarring, nerve fiber entrapment or even denervation. Patient psychology and mental health affected by hysterectomy, sterility and her neonatal outcome (3).

Quality of life was assessed by the world health organization (WHO) quality of life-BREF (WHOQOL-Bref) questionnaire. This questionnaire could be used in the whole population and corresponds with the subjective character of QoL. It contains 26 items, divided into four domains (physical health, psychological health, social relationships, and environment) and a general QoL facet (4).

Medical counselling is the corner stone in daily practice, however there is lack of information for care provider about long-term risk and complications despite rapid rise in PAS (5). Thus, we aimed to describe the quality of life in women with PAS by using WHO questionnaire.

Materials and methods

This study was approved by Medical Ethics Committee of the Institutional Review Board of The Faculty of Medicine Assiut University, Egypt (IRB no 17101345, 26/01/2021). Informed consent was obtained from all participants according to the declaration of Helsinki. The study was registered at Clinical trial.gov (NCT04583540, 12/10/2020).

Study setting and design.

This is a cross-sectional study which was conducted at Assiut Woman's Health Hospital, Assiut, Egypt in the period between October 2020 and October 2021.

Patients' selection

Inclusion criteria

All women (aged 18-45years old) with confirmed diagnosis of PAS above 36 weeks of gestation with the following criteria: peripartum hysterectomy for PAS, complicated cesarean section (CS) without hysterectomy were recruited.

Exclusion criteria :

We excluded women with; emergency CS before confirming PAS diagnosis, preterm delivery (before 36 weeks in case of PAS), and peripartum hysterectomy for any cause other than PAS, other medical diseases that affect the quality of life, and/or postpartum depression.

Methodology

All included women were invited to hospital visit for detailed history and clinical examination. Moreover, abdominal ultrasound was performed for full fetal assessment, and duplex examination for placental invasion.

WHO questionnaire to assess Qol

After 6-8 weeks and 12 months postpartum face to face interview was conducted in the health center and the copy of WHOQOL-BREF scoring was fulfilled by patients.

The WHOQOL-Bref questionnaire was utilized to assess health status and produces a quality-of-life profile using four domain scores; the four domain scores denote an individual's perception of quality of life in each domain. Domain scores were scaled in a positive direction (i.e., higher scores denote higher quality of life).

Sample size calculation

A Sample size was calculated using G power program version 3.1.3. To detect a significant difference in mean value of quality of life between two independent groups under the study (placenta accreta developed post-partum complication and those who do not), and based on the next parameters one tailed, effect size 0.8 (largest effect size), alpha error 0.05, and power 0.95, a total of 80 women were enrolled.

Statistical analysis

Data were collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Quantitative data were expressed as mean±SD and compared with Student t test (different two means) and paired t test (between baseline and follow data). Nominal data were expressed as number (n) and percentage (%). Chi2 test was implemented on such data. Baseline and follow up WHOQOL domains were compared by paired t test. Level of confidence was kept at 95% and hence, P value was considered significant if < 0.05.

The mean scores were calculated and compared between women by pregnancy outcomes. Continuous variables were presented as mean±SD and were compared to assess for significance between groups using independent t- test and one way analysis of variance.

Results

Baseline data of studied patients (table 1):

Mean age of enrolled women was 30.86 ± 4.68 years old. A total of 38 (47.5%) women developed different forms of complications as urinary bladder injury (28.7%), ureteric injuries (2.7%), hysterectomy (15%), re-hospitalization (5.2%), and other complications (1.3%).

Baseline and follow up WHOQOL scoring based on complications (table 2):

Both groups based on complications had no difference as regards to baseline and follow up different parameters of WHOQOL scoring with except for significantly lower environment among those women with complications (31.97 ± 2.03 vs. 33.02 ± 2.12; $p= 0.02$).

Baseline and follow up WHOQOL scoring in patients in each separate group based on complications (tables 3-4):

In each separate group either with or without complications, there was significant improvement in different parameters of WHOQOL questionnaire, physical health, psychological health, social relationship, and environment.

Correlation of baseline WHOQOL with other variables (table 5):

Social relationship had significant positive correlation with number of previous CS ($r= 0.26$, $p= 0.01$) and parity ($r =0.32$, $p< 0.001$). All other correlations were insignificant ($p> 0.05$).

Discussion

It is important to note that although women with PAS differed substantially from women without PAS in their obstetric outcomes, demographics were similar and not significantly different between groups (5). In our study, we used WHOQOL-BREF survey for quality-of-life assessment in women with PAS. This is the first study to use WHOQOL-BREF survey on PAS patients.

In WHOQOL-BREF scoring the lowest scores were on the social relationship domain

(10.5%) followed by psychological health (19.7%), environmental health (22.9%) then physical health (25.7%).

Correlation between WHOQOL score with different demographic or obstetric characteristics of participants as (maternal age, gravidity, parity, gestational age, and number of previous cesarean section) showed no differences in quality of life with exception of; Social relationship domain in WHOQOL-BREF survey had positive correlation with previous cesarean section (r (p)= 0.26 (0.01)) and parity (r (p)= 32 (< 0.001).

Our results reported that mean parity of our participants were three or more; this is the same as reported by Tuzović et al. who considered the multiparity as a significant risk factor for development of PAS (6). Uterine surgery is still the main risk factor for development of PAS, The CS reported in about 100 % of our study participants with mean number of previous CS 3 or more.

Betran et al. reported a high CS rate reaching about 52 % (7), the fact that the CS is the most common risk factor for development of PAS was proved in many previous studies keeping us in the same way (8-11).

In our study, we found that (56.3%) of placenta Previa accrete women had anterior situated placenta, while the remaining PAS women (43.7%) had a placenta previa centralis. This with agreement with the study of Kumari et al. who found that most of PAS women had anterior placenta (12). A higher number of anterior placentae previa in our study may be a result from higher rate CS.

This study showed that women who had a pregnancy complicated by PAS, WHOQOL-BBRE domains are higher in the long term compared to the immediate postpartum period. During follow up, there was significant improvement in all parameters of WHOQOL scoring in comparison to baseline data.

As we mentioned above, this is the first study that evaluated the Qol in women with PAS by using WHOQOL scoring system. And yet, the study had some limitations; relatively small sample size and conducted in single center, recall bias might have been introduced since the questionnaire was completed at 6th week and 1 year after childbirth.

A further drawback was the absence of a control group. However, it is challenging to determine what makes a good control group given the special features of PAS. Other studies used complicated cesarean section as a control which is not fair as PAS patient suffer from long-term complications, however we suggest using patient who underwent peripartum hysterectomy for other reasons other than PAS as control as they also suffer from loss of fertility, long hospital admissions and family separation.

Because this was an exploratory study and the power to detect potential differences between the groups was low, care should be used when interpreting the findings. However, the results could be used as an indication for future research. Further trials should be conducted with larger sample size, more pregnancy outcomes, and different control groups with longer periods of follow up.

Conclusion

It seems that women with a pregnancy complicated by PAS, reported significant improvement almost in all domains at long-term follow- up as been evaluated by WHOQOL scoring system.

Acknowledgments

We are most grateful to Woman Health Hospital, Assiut University, Egypt for conducting this study.

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Legends of Tables

Table 1: Baseline characteristics of the studied patients

	N= 80
Age (years)	30.86 ± 4.68
Range	21-40
Class	
18-24 years	7 (8.8%)
25-34 years	52 (65%)
> 34 years	21 (26.3%)
Gestational age (weeks)	36.83 ± 0.65
Previous cesarean section	3 (1-6)
Parity	3 (1-7)
Type of placenta previa	
Anterior	45 (56.3%)
Centralis	35 (43.8%)
Bladder injury	23 (28.7%)
Ureteric injuries	2 (2.7%)
Hysterectomy	12 (15%)
Intensive care unit	14 (17.5%)
Other complications	1 (1.3%)
Re-hospitalization	4 (5.2%)
Outcome	
Complicated cases	38 (47.5%)
No- complicated cases	42 (52.5%)

Data expressed as mean (SD), frequency (percentage). **N**: number

Table 2: Baseline and follow up WHOQOL scoring based on complications.

	Complications		**P**
	Yes (n= 38)	**No (n= 42)**	
Baseline			
Physical health	25.45 ± 2.85	25.92 ± 3.06	0.47
Psychological health	19.47 ± 1.94	19.97 ± 1.89	0.24
Social relationship	10.50 ± 1.08	10.59 ± 1.17	0.70
Environment	22.84 ± 1.82	23 ± 2.08	0.72
Follow up			
Physical health	32.42 ± 1.75	32.90 ± 1.54	0.19
Psychological health	26.18 ± 1.43	26.28 ± 1.53	0.76
Social relationship	13.84 ± 1.02	13.92 ± 1.02	0.70
Environment	31.97 ± 2.03	33.02 ± 2.12	**0.02**

Data expressed as mean (SD). P value was significant if < 0.05. N: number; **WHOQOL**: world health organization-quality of health

Table 3: Baseline and follow up WHOQOL scoring in patients with complications.

	Baseline	Follow up	P value
WHOQOL scoring.			
Physical health	25.45 ± 2.85	32.42 ± 1.75	**< 0.001**
Psychological health	19.47 ± 1.94	26.18 ± 1.43	**< 0.001**
Social relationship	10.50 ± 1.08	13.84 ± 1.02	**< 0.001**
Environment	22.84 ± 1.82	31.97 ± 2.03	**< 0.001**

Data expressed as mean (SD). P value was significant if < 0.05. **WHOQOL**: world health organization-quality of health

Table 4: Baseline and follow up WHOQOL scoring in patients without complications.

	Baseline	Follow up	P value
WHOQOL scoring.			
Physical health	25.92 ± 3.06	32.90 ± 1.54	**< 0.001**
Psychological health	19.97 ± 1.89	26.28 ± 1.53	**< 0.001**
Social relationship	10.59 ± 1.17	13.92 ± 1.02	**< 0.001**
Environment	23 ± 2.08	33.02 ± 2.12	**< 0.001**

Data expressed as mean (SD). P value was significant if < 0.05. **WHOQOL**: world health organization-quality of health

Table 5: Correlation of baseline WHOQOL with other variables

	Age	Cesarean section	Parity	Gestational age	Transfused units
WHOQOL scoring.					
Physical health	-0.14 (0.18)	0.03 (0.77)	-0.08 (0.47)	0.09 (0.42)	0.01 (0.91)
Psychological health	-0.09 (0.39)	0.05 (0.60)	-0.03 (0.77)	0.04 (0.40)	0.03 (0.97)
Social relationship	0.12 (0.26)	**0.26 (0.01)**	**0.32 (< 0.001)**	0.08 (0.47)	0.01 (0.89)
Environment	-0.19 (0.07)	0.06 (0.57)	-0.09 (0.42)	-0.02 (0.85)	-0.06 (0.57)

Assessment of Pre-Procedural Anxiety and Its Impact on Pain and Difficulty of Office Hysteroscopy

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Abstract

Background: Prior medical interventions, anxiety is virtually constant presence and may affect how patients perceive pain. The aim of this work was to evaluate the correlation between pre-procedural anxiety level measured by Eysenck Personality Questionnaire (EPQ) and Taylor Manifest Anxiety Scale (TMAS) and pain score during office hysteroscopy and Assessment of difficulty of office hysteroscopy.

Methods: This Observational cross-sectional work was performed on 75 female patients with clinical criteria of Women undergo office hysteroscopy for various gynecological indications (infertility assessment, abnormal uterine bleeding, recurrent pregnancy loss, suspect uterine anomaly, suspect of endometrial pathology). Patients were subdivided into four groups according to TMAS (normal, mild, moderate and sever), three groups according to EPQ (significant, Normal and Anxiety) and also into three groups according to VAS levels (mild, moderate and sever).

Result: a statistically substantial positive correlation was existed among VAS score with difficulty of hysteroscopic procedure, with p-value ($p=0.034$ & $p<0.001$), correspondingly. There was a statistically substantial association between TAMS with main complain among all studied patients, with p-value ($p<0.05$). There is no statistically substantial association between EPQ with main complain, with p-value ($p>0.05$). There was a statistically substantial variation among main complain according to VAS level with p-value ($p<0.05$). There was a highly statistically substantial positive correlation among TAMS with EPQ and VAS score. EPQ and VAS score have insignificant correlation.

Conclusions: Pain during office hysteroscopy affected by main complaints and the difficulty of hysteroscopic procedure in terms of duration and scope introduction also pain increased by increasing anxiety score. However, no correlation was found between pain and age, or parity.

Keywords: Taylor Manifest Anxiety Scale, Eysenck Personality Questionnaire, visual analogue scale, Anxiety, Office Hysteroscopy.

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Introduction

For the diagnosis and treatment of gynecological disorders that develop in the uterus, hysteroscopy is a frequent and effective intervention. The majority of women report having a favorable hysteroscopy experience, with levels of pain they can tolerate, quick recovery, and no need for a general anesthetic. It is crucial that women believe they are capable of making authentic and informed decisions. If patients want to continue with a hysteroscopic operation, they should also state their choices for the treatment location, pain management, and anesthesia type [1].

The procedure ought to be "one-stop," meaning she is effectively cared for in just one clinic visit, wherever this is feasible and to the woman's satisfaction. Where necessary, a "see and treat" strategy should be used to help with this. Concomitant treatments include endometrial biopsy, intrauterine device placement or removal, endometrial or cervical polypectomy, removing submucosal fibroids, and division of small adhesions should be made available to the patient. Any indicated drug may also be prescribed [2].

The effectiveness of hysteroscopy, either diagnostic or therapeutic, is correlated with pain, making it more than just an issue on its own. The treatment of anxiety and its function in office hysteroscopy are still not well understood, despite their significance [3].

Using central and peripheral neurobiological processes, anxiety modulates pain in an unusual way and is a significant, underappreciated, patient-related factor that might impair procedure tolerance [4]. Pain perception may be impacted by anxiety. The correlation between anxiety as evaluated by the Taylor Manifest Anxiety Scale (TMAS) and Eysenck Personality Questionnaire (EPQ) and pain as assessed by a visual analogue scale (VAS) is positive, and stress might result in disaster (exaggerated negative orientation towards pain stimulus). There is widespread usage of these validated anxiety measures. The effect of anxiety on OH pain perception is unclear [5].

The purpose of this study was to assess the correlation between pre-procedural anxiety level measured by EPQ and TMAS and pain score during office hysteroscopy and Assessment of difficulty of office hysteroscopy.

Patients and Methods

This Observational cross-sectional work was performed on 75 female patients, with clinical criteria of infertility assessment, abnormal uterine bleeding, recurrent pregnancy loss, suspect uterine anomaly and suspect of endometrial pathology. After receiving permission from the Ethics Committee of the Maternity Hospital, Ain Shams University, the research was carried out. All patients provided written approval after being fully briefed.

Exclusion criteria were other causes of anxiety or any psychiatric diseases because it effects on the score anxiety, pelvic inflammatory disease because it leads to the spread of infection, heavy bleeding interferes with the procedure and avoids endometriosis, severe cardiovascular disease reduces the risk of heart failure and suspected pregnancy to avoid abortion.

All patients were further subdivided in to four groups according to TMAS (normal, mild, moderate and sever), three groups according to EPQ (significant, normal and anxiety) and into three groups according to VAS levels (mild, moderate and sever).

All patients were subjected to sociodemographic characteristics and routine laboratory investigations [blood tests and pregnancy tests detecting human chorionic gonadotropin (HCG)]. Anxiety was measured using TMAS and EPQ.

Eysenck Personality Questionnaire

The EPQ uses four scales to evaluate the temperamental qualities that make up personality: The component we employed in this research was N, which stands for emotionality or neuroticism (evaluated by 24 questions). P, psychoticism, or toughness of mind, was examined using 25 questions; E, extraversion, was evaluated using 20 questions; and L, lying, was evaluated using 23 questions.

Calculation of EPQ: 'Lie score' is a rating out of nine. Your responses are graded on how socially acceptable you attempt to be. Those that get a 5 or higher on this scale are likely attempting to seem good and are not being completely honest with their answers. Your extrovert level was assessed using the "E score" out of 24. The "N score," which ranged from 0 to 24, indicated how neurotic you are. The E score and the N score are displayed on a graph, allowing you to determine your personality traits from the results.

Taylor's Manifest Anxiety Scale

We are utilizing the extended version of this early instrument, which contains 49 questions, to measure anxiety state. It is developed from the Minnesota Multiphasic personality inventory (MMPI), and it is available in two formats. The Arabic translation was also used [6]. Scores between 0 and 16 are regarded as normal, between 17 and 25 as mild anxiety, between 25 and 36 as moderate anxiety, and beyond 36 as severe anxiety. The total score represents the intensity of the anxiety condition. Vaginoscopy technique which is performed by avoiding the need to introduce a speculum and a tenaculum. The Hysteroscope was conducted A rigid, 2.9 mm outer diameter with a 30 fore -oblique view. With a 0° grade optic.

Grading for assessment of difficulty of hysteroscopy[7]

Very easy: getting into the cavity with no resistance or having to withdraw the scope tip.

Easy: having to withdraw and reintroduce the scope tip once.

Equivocal: having to withdraw and reintroduce the scope tip more than once or resistance at the int. Os.

Difficult: getting into the cavity with significant patient discomfort but not to the extent to interrupt the procedure.

Failed: failure of entering the cavity or patient discomfort necessitating procedure interruption.

Sample Size Calculation

Sample Size was calculated utilizing NCSS 11.0 and according to work performed by [8] A sample size of 30 women planned to undergo office hysteroscopy achieve 95% power to determine a variance of -0.68700 among the null hypothesis correlation of 0.00000 and the alternative hypothesis correlation of 0.68700 utilizing a two-sided hypothesis test with a significance level of 0.01000.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was used for the statistical analysis. Histograms and the Shapiro-Wilks test were utilized to assess the normality of the data distribution. The mean and standard deviation (SD) of quantitative parameters were provided, and they were contrasted using a paired T-test. Chi-square test was used to compare qualitative parameters that were reported as frequencies and percentages (%). Spearman rank correlation equation: non-normal parameters/non-linear monotonic relationships. A two-tailed P value < 0.05 was considered statistically significant.

Results

Regarding personal data, mean age value was 37.47, mean parity numbers were 2, the mean abortion times was 1 and 100% of the patients have vaginoscopy method of

introduction. Regarding office hysteroscopy procedure details, the main patients complaints were infertility, bleeding, recurrent pregnancy loss, uterine anomaly, endometrial pathology. Introduction of scope was easy in 92%, difficult in 607%, and failed in 1.3%. The mean duration of the procedure was 4.59. (Table 1).

Table 1: Different parameters distribution among all study group

Parameters		Total (n=75)
Age (years)		37.47±10.83
Parity		2.00±1.00
Abortion		1.00±1.00
Method of Introduction	**Vaginoscopy**	75 (100.0%)
Office hysteroscopy Procedure details		
Main Complain	**Infertility**	15 (20.0%)
	Bleeding	15 (20.0%)
	Recurrent pregnancy loss	15 (20.0%)
	Uterine Anomaly	15 (20.0%)
	Endometrial Pathology	15 (20.0%)
Uterus	**AVF**	72 (96.0%)
	RVF	3 (4.0%)
Vision	**No**	1 (1.3%)
	Floggy	1 (1.3%)
	Dim	3 (4.0%)
	Clear	70 (93.3%)
Difficulty of Hysteroscopic Procedure		
Introduction of scope	**Easy**	69 (92.0%)
	Difficult	5 (6.7%)
	Failed	1 (1.3%)
Duration of the procedure (min)		4.59±2.97
Main Lesion	**Polyp**	24 (32.0%)
	Un-remarkable study	15 (20.0%)
	uterine anomaly	15 (20.0%)
	Endometrial Pathology	12 (16.0%)
	Tubal pathology	4 (5.3%)
	Faild	1 (1.3%)
	Mass	1 (1.3%)
	Scare niche	1 (1.3%)
	Adenomyosis	1 (1.3%)
	Adhesion	1 (1.3%)
TAMS	**0-16 Normal**	9 (12.0%)
	17-25 Mild	23 (30.7%)
	26-36 Moderate	28 (37.3%)
	Above 36 Severe	15 (20.0%)
	27.23±9.30	

EPQ	**0-11 Not significant**	17 (22.7%)
	12-17 Normal	26 (34.7%)
	17-24 Anxiety	32 (42.7%)
	15.71±5.84	
VAS Score		5.73±2.95

Data are presented as mean ± SD and numbers of (%). AVF: Arteriovenous fistulas. RVF: rectovaginal fistula. TAMS: Taylor's Manifest Anxiety Scale. VAS: visual analog scale. EPQ: Eysenck Personality Questionnaire.

There was a statistically significant association between TAMS and VAS level with main complain among all studied patients, with p-value ($p<0.05$). There is no statistically significant association between EPQ with main complain, with p-value ($p>0.05$) (Table 2).

Table 2: Association between TAMS, EPQ and VAS level with main complain among all studied patients

Main Complain		**Infertility (n=15)**	**Bleeding (n=15)**	**Recurrent pregnancy loss (n=15)**	**Uterine Anomaly (n=15)**	**Endometrial Pathology (n=15)**	**p-value**
TAMS	**0-16 Normal (n=9)**	4 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (33.3%)	FE0.034*
	17-25 Mild (n=23)	4 (26.7%)	4 (26.7%)	7 (46.7%)	4 (26.7%)	4 (26.7%)	
	26-36 Moderate (n=28)	3 (20.0%)	7 (46.7%)	6 (40.0%)	6 (40.0%)	6 (40.0%)	
	Above 36 Severe (n=15)	4 (26.7%)	4 (26.7%)	2 (13.3%)	5 (33.3%)	0 (0.0%)	
EPQ	**0-11 Not significant (n=17)**	4 (23.5%)	2 (11.8%)	1 (5.9%)	2 (11.8%)	8 (47.1%)	FE0.118
	12-17 Normal (n=26)	5 (19.2%)	6 (23.1%)	6 (23.1%)	7 (26.9%)	2 (7.7%)	
	17-24 Anxiety (n=32)	6 (18.8%)	7 (21.9%)	8 (25.0%)	6 (18.8%)	5 (15.6%)	
VAS levels	**Mild**	5 (22.7%)	3 (13.6%)	9 (40.9%)	2 (9.1%)	3 (13.6%)	0.049*
	Moderate	6 (20.7%)	6 (20.7%)	5 (17.2%)	5 (17.2%)	7 (24.1%)	
	Severe	4 (16.7%)	6 (25.0%)	1 (4.2%)	8 (33.3%)	5 (20.8%)	

Data are presented as numbers of (%). TAMS: Taylor's Manifest Anxiety Scale. VAS: visual analog scale. EPQ: Eysenck Personality Questionnaire. *Significant.

There was a highly statistically significant positive correlation between TAMS with EPQ and VAS. While EPQ and VAS score insignificant correlation. (Table 3).

Table 3: Correlation matrix between TAMS, EPQ & VAS score, using Spearman's rank correlation coefficient (rs) among all patients

		TAMS	EPQ	VAS score
TAMS	**rs**		0.711	0.304
	p-value		<0.001**	0.008*
EPQ	**rs**	0.711		0.078
	p-value	<0.001**		0.507
VAS score	**rs**	0.304	0.078	
	p-value	0.008*	0.507	

TAMS: Taylor's Manifest Anxiety Scale. VAS: visual analog scale. EPQ: Eysenck Personality Questionnaire *Significant

Discussion

Anxiety may affect pain perception. Anxiety measured by EPQ and TMAS and pain measured by VAS are positively correlated, and nervousness may lead to catastrophizing (exaggerated negative orientation toward pain stimuli). Validated anxiety scales are extensively utilized. Anxiety's influence on OH pain perception is unclear [5, 9].

Our study's findings are consistent with those of other recent investigations. According to Zayed et al. [10], out of 254 patients, 33.86% reported minimal or minor pain, 46.46% described moderate pain, 17.32% suffered severe pain, and six individuals (2.36%) had intolerable pain that required stopping the procedures. Rolim et al.'s study [5] of 252 patients revealed that mild pain (41.7%), moderate pain (29.8%), and severe pain (28.6%) were all experienced throughout hysteroscopy. According to Sorrentino et al., [3] of 104 patients who underwent office hysteroscopy, (27%) reported mild pain, (33%) reported moderate pain, and 42 (40%) reported severe pain. The STAI-Y1 and VAS showed a statistically substantial positive relationship, showing that individuals with higher state anxiety throughout hysteroscopy report pain as being more intense. Involving 75 patients, Malu et al., [11] 66% of the participants reported mild pain, 22% suffered moderate pain, and 12% suffered severe pain. The length of the process was statistically significantly correlated with pain.

In current study pain is not affected by age and parity. In contrast to the current study Campo et al. and other study [5, 9, 10, 12] found that pain affected by parity may be because using conventional Technique or number of patients.

In current study the only study that assessment of difficulty of hysteroscopic procedure by measuring the time of the procedure and failure of entering. In contrast to the current study [10-13] pain affected by procedural duration only.

In our study pain increased in subjects with a high score of anxiety. In contrast to the current study [9, 14] pain not affected by anxiety score this may because using conventional Technique or number of patients.

Conclusions

An important component of ambulatory hysteroscopy's success is overcoming anxiety. Pain during office hysteroscopy increased by increasing anxiety score also pain affected by main complaints and the difficulty of hysteroscopic procedure in terms of duration and scope introduction. However, no correlation was found between pain and age, or parity.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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Maternal Outcome in Conservative Surgery versus Hysterectomy in Placenta Accreta Spectrum

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Statement of prior presentation or publication and/or abstract/poster presentation:

The manuscript has no prior presentation or publication and/or abstract/poster presentation.

Source of funding:

The study has no funding interest

Conflict of interest Statement:

Declarations of interest none

Word count: 4498

IRB (Date & No.):

The study protocol was reviewed and approved by the Mansoura Faculty of Medicine Institutional Research Board **(Code number # MS.21.05.1510; Date: 19/06/2021).**

Short Running Title

Maternal Outcome in in Placenta Accreta Spectrum.

Abstract

Objective: to determine maternal outcome with conservative surgery versus hysterectomy in pregnant women with placenta accreta spectrum according to operative time, intraoperative blood loss, need for blood transfusion, postoperative complications, and hospital stay.

Design: prospective cross section study.

Setting: Mansoura University Hospitals.

Patients : 100 pregnant women with a diagnosis of placenta accrete spectrum who underwent conservative surgery and hysterectomy in department of obstetrics and gynecology, Mansoura University Hospitals.

Interventions: Patients were divided into two groups; group 1 (n = 50) conservative and group 2 (n =50) hysterectomy at 1:1 ratio.

Measurements and Main Results: There was a high significant difference among both groups as regard operative time, need for blood products transfusion, blood loss, hemoglobin assessment after surgery, and

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postoperative complications. In conservative group, the mean operative time (min) was 140.70 ± 54.986, packed RBCs units was 2.86 ± 1.750, plasma units were 1.62 ± 1.510, blood loss 1580 ± 321 ml, mean hemoglobin before and after surgery was 10.71 ± 0.835 and 10.12 ± 0.779 mg/dl, and none had Bladder injury. In hysterectomy group, the mean operative time (min) was 267.60 ± 48.469, packed RBCs units was 5.94 ± 2.683, plasma units were 5.22 ± 2.613, and blood loss 2343 ± 665.4 ml, mean hemoglobin before and after surgery was 10.66 ± 0.616 and 9.72 ± 0.856 mg/dl, and 10% had Bladder injury.

Conclusions: conservative surgery (preservation of the uterus) is a suitable treatment of placenta accrete spectrum especially in communities like Egypt in which women want to preserve fertility and refuse hysterectomy, but the woman must be diagnosed during pregnancy and admitted before surgery to tertiary care hospital to be operated under care of multidisciplinary team expert in dealing with this condition with possibility of hysterectomy if needed.

Keywords: Placenta Accreta Spectrum (PAS), Hysterectomy, Conservative Surgery, Maternal Outcomes, Risk Factors for PAS, Management of PA.

Introduction

Placenta accreta spectrum disorder (PAS) is described as a clinical situation where the placenta does not detach spontaneously from the myometrium after delivery of the baby and cannot be forcibly removed without causing excessive hemorrhage. The incidence of PAS is increasing worldwide mostly due to the increasing rates of cesarean section, and subsequently repeated cesarean sections (1, 2). PAS is one of the most dangerous conditions of pregnancy as it is significantly associated with maternal morbidity and mortality. Maternal and neonatal outcomes are generally improved when diagnosis is made before delivery, and the woman is managed by a multidisciplinary team in the tertiary centers (3, 4).

One of the cornerstones during the operation of PAS is to avoid any attempt to detach the placenta, either in the conservative surgery or during hysterectomy as any attempt to remove the placenta will leave some placental tissue within a deficient myometrium leading to uncontrolled severe bleeding. Leaving the placenta without separation from the myometrium is associated with decreased levels of bleeding and need for blood transfusion (4, 5).

There are many challenges facing the obstetrician when dealing with PAS. The first challenge is to define the best time of delivery to ensure maternal and neonatal outcome. Despite earlier elective cesarean section may decrease the risk of bleeding but increase the risk of prematurity and need for intensive neonatal care. Delayed delivery of the baby beyond 38 weeks or emergency delivery is associated with higher maternal complications (6, 7).

Another challenge when dealing with PAS especially in developing countries and nations which prefer large families is a loss of fertility after hysterectomy especially when this is the second pregnancy to the patient who has no living child due to death of the first baby from congenital anomalies or prematurity complications, or the patient refuses hysterectomy despite she has more than 2 children. In these cases, the counselling of the patient to do hysterectomy from the start or after trial of conservative surgery is very difficult.

Materials and Methods

A prospective cross-sectional study was conducted in department of Obstetrics and Gynecology at Mansoura University Hospitals on 108 pregnant women with placenta accrete spectrum who underwent conservative surgery and hysterectomy. The

study was approved by the Mansoura Faculty of Medicine Institutional Research Board **(Code number # MS.21.05.1510; Date: 19/06/2021)**. All pregnant women with PAS with one or more of the following risk factors had been included in this study: Patient age (18-42 years), Pregnancy: Spontaneous, in-vitro fertilization (IVF), gestational age: more than 34 weeks, Previous caesarean section, Previous placenta previa and Past history of prior uterine surgeries or curettage. Pregnant women with PAS with one of the following: vaginal bleeding, rupture uterus, Incomplete data, conversion from conservative treatment to hysterectomy and refused to participate in the study were excluded from this study.

Methods

All pregnant women more than 34 weeks with PAS admitted from outpatient clinic in obstetrics and gynecology center to obstetrics and gynecology department at Mansoura university hospital (main hospital) were subjected to the following:

A. Before admission:

1. Gravidity, parity, previous caesarean delivery, uterine surgery as myomectomy, repeated endometrial curettage and history of placenta accreta in previous pregnancy.
2. General and Abdominal examination were done.
3. Ultrasound was done to confirm abnormally adherent placenta. ultrasound findings were placenta previa, multiple placental lacunae, irregularity of bladder border, decrease myometrial thickness and loss of normal hypoechoic retroplacental space. Color Doppler finding in placenta accreta were turbulent flow in placental lacunae, increase vascularity around placental lacunae and irregular bladder wall with extensive associated vascularity.

B. After admission:

1. Basic investigations including: blood group type, CBC, liver function tests, kidney function tests and preparation for blood transfusion.
2. Informed written consent: Discussion with the patient and her husband about what is meaning by placenta accreta, management options during the operation, possibility of hysterectomy, intraoperative complications as ureteric and bladder injury, conversion from conservative surgery to hysterectomy due to bleeding and severe accretion.
3. Cross matched blood: at least 5 units RBCs, platelets, and fresh frozen plasma should be available in the blood bank.

C. Before operation:

1. Checklist of the patient file: Check the Hb level, consent either hysterectomy from the start or trial of preservation of uterus and possibility of hysterectomy if needed.
2. check the number of packed RBCs, plasma and platelets unit and availability of blood products from blood bank if needed during operation.
3. Insertion of at least 2 large intravenous lines
4. Give the patient antibiotics ceftriaxone 1gm (ceftriaxone 1000mg, Sandoz, Novartis, Switzerland) and at least 500 ml of normal saline before operation.

D. At the operating room:

1. Anaesthia: general anesthesia was the most performed, but in some selective cases spinal anesthesia was used.
2. Insertion of urinary catheter and 4 tablets of misoprostol rectally (Misotac,200 micrograms, Sigma) in conservative group only.
3. Sterilization: Abdomen was cleaned with an antiseptic (uccmadine 10% Povidone-Iodine U.S.P, UCCMA) and was covered with sterile cloths to reduce the risk of infection
4. Abdominal incision: in conservative transverse incision (Pfannenstiel incision) and in hysterectomy group midline incision was preferred.
5. Inspection of uterus after peritoneal entry to determine the level of placental invasion and placental location according FIGO Classification of PAS. **Grade 1:** abnormally adherent placenta (placenta adherent or accreta) - attached directly

to the surface of the middle layer of the uterine wall (myometrium) without invading it. **Grade 2:** abnormally invasive placenta (increta) - invasion into the myometrium. **Grade 3:** abnormally invasive placenta (percreta) invasion may reach surrounding pelvic tissues, vessels and organs (8).

6. Opening of the uterus: uterus was opened above the site suspected to be placental site. In conservative group, the incision was done in upper transverse away from placenta. In hysterectomy group, vertical incision was done in the uterine fundus then delivery of the baby.

7. If we decided to conserve the uterus:

a. We approximated the edge of uterine incision by three or four Allis forceps after delivery of the baby without trial of manual separation of the placenta.
b. Dissection of the bladder from the lower uterine segment.
c. Bilateral uterine artery ligation
d. Waiting for spontaneous separation of the placenta: After ligation of uterine arteries, we removed three or four Allis forceps from uterine incision edges then waited for spontaneous placental separation from lower uterine. If the placenta was separated spontaneously, we started to give ecbolic and closure of uterine incision in 2 layers and control bleeding from placental site by hemostatic sutures (simple suture or eight of figure suture). If the placenta was focally adherent with myometrium, we resected the myometrium with adherent placenta then repair of uterus.

8. If we decided to do hysterectomy:

a. We approximated the edge of uterine incision by three or four Allis forceps or closed the uterine incision.
b. The uterus was exteriorized and kept under upward traction.
c. The round ligaments and utero-ovarian ligaments were divided and ligated bilaterally.
d. Dissection of broad ligament alongside the uterus using monopolar diathermy
e. The bladder was dissected from lower uterine segment.
f. Uterine arteries were clamped, ligated, and divided.
g. Colpotomy was performed and removal of the uterus and the cervix (if the placenta was infiltrating it) or removal of the uterus only.
h. Closure of vaginal cuff with 2 layers of absorbable suture (1-0 vicryl sutures).

9. Intraoperative data were collected:

a. Operative time: defined as time starting with induction of anesthesia up to end of the operation.
b. Amount of blood loss (ml): we used combination of direct and gravimetric methods. We collected blood loss from a suction bottle using a suction apparatus (direct method). we calculated the amount of blood loss in the surgical towels and gauzes by weighing them before and after surgery (gravimetric method). the estimated amount of blood loss was calculated by the following formula (9):-

- Amount of blood loss in suction apparatus (in ml) = total amount of fluid in suction apparatus - amount of amniotic fluid suctioned during delivery of the baby.
- Amount of blood loss from surgical field (in ml) = weight of the collected soaked towels, gauzes, and drapes after surgery (in grams) - weight of the dry towels, gauzes, and drapes before surgery. After that, the estimated blood loss equals blood in suction apparatus plus blood in surgical field.

c. Number of packed RBCs needed during operation.
d. Intraoperative complications: bladder injury, ureteric injury, intestinal injury, and conversion from conservative management to hysterectomy.

E. At the department:

The patients were assessed after transfer

from operation to department ward:

1. Vital signs: pulse, blood pressure, and temperature every hour after surgery at the first 6 hours then every 6 hours.
2. Uterine contraction: uterine contractility and vaginal bleeding were assessed every half an hour in conservative group.
3. Hemoglobin level and need for blood transfusion.
4. Postoperative antibiotics and ecbolics.
5. Postoperative complications: vaginal bleeding, need for relaparotomy, and paralytic ileus.

Results

As shown in the study flow chart (Figure 1), Three hundred women diagnosed with low lying placenta admitted in Mansoura university hospital from June 2021 to December 2022 were assessed for eligibility to participate in the study; we excluded 192 cases not meeting the inclusion criteria. 108 cases diagnosed with PAS were divided into 2 groups. Group 1 conservative group (58 patients) then 8 patients excluded due to conversion from conservative treatment to hysterectomy. Group 2 hysterectomy group (50 patients). Therefore, data of 50 women in the conservative group and 50 patients in the hysterectomy group were subjected to final analysis.

The mean age in the conservative group was 33.52 ± 5.183, BMI was 36.69 ± 3.496, 44% were urban, 56% were rural. In the hysterectomy group, mean age was 33.66 ± 4.104, BMI was 36.45 ± 1.338, 50% were urban, 50% were rural. There was insignificant difference between both groups as regard age, BMI or residency **(Table 1).**

In conservative group the mean gestational age was 37.08 ± 0.601, Gravidity median value was 4 ranged from 3 - 6, parity median value was 3 ranged from 1- 4, abortion median value was 0 ranged from 0 - 3, 6% had previous 1 cs, 46% had previous 2 cs, 36% had previous 3 cs, 12% had previous 4 cs, 16% had D&C, 2% had myomectomy, 0% had hysteroscopy, 2% had PTL, 2% had twins, 2% had stillbirth. In hysterectomy group, mean gestational age was 36.06 ± 2.045, gravidity median value was 5 ranged from 2 - 9, parity median value was 3 ranged from 1 - 6, abortion median value was 0 ranged from 0 - 9, 4% had previous 1 cs, 26% had previous 2 cs, 44% had previous 3 cs, 26% had previous 4 cs, 18% had D&C, 6% had myomectomy, 4% had hysteroscopy, 2% had PTL, 4% had twins, 4% had stillbirth. There was significant difference among both groups regarding gestational age, history of previous 2 cs. **(Table 2)**.

In the conservative group, the mean operative time (min) was 140.70 ± 54.986, packed RBCs units was 2.86 ± 1.750, plasma units were 1.62 ± 1.510, blood loss 1580 ± 321 ml. In the hysterectomy group, the mean operative time (min) was 206.4 ± 25.29, packed RBCs units was 5.94 ± 2.683, plasma units were 5.22 ± 2.613, and blood loss 2343 ± 665.4 ml. The mean hemoglobin in the conservative group, before and after surgery was 11.71 ± 0.835 and 10.12 ± 0.779 respectively. In hysterectomy group, the mean hemoglobin before and after surgery was 11.66 ± 0.580 and 9.72 ± 0.856 respectively. There was a high significant difference among both groups as regard operative time, need for blood products transfusion, blood loss and hemoglobin assessment after surgery **(Table 3)**.

In the conservative group, the mean hospital stay (days) was 6.18 ± 0.825, none had bladder injury, or Paralytic ileus but 2% had post-partum hemorrhage and 2% had Wound sepsis. In hysterectomy group, the mean hospital stay (days) was 10.24 ± 3.25, 10% had bladder injury, 4% had Paralytic ileus, and 4% had wound sepsis and none had post-partum hemorrhage. There was high significant difference between both groups as regards hospital and postoperative bladder injury **(Table 4)**.

Discussion

Despite CS hysterectomy is the most common treatment for PAS, according to the American College of Obstetricians & Gynecologists, it carries the most serious complications as urological injuries (bladder and ureter), pelvic blood vessel injury, and loss of future fertility. Hysterectomy cannot be the first line therapy in young pregnant women with PAS who want to preserve their fertility (10).

The increasing numbers of CS lead to increase rate of PAS from 0.3% after 1 previous cs to 6.74% after five or more cs (11) . The increase rates of cs in Egypt especially in last ten years from 52 % in 2014 to 72 % in 2021 according to the Central Agency for Public Mobilization and Statistics (CAPMAS) (12) places a significant burden on young obstetricians to deal with PAS especially on women refusing hysterectomy and wanting to preserve the uterus .

The purpose of this study was to compare maternal outcomes between conservative surgery and hysterectomy for women with placenta accrete spectrum disorders during pregnancy.

Jafari et al., evaluated 68 patients with placenta accreta and compared uterine preservation to hysterectomy. Group I hysterectomy: 24 women and Group II uterine preservation: 44 women. All women 68 between the ages of 24-45 yr. (mean age of 32.88 ± 5.08 years) were multiparous and underwent cesarean section. 28 women (41.2%) had a history of dilatation and curettage. There were no significant differences between both groups regard the need for blood transfusion, operative time, hospital stay, and maternal mortality (13).

Our findings are consistent with those of Alloush et al., who evaluated 50 patients diagnosed with PAS. There was no statistical difference between different management modalities regarding to the parity, gestational age and the placental site but there was significant statistically difference according to the degree of placenta, number of cs, blood transfusion, operative time, visceral injury, and postoperative wound infection (14).

Siraj et al., evaluated 20 patients with PAS. Goup1 (10 patients): hysterectomy and Group 2(10 patients): conservative surgery. Similar to our findings, that operative time was significantly higher in the hysterectomy group (p=0.05). Conservative group had a decreased risk of complications and estimated blood loss and less blood transfusions. One bladder damage in the hysterectomy group (15).

Wang et al., evaluated 2219 women diagnosed with PAS; 398 (17.9%) had hysterectomy and 1821 (82.1%) had conservative surgery. Conservative group had less blood loss within 24 h of surgery (1518 ± 1275 vs. 4309 ± 2550 ml in hysterectomy group, p<.001). There was more received blood transfusions in hysterectomy group (p=.014). There was no significant difference between the groups in terms of bladder injury (7).

El Gelany et al. divided 102 women with PAS into 3 groups: Group A : 38 had hysterectomy, Group B: 48 had cs with cervical inversion and ligation of both uterine arteries, and Group C: 16 had the placenta left in place. Estimated blood loss and blood transfusion were significantly higher in group A than other groups. Group C had higher mean hospital stay duration (16).

Our findings are similarly consistent with those of Epstein et al., who examined 77 women with PAS, 43 had hysterectomy, 34 had conservative management. the hysterectomy group had a significantly greater estimated blood loss (2989 ml vs. 1410 ml), greater complications rate and more hospital stays (17).

Pala et al., evaluated 36 cases with PAS: Group 1 (19 patients) had conservative surgery and Group 2 (17 patients) had hysterectomy. There were significant differences in favor of conservative surgery in less blood loss (1794 ± 725 ml vs 2694 ± 893 ml), less Blood transfusion (2.7 ± 2.6 units vs 5.7 ± 2.4 units), and less operative time (64.5 ± 29 min vs 140 ± 51) (18).

Finally, in our study we found that there is significant difference among both groups as regard gestational age, previous 2 CS, placental site, operative time, Blood loss, need for blood products transfusion, hemoglobin level after surgery, hospital stays and postoperative complications.

Limitations of our study are selections of the cases with planned surgery diagnosed with PAS during pregnancy either hysterectomy or conservative surgery and exclude the cases with emergency conditions. We still do not know what is the suitable treatment to the cases with PAS presented in emergency if the patient still wants to preserve the uterus? We need more studies to fill this gap of the research in the future.

Conclusion

conservative surgery (preservation of the uterus) is a suitable treatment of placenta accrete spectrum especially in communities like Egypt in which women want to preserve fertility and refuse hysterectomy, but the woman must be diagnosed during pregnancy and admitted before surgery to tertiary care hospital to be operated under care of multidisciplinary team expert in dealing with this condition with possibility of hysterectomy if needed.

Results

Figure 1: study flowchart

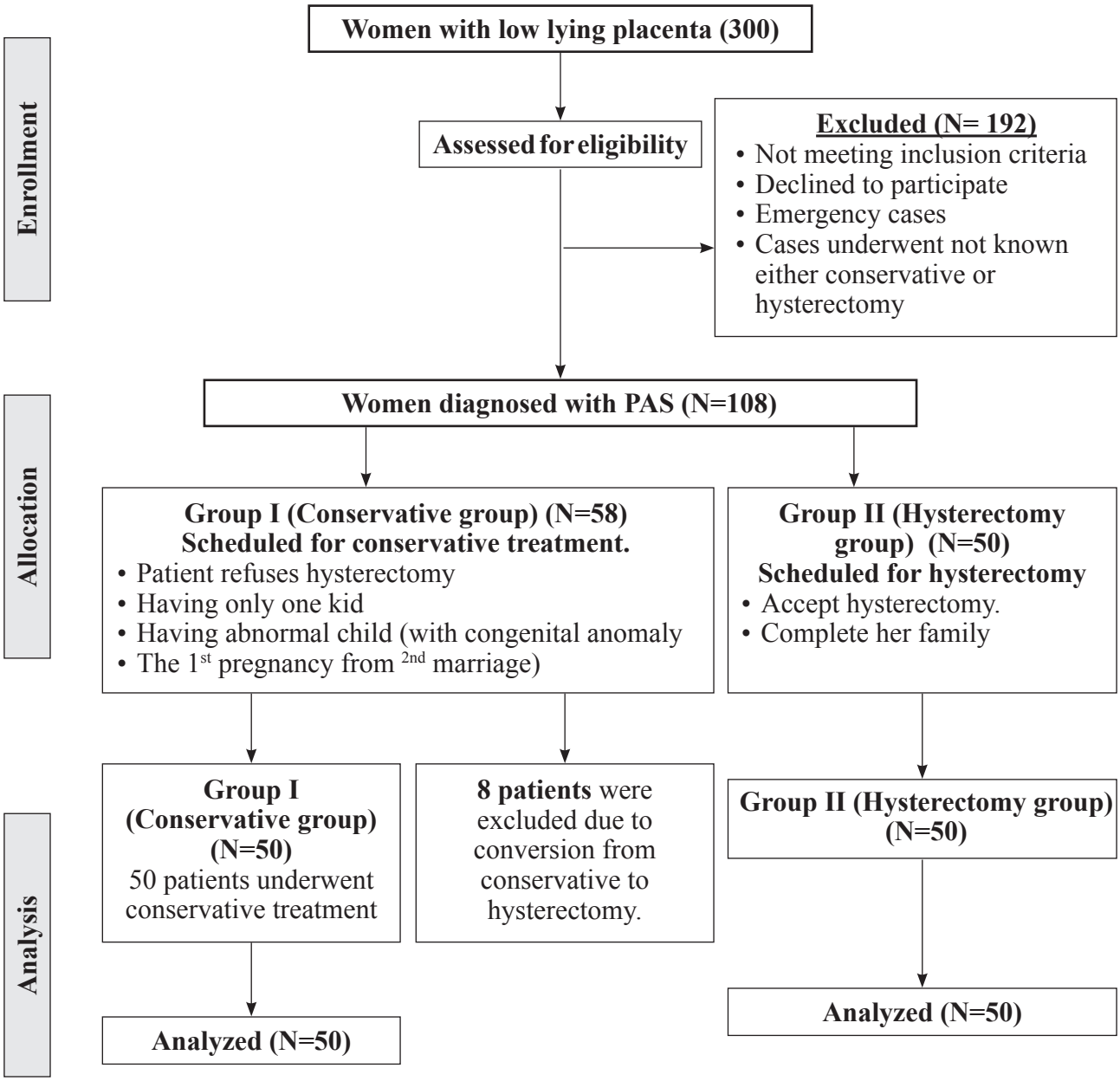

Table 1: Demographic characteristics of the studied groups:

		Conservative group (n= 50)	Hysterectomy group (n= 50)	95% CI	p-value
Age (years)		33.52 ± 5.183	33.66 ± 4.104	-2.00, 1.72	0.881
BMI		36.69 ± 3.496	36.45 ± 1.338	-0.81, 1.29	0.655
Residency	**Urban**	44.0% (22)	50.0% (25)	-	0.548
	Rural	56.0% (28)	50.0% (25)		
Data is reported as mean, standard deviation, percentage, or frequency. 95% CI: Mean difference between groups. p<0.05 is significant.					

Table 2: obstetric data of the studied patients:

		Conservative group (n= 50)	Hysterectomy group (n= 50)	p-value
Gestational age (mean ± SD)		37.08 ± 0.601	36.06 ± 2.045	**0.001**
Gravidity	median (range)	4 (3-6)	5 (2-9)	0.088
Parity	median (range)	3 (1-4)	3 (1-6)	0.097
Abortion	median (range)	0 (0-3)	0 (0-9)	0.242
History of previous CS				
Previous 1 CS		6.0% (3)	4.0% (2)	0.315
Previous 2 CS		46.0% (23)	26.0% (13)	**0.037**
Previous 3 CS		36.0% (18)	44.0% (22)	0.414
Previous 4 CS		12.0% (6)	26.0% (13)	0.074
D&C		16.0% (8)	18.0% (9)	0.790
Myomectomy		2.0% (1)	6.0% (3)	0.307
Hysteroscopy		0.0% (0)	4.0% (2)	0.153
Preterm labor		2.0% (1)	2.0% (1)	1
Twins		2.0% (1)	4.0% (2)	0.558
Stillbirth		2.0% (1)	4.0% (2)	0.558

Table 3: Maternal outcome during operation in the current study:

	Conservative group (n= 50)	Hysterectomy group (n= 50)	95% CI	p-value
Operative time (min)	140.70 ± 54.986	206.60 ± 25.29	-137, -96	**< 0.001**
Blood loss (ml)	1580 ± 321	2343 ± 665.4	-1903, - 205	**< 0.001**
Packed RBCs units	2.86 ± 1.750	5.94 ± 2.683	-3.98, -2.18	**< 0.001**
Plasma units	1.62 ± 1.510	5.22 ± 2.613	-4.45, -2.75	**< 0.001**
Hb level (gm/dl)				
Before	11.71 ± 0.835	11.66 ± 0.580	-0.24, 0.35	**0.714**
After	10.12 ± 0.779	9.72 ± 0.856	0.07, 0.72	**0.017**

Table 4: Postoperative outcome in the studied groups:

	Conservative group (n= 50)	Hysterectomy group (n= 50)	95% CI	p-value
Bladder injury	0.0% (0)	10.0% (5)	5.32	**< 0.001**
Wound sepsis	2.0% (1)	4.0% (2)	0.344	**0.558**
Paralytic ileus	0.0% (0)	4.0% (2)	2.041	**0.153**
Post-partum hemorrhage	2.0% (1)	0.0% (0)	1.010	**0.315**
Hospital stay (days)	6.18 ± 0.825	10.24 ± 3.25	-6.06, - 4.06	**< 0.001**

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The Effect of Oral Isosorbide Mononitrate Therapy on Umbilical Artery Doppler Resistance Index in Pregnancies with Intrauterine Growth Restriction: A Prospective Randomized Control Trial

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Abstract

Background: There is no clear evidence that any intervention improves the growth of growth limited fetuses in healthy pregnant women. In limited, randomized trials, a variety of therapies have been tested, including maternal nutritional supplementation, interventions to enhance blood flow to the placenta, such as low-dose aspirin, bed rest, and anticoagulation. The use of nitric oxide (NO) donors such isosorbid mononitrate appeared promising and was being researched.

Objective: Evaluation of the efficacy and tolerability of isosorbide mononitrate in reducing umbilical artery Doppler resistance index.

Methods: This randomized controlled trial included 46 pregnant women who had early onset fetal growth restriction. They were randomly assigned into two groups were group A received Isosorbide-5-mononitrate (Imdur®, 30 mg) and group B received Osteocare ®. Both were taken twice daily for 4 to 6 weeks them umbilical artery Doppler resistance index, fetal growth was compared before and after treatment.

Results: Mean umbilical artery Doppler resistance index was statistically significant improved in isosorbide mononitrate group 0.81 ± 0.02 versus 0.75 ± 0.05, before and after treatment respectively with a mean decrease of 0.06. In the isosorbide mononitrate group, the mean EFW is 1113.22 gm before treatment that is increased to 1419.78 gm after treatment, showing an increase in weight by 27.538 %. Also, the mean gestational age at delivery was statistically non-significant difference between the two groups where in group A it was 36.75 weeks ± 0.8 while in group B 36.25 weeks ± 0.95.

Conclusion: NO donor plays no role in the therapy of FGR with minor Doppler alterations and maternal side effects. It had a minor positive effect on the umbilical artery Doppler and placental circulation.

Keywords: Isosorbide Mononitrate; Umbilical Artery Doppler; Intrauterine Growth Restriction.

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Introduction

Intrauterine growth restriction (IUGR) occurs when a foetus is unable to grow to its genetically determined potential size. This definition excludes fetuses that are small for gestational age (SGA) but not pathologically tiny. Weight increase that is at or below the 10th percentile for all foetuses at that gestational age is defined as SGA. Not all SGA foetuses are pathologically stunted; in fact, some may be constitutionally small.[1]

Nearly 40% of all foetuses with growth at or below the 10th percentile face perinatal death, which may be preventable. Another 40% of these foetuses are of average size. Because this diagnosis can only be made with certainty in infants, many healthy foetuses with SGA will be subjected to high-risk operations, which may result in iatrogenic prematurity.[2]

The remaining 20% of SGA foetuses are essentially small due to genetic or environmental factors. Examples include fetuses with trisomy 18, CMV infection, or foetal alcohol syndrome. Prenatal intervention is less likely to benefit these foetuses, and their prognosis is most strongly linked to the underlying cause.[3]

FGR can be caused by intrauterine infections and chromosomal abnormalities (Trisomy 13, 18, and 21). (STORCH). As potential causal reasons, a foetal karyotype, maternal serology for infectious processes, and a history of environmental exposure can all be considered.[4]

However, the more common cause of FGR is extrinsic (utero-placental) insufficiency, in which the fetus' nutrition and gastric exchange are insufficient to support its growth in utero. This process can also be caused by a dysfunctional oxygen delivery system caused by maternal vascular disease (e.g., chronic or pregnancy-related hypertension, diabetes with vascular disease, autoimmune disease causing vasculopathy, thrombophilia, chronic placental abruption, cord & placental agenesis). Cyanococcal heart disease, hemoglobinopathies, smoking, substance addiction, and autoimmune disorders that produce vasculopathy are examples of these ailments.[5]

In growth-restricted foetuses with severe impairment of umbilical artery (UA) blood flow, adverse outcomes such as intrauterine foetal death and neonatal death, as well as increased neonatal morbidity such as hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, and RDS, are more likely to occur.[6]

Furthermore, epidemiological studies have shown that FGR foetuses are predisposed to the development of metabolic syndrome in adults as well as cognitive impairment in children (e.g., obesity, diabetes, coronary artery disease, and stroke).[7]

The trophoblast produces nitric oxide (NO), a potent venous and arterial vasodilator that also inhibits platelet aggregation, during a healthy pregnancy. In FGR-complicated pregnancies, placental hypoxia and endothelial dysfunction are associated to decreased NO release and increased phosphodiesterase type 5 (PDE-5) activity. As a result, the NO donor isosorbide mononitrate and the PDE-5 inhibitor sildenafil citrate can prevent and treat FGR.[8]

L-arginine is a substrate for the nitric oxide synthases (NOS) that produce nitric oxide (NO). It is produced by vascular endothelial cells and diffuses into neighboring vascular smooth muscle cells to increase the concentration of the second messenger cyclic guanosine monophosphate (cGMP), causing the smooth muscle to relax.[9]

The study's idea was that oral isosorbide mononitrate might offer advantage in reducing umbilical artery Doppler indices in pregnancies with intrauterine growth restriction.

METHODS

This randomized controlled trial was registered on clinicaltrial.gov with the following ID: NCT05800938. Before the study began, the Faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC) granted ethical permission with the following number MS 382/ 2022 and all subjects provided verbal agreement.

It was conducted in Obstetrics and Gynecology Department at Ain Shams University Maternity Hospital from February 2022 till February 2023. This study included 46 pregnant women attended outpatient clinic with FGR for routine antenatal care.

Inclusion criteria

Pregnant women aged 18-35 years old had BMI ranged between 18-30 kg/m2, with singleton pregnancy, gestational age between 28-30 weeks, reactive nonstress test (NST) and all criteria of FGR were enrolled.

Exclusion criteria

Women with multifetal pregnancy, known or suspected chromosomal or structural anomalies or had a condition required urgent delivery as preeclampsia, persistent reversed a-wave of the ductus venosus with gestational age $\geq$ 30 weeks or fetal surveillance tests indicated fetal compromise (eg, nonreactive NST, poor fetal heart rate baseline variability, persistent late decelerations, oligohydraminos, or BBP score < 4) were excluded.

Randomization

Women who met the inclusion criteria and gave their agreement were randomly allocated to one of two groups. Forty sex opaque envelopes were serially numbered, and the appropriate letter, which designated the assigned group, was placed in each envelope according to a randomization table. The envelopes were then sealed and placed in a single box. MedCalc version 13 was used to build a computer generated randomization sheet.

Allocation and concealment

A computer-generated randomization sheet using MedCalc version 13 was used to assign women to the research. A total of 46 envelopes were serially numbered, and the appropriate letter denoting the assigned group was placed in each envelope according to the randomization table. The envelopes were then sealed and placed in a single box. When the first patient arrived, who opened the first envelope, and the patient was assigned based on the letter inside, and so on.

Blinding

The study was double-blinded, where neither the researcher, nor the participants knew what type of medication each participant received, as a nurse gave each patient a closed envelope containing 21 tablets of one of the two medications in a randomized fashion.

Ethical considerations

Before the beginning of the study, ethical approval from faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC) was obtained with the following number MS 382/ 2022 and consents from all the participants were obtained.

Before being enrolled into the study, the patient consented to participate after explanation of study interventions to her. Only the patient initials were recorded in the case report form. Protocol approval was obtained from ethical committee of OB/GYN department.

Study procedures

Patients were randomized into one of the following two groups; group A received (IMDUR®, 30 mg, tablet, AstraZeneca, Egypt) (Isosorbide-5-mononitrate Biphasic) twice daily for 4-6 weeks and group B (n=23) received (Osteocare®, tab, VITABIOTICS, Egypt) twice daily for 4-6 weeks.

All women who met the inclusion criteria were completely assessed. This assessment included full history taking with special

emphasis on factors for FGR as maternal age, previous stillbirth, previous SGA fetuses, cocaine intake, cigarette smoking, and maternal diseases as preeclampsia.

Complete clinical examination was done with special emphasis on local abdominal examination; symphysio-fundal height (measured from fundus {variable point} to symphysis pubis {fixed point} with centimeters values).

Investigations included blood pressure measurement, urine dipstick, CBC, KFTs, LFTs and coagulation profile.

Ultrasound was performed for basic fetal biometry as estimated fetal weight (EFW) using Hadlock's formula, liquor and placental assessment.

The same operator performed umbilical artery Doppler using a Samsung HS 60 ultrasound scanner with a 3.5-MHz convex probe. It was done with the patients in semi-Fowler position, during a period of absent fetal movement and breathing. A minimum of three uniform Doppler waveforms were measured.

Fetal wellbeing was done including a biophysical profile (BPP) that is a test that combines a nonstress test with ultrasound to check the health of the fetus.

A course of antenatal corticosteroids was given to pregnancies in the week before preterm delivery is anticipated (<34 weeks).

When fetal surveillance tests indicated, fetal compromise delivery was considered and taken by expert supervisors. Patients were assessed for properly taking their medication in the right dose or development of any maternal side effects.

Study outcomes

Primary outcome was reduction in umbilical artery Doppler resistance index. Secondary outcomes were enhancement of fetal growth as measured by the increase in estimated fetal weight (EFW) and abdominal circumference (AC), in percentiles, development of fetal complications as IUFD, fetal distress and deterioration of Doppler indices requiring delivery, interval to delivery and maternal side effects caused by the medication such as headache, palpitations and postural hypotension.

STATISTICAL ANALYSIS

The statistical software for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the collected data. The quantitative data was presented in the form of mean, standard deviation, and ranges. Qualitative variables were also given numerically and as percentages. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the data for normality.

RESULTS

Table 1: Comparison between Group A and Group B according to baseline characteristics.

Baseline characteristics	Group A (n=23)	Group B (n=23)	t-test	p-value
Age (years) Mean±SD Range	28.83±4.66 22-35	27.00±5.33 18-36	1.237	0.223
BMI (kg/m^2) Mean±SD Range	28.26±5.03 20-38	26.04±4.54 19-37	1.570	0.124
Gestational age (wks) Mean±SD Range	30.00±0.67 29-31	30.13±0.97 28-33	0.530	0.599

Table 2: Comparison before treatment and after treatment according to umbilical artery Doppler resistance index, estimated fetal weight and abdominal circumference in group A

Variable	Group A (n=23)		Paired Sample t-test		
	Before treatment	After treatment	MD±SE	t-test	p-value
Umbilical artery Doppler resistance Index					
Mean±SD	0.81±0.02	0.75±0.05	0.06±0.01	6.005	<0.001**
Range	0.75-0.85	0.68-0.85			
Estimated fetal weight					
Mean±SD	1113.22±176.42	1419.78±209.30	306.6±40.20	7.626	<0.001**
Range	950-1590	1030-1760			
Abdominal circumference					
Mean±SD	212.48±11.06	248.43±17.03	36.0±3.74	9.617	<0.001**
Range	190-240	210-280			

Table 3: Comparison before treatment and after treatment according to umbilical artery Doppler resistance index, estimated fetal weight and abdominal circumference in group B

Variable	Group A (n=23)		Paired Sample t-test		
	Before treatment	After treatment	MD±SE	t-test	p-value
Umbilical artery Doppler resistance Index					
Mean±SD	0.79±0.03	0.77±0.04	0.02±0.01	2.025	0.055
Range	0.75-0.85	0.71-0.85			
Estimated fetal weight					
Mean±SD	1163.48±176.82	1339.78±248.46	176.3±46.03	3.830	<0.001**
Range	966-1490	980-1760			
Abdominal circumference					
Mean±SD	216.78±7.54	237.22±17.35	20.4±3.00	6.806	<0.001**
Range	200-237	210-275			

Table 4: Comparing the outcomes between the two groups after treatment

Umbilical artery Doppler	Group A (n=23)	Group B (n=23)	T-test	p-value
Mean+SD Range	0.75±0.05 0.88-0.85	0.77±0.04 0.71-0.85	1.359	0.181
Estimated Fetal weight				
Mean+SD Range	1419.78±209.30 1030-1760	1339.78±248.46 980-1760	1.181	0.244
Abdominal circumference				
Mean+SD Range	248.43±17.03 210-280	248.43±17.03 210-280	2.213	0.032

Table 5: Comparison between Group A and Group B according to incidence of IUFD, fetal distress and deterioration of Doppler indices requiring delivery

	Group A (n=23)	Group B (n=23)	x^2	p-value
IUFD	0 (0%)	0 (0%)	--	--
Fetal distress	0 (0%)	0 (0%)	--	--
Deterioration of Doppler indices requiring delivery	0 (0%)	3 (13.0%)	3.209	0.073

Table 6: Comparison between Group A and Group B according to side effects

Side effects	Group A (n=23)	Group B (n=23)	x^2	p-value
Headache	7 (30.4%)	0 (0.0%)	8.066	0.005*
Palpitation	2 (8.7%)	0 (0.0%)	2.047	0.153
Postural hypotension	2 (8.7%)	0 (0.0%)	2.047	0.153
Overall all side effects	11 (47.8%)	0 (0.0%)	14.133	<0.001**

Table 7: Comparison between Group A and Group B according to interval to deliver

Interval to delivery	Group A (n=23)	Group B (n=23)	T-test	p-value
Mean+SD Range	36.75 ± 0.8 36.2 - 37	36.25 ± 0.95 35 - 36.5	-1.931	0.060

Discussion

The same findings were reported in a randomized controlled trial comparing isosorbide mononitrate to sildenafil citrate in pregnancies complicated by FGR by Abd El Fatah et al. The results showed that isosorbide mononitrate 30 mg twice daily is as effective as sildenafil citrate 50 mg twice daily in lowering the umbilical artery Doppler resistance index (RI), thereby improving fetal growth in FGR pregnancies and lowering overall perinatal morbidity and mortality caused by iatrogenic prematurity or FGR itself.[10]

Similar findings were observed in NO donor (L-Arginine) trials, emphasizing the relevance of NO in pregnancy and fetal growth, and how its deficit contributes to the development of asymmetrical FGR; hence, supplementing improves fetal growth. According to Singh et al, Xiao et al, and Sieroszewski et al, maternal L-Arginine supplementation raises NO levels, which results in a moderate reduction in systolic/end-diastolic velocity ratio (S/D ratio) on doppler blood flow research, and hastened fetal growth.[11-13]

Furthermore, Chen et colleagues found that NO donor (L-Arginine) enhanced birth weight and delayed gestational age at labor in IUGR fetuses.[14]

The current study, on the other hand, compares the intervention group to a placebo (using calcium supplementation) and finds that the improvement in umbilical artery Doppler resistance index was statistically non-significant (P= 0.181). The same was true for EFW enhancement, where the increase was suboptimal when compared to the growth curve at this gestational age and did not achieve a significant value (P= 0.244). In contrast to the statistically significant (P= 0.032) improvement in AC measurement. Furthermore, the mean gestational age at delivery was statistically non-significantly different between the two groups, with group A having 36.75 weeks 0.8 and group B having 36.25 weeks 0.95 (P= 0.060).

Unlike Dastjerdi et al, who wanted to know if isosorbide mononitrate and sildenafil

citrate affected uteroplacental perfusion. Forty-one pregnant women with proven intrauterine growth retardation at 24-37 weeks of gestation were investigated in a randomized double-blind, placebo-controlled experiment. They discovered that patients with FGR-complicated pregnancies who got a single dose of sildenafil citrate (50 mg) plus isosorbide improved significantly in umbilical artery Doppler indices 2 hours after receiving the medication.[15]

Lampariello et al conducted a study on the basis of the dual activity of NO, vasodilation, and GH-RH induction, 43 pregnant women were treated from the 30th week of gestation with L-arginine (Bioarginina, 6 g per os/day), diagnosed by ultrasonic examination and evaluation of Doppler velocimetry values. They reported that 32 individuals improved their clinical course of pregnancy: 19 recovered the entire retardation; 9 recovered in one week; and 4 had premature birth after 36 weeks with fetal weight matching gestational age.[16]

Schleussner et al investigated the efficacy of the NO-donor PETN for secondary prevention of IUGR, PE, and preterm birth in high-risk pregnancies. A prospective, randomized, placebo-controlled, double-blind trial of 111 women with impaired placental perfusion at 19-24 weeks of gestation (w.o.g.) was conducted. They disagreed with us, reporting that pentaerithrityl-tetranitrate greatly reduced the chance of IUGR and/or perinatal death, as well as IUGR. Preterm birth before 32 weeks of gestation was lowered, but not the risk of PE. There were no placental abruptions in the PETN group, but five in the placebo group. These findings suggested that secondary prevention of unfavorable pregnancy outcomes by PETN would be feasible in pregnancies with aberrant placentation.[17]

Thaler et al. reported contradictory evidence on isosorbide mononitrate. In 23 women with pregnancy-induced hypertension (PIH), they studied the effect of isosorbide dinitrate (ISDN) on maternal and fetal circulation. A randomized double-blind design was used. Each lady was given either an ISDN (5 mg) sublingual tablet or a placebo. For a total of 20 minutes, maternal blood pressure (BP) and heart rate (HR) were recorded before and every 2 minutes following the treatment or placebo. Using pulsed Doppler ultrasonography, flow velocity waveforms in the uterine and umbilical arteries were obtained at the same time intervals. In those arteries, the peak systolic to end-diastolic flow velocity ratio (S/D) was measured. After ISDN, mean maternal blood pressure dropped from 103 6 1.8 mm Hg to 90.5 6 2.9 mm Hg at 14 minutes (P.0001), but mean maternal heart rate increased from 97.3 6 3.8 beats/min to 115.7 6 3.5 beats/min at 12 minutes (P.0001). At 8 minutes, the mean S/D in the umbilical artery decreased from 3.07 6 0.33 to 2.58 6 0.23 (P.0007). At 10 minutes, the mean S/D in the uterine artery decreased from 3.27 6 0.6 to 2.38 6 0.28 (P.0001). Seven of the twelve women who had an early diastolic notch in their uterine artery flow velocity waveform saw the notch reduce or disappear within the first six minutes after taking the medicine. The placebo group showed no significant change in any of the evaluated measures. Their discovery that ISDN affected maternal and fetal hemodynamics in PIH lends credence to additional research into nitric oxide donors in the treatment and prevention of pregnancy-induced hypertension.[18]

The overall side effects of Isosorbide Mononitrate (Group A) were recorded in 11/23 (47.8%). Headache was the most prevalent side effect (7/23 (30.4%), followed by postural hypotension 2/23 (8.7%) and palpitation 2/23 (8.7%). These adverse effects were minor and did not necessitate a treatment interruption.

There were also no statistically significant differences between study groups in terms of IUFD, fetal distress, deterioration of Doppler indices necessitating delivery, and interval

to delivery, with p= 0.130, 0.32, 0.073, and 0.060, respectively.

In contrast to Chen et al., who reported higher incidences of delayed delivery. Chen et al. confirmed our findings in instances of IUFD.[14]

CONCLUSION

NO donor has no role in management of FGR with mild Doppler changes and associated with maternal side effects. It had mild improving effect on umbilical artery Doppler and placental circulation.

ACKNOWLEDGMENTS

Authors would like to thanks to Ain Shams University and the patients recruited in the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Comparison of the efficacy between ultrasound measurement of cross-sectional area of the umbilical cord and Hadlock's formula in the prediction of neonatal birth weight at term gestation: cross-sectional study

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Abstract

The accurate calculation of birth weight at term gestation is critical in labor and delivery management. Hadlock's formula is the most commonly used ultrasonic approach, but it is still prone to error.

Aim: To evaluate the efficacy and accuracy of ultrasound assessment of umbilical cord cross-sectional area to Hadlock's formula in predicting birth weight at term gestation.

Patients and Methods: This cross-sectional study comprised 220 pregnant women with an uncomplicated, singleton pregnancy and a gestational age of 37 to 41 weeks + 6 days who were admitted with early labor or were scheduled for elective cesarean section. All women had EFW using Hadlock's formula (HC, BPD, AC, and FL), as well as measurement of the cross-sectional area of the umbilical cord, umbilical arteries, and umbilical vein within one cm of the umbilical cord's insertion into the fetal abdomen, and the results were compared to neonatal birth weight.

Results: There was a significant positive correlation between measurement of EFW using Hadlock's formula and umbilical cord and its components when compared to birth weight (P= 0.001). The correlation strength of the umbilical cord with the birth weight was higher than that by Hadlock's formula with the value of coefficient of determinant R2= 0.493 for umbilical cord area versus R2= 0.274 for Hadlock's.

Conclusion: The cross-sectional area of the umbilical chord predicted birth weight more accurately. This study's normalcy metrics can be used as a reference for future studies that may associate such characteristics with embryonic growth problems.

Keywords: umbilical cord, Hadlock's formula, estimated fetal weight, neonatal birth weight.

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Introduction

Estimating songoraphic fetal weight is an important aspect of routine work in obstetric departments. Accurate fetal weight assessment would aid in the proper management of labor and delivery, as well as the avoidance of difficulties associated with both low and high fetal weight at the time of birth, as well as the reduction of perinatal morbidity and mortality (1).

In recent years, the prevalence of fetal macrosomia and the risks it poses to both mother and child has steadily increased. Prolonged second stage of labor, major maternal birth canal injuries, postpartum hemorrhage, and fetal delivery traumas such as shoulder dystocia, brachial plexus paralysis, and clavicular fracture are common concerns (2). On the other hand, identifying fetuses with growth restriction is critical in order to reduce perinatal hazards such as intrauterine fetal death (IUFD) and newborn morbidity (3).

In current obstetrics, the two main methods for predicting birth weight are: (a) clinical examination based on abdominal palpation of fetal body parts using Leopold's maneuver and calculation based on fundal height, and (b) ultrasound measurement of skeletal fetal parts that are then inserted into equations to calculate estimated fetal weight (1). Although the clinical approach is straightforward, easy, and inexpensive, it is the oldest method, and its utility has been questioned because it is subjective (1).

The accuracy of employing several ultrasound parameters to estimate fetal weight is receiving increasing attention. Multiple fetal parameters are used to predict fetal weight. Hadlock's formula, which includes fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) (4), is the most widely used formula. Despite developments in ultrasound technology for acquiring fetal biometric data, there is still an error range of 6 to 11% depending on the factors collected and the equation employed for estimation (5,6).

Researchers have attempted to enhance ultrasound-based fetal weight prediction through a variety of ways, including evaluation of fat deposition at multiple places, the use of three-dimensional ultrasound equipment, and more advanced bioinformatics processing systems. None of them have gained traction, and ultrasound approaches that account for subcutaneous fat thickness have not been shown to increase our capacity to reliably estimate fetal weight using equations derived from standard biometric factors (5,6).

Improved ultrasound techniques for assessing the diameter of the umbilical cord and its components have resulted in more advanced perinatal diagnostics over the last decade. Heavier neonates have a bigger umbilical cord circumference at birth, according to research (7).

The umbilical cord is physiologically and genetically part of the fetus and contains two arteries and one vein buried within Wharton's jelly (8). It has been found that umbilical cord diameter has a linear association with fetal growth. However, situations such as prenatal and umbilical cord anomalies, polyhydraminos, and oligohydraminos may influence this measurement. Furthermore, maternal illnesses such as hypertension, diabetes, and anemia may influence umbilical cord diameter (9).

The diameter of the umbilical cord is determined by the amount of Wharton's jelly present; a short diameter is suggested by insufficient nutrition and a lack of glycogen in fetal tissues, as well as a tiny amount of Wharton's jelly. Males are said to have more Wharton's jelly than females, and excellent eating increases the amount. It tends to decrease with gestational age and may disappear in pregnancies that last longer than 40 weeks (10).

The hypothesis of this study is that the cross sectional area of the umbilical cord

may provide an advantage over the usual Hadlock's formula for accurate estimation of real birth weight at term gestation, hence preventing a substantial number of maternal and newborn deaths and morbidities.

Patients and methods

This cross-sectional study has been registered on clinicaltrials.gov as NCT 05362175. From July 2021 to May 2022, it was held in the Obstetrics and Gynecology Department of Ain Shams University Maternity Hospital. This study comprised 220 women with an uncomplicated singleton pregnancy, term gestation (37 to 41+6 weeks), who were admitted to the hospital in early labor or for elective cesarean delivery. Intrauterine fetal death, structurally malformed fetus or umbilical cord, multiple pregnancies, oligohydramnios or polyhydramnios, uterine fibroid, abnormal Doppler flowmetry of umbilical artery, and presence of maternal diseases (Diabetes mellitus, Hypertensive disorders, renal diseases, ischemic heart diseases) were all exclusion criteria.

Before the study began, the Faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC) granted ethical permission with the following number MS 488/2021 and all subjects provided verbal agreement.

A comprehensive history is taken from each patient, followed by a computation of gestational age based on the last menstrual cycle if reliable or an early dating ultrasound, followed by a general and abdominal examination. Ain Shams University Hospital's Fetal Medicine unit performed obstetric ultrasonography utilizing a Samsung HS 60 ultrasound scanner with a 3.5 MHz convex probe. The ultrasound was performed first to discover any of the study's exclusion criteria.

Fetal weight estimation is done automatically by software in the ultrasound scanner using the standard Hadlock's formula. Aside from the cross sectional area of the umbilical cord, the umbilical arteries and veins were measured in a plane adjacent to the insertion into the fetal abdomen within a maximum distance of 1 cm. Using the image's greatest magnification, place the markers at its outer edges (Figures 1 and 2). Wharton's jelly surface cross sectional area was calculated by subtracting the cross sectional area of the vessels from that of the umbilical cord. Actual birth weight = 7.276X umbilical cord cross sectional area + 1785.996 (11).

Depending on the technique of delivery, the patients were directed to the labor ward or the operating theater. Following delivery, the following items were collected: neonatal birth weight assessed during the first hour using a digital weighted scale calibrated in kilos (LAICA PS3004), gender, Apgar score, and method of delivery.

Sample size justification:

The required sample size was estimated using NCSS, LLC's Power Analysis and Sample Size software (PASS) version 11.0.10 (Kaysville, Utah). The key outcome measure is the correlation between the anticipated fetal weight (EFW) or cross sectional area of the umbilical cord and the actual birth weight (ABW). According to (11), the expected correlation coefficient between cross sectional area of umbilical cord and neonatal birth weight (r) =0.44 and between Hadlock's formula and neonatal birth weight (r) =0.62 will require a sample size of 220 women to detect a difference between two correlation coefficients with power =80% and x- error =0.05 (12).

Statistical Methods

The Statistical Package for Social Sciences (SPSS) version 20 was used to analyze the data. The categorical data was provided in the form of frequency and percentage tables. The continuous variables were provided in the form of averages, standard deviations, medians, and ranges. Pearson's correlation test was performed to examine the relationship

between fetal birth weight and According to earlier research, the link between fetal weight estimated by Hadlock's formula and umbilical cord area was weak when the coefficient of correlation (r) (0 - 0.3), moderate when (r= 0.3 - 0.7), and significant when (r>0.7) (11). Simple linear regression was used to compute regression formulas and the coefficient of determinant (R2). P-value: P>0.05 indicates nonsignificant (NS), P0.05 indicates significant (S), and P0.01 indicates highly significant (HS).

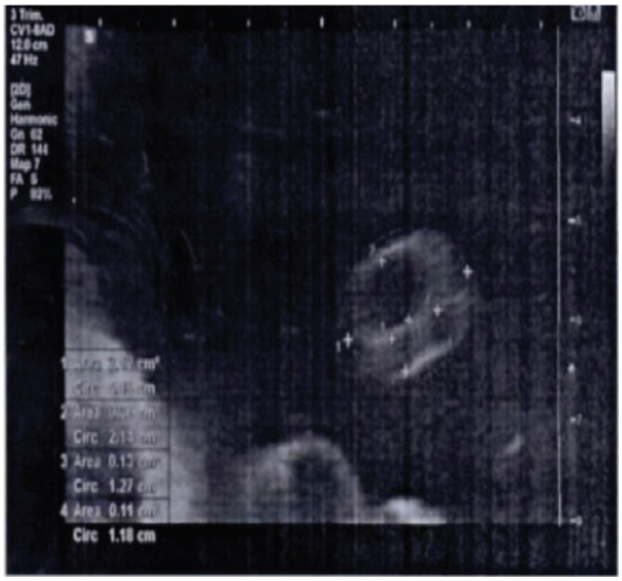

Figure 1 and 2: Measurement of the umbilical cord cross sectional area, umbilical arteries, and umbilical vein.
Fetal Medicine Unit, Ain Shams University Maternity Hospital.

RESULTS

A total of 250 women with uncomplicated singleton pregnancy were assessed for eligibility. Of those 30 were excluded due to diagnosis of fetal structural anomalies or single umbilical artery or presence of amniotic fluid abnormality. 220 were enrolled in the study.

Table (1): Initial Characteristics of the participants.

		Mean	±SD
Age (Yrs.)		28.66	7.51
Weight(kg)		85.25	12.37
Gestational age(weeks)		38.90	1.16
Parity	P0	52	23.6%
	P1-2	117	53.2%
	P>2	51	23.2%
Abortions	None	169	76.8%
	=<2	43	19.5%
	>2	8	3.6%
Prev. CS	None	117	53.2%
	=<2	78	35.5%
	>2	25	11.4%
Livings children	None	52	23.6%
	=<2	119	54.1%
	>2	49	22.3%

Conclusion

Patients' characteristics are summarized in Table (1) where the mean age of the participants was 28.6 ± 7.5 years, the mean weight was 85.3 ± 12.4 Kg, and the mean gestational age at delivery was 38.9 ± 1.2 weeks. About 24%, 77%, 53.2% and 24% of cases were P0, had no previous abortions, No previous caesarian and no children respectively.

Table (2): Description of US measurements of BPD, FL, AC, HC, and EFW (1) using Hadlock's formula and umbilical cord diameter, umbilical arteries, umbilical vein, Wharton's jelly and EFW (2) using regression equation.

	Mean	±SD	Minimum	Maximum
BPD (cm)	9.04	0.45	6.50	10.60
FL(cm)	7.29	0.38	6.39	8.80
AC(cm)	32.83	2.21	21.50	40.10
HC(cm)	32.52	1.74	27.90	39.30
EFW(1) kgs	3.16	0.41	2.20	4.57
A1(mm^2)	179.63	45.24	106.00	310.00
A2 (mm^2)	53.17	18.48	22.00	115.00
A3(mm^2)	16.74	6.14	6.00	42.00
A4(mm^2)	13.17	5.20	6.00	31.0
Wharton`s jelly area (mm^2)	96.55	34.30	20.0	205.00
EFW(2) kgs	3.09	0.33	2.50	4.04

The estimation of fetal weight (EFW) is shown in Table (2) according to Hadlock's formula with average 3.19 kg ± 0.41 kg, through measuring of biparital diameter (BPD), femur length (FL), abdominal circumference (AC), and head circumference (HC) with mean values of 9.04 ± 0.45 cm, 7.29 ± 0.38 cm, 32.83 ± 2.21 cm, 35.52 ± 1.74 cm respectively. While according to the regression equation for the cross sectional area of the umbilical cord with average weight 3.09 ± 0.33 Kg, through measuring of umbilical cord cross sectional diameter, umbilical vein, umbilical arteries, and Wharton's jelly area with mean values of 179.63±45.24 mm^2,53.17±18.48 mm^2,16.74±6.14 mm^2,13.17±5.20 mm^2,96.55±34.30 mm^2 respectively.

Table (3): Description of neonatal birth weight, Apgar score, gender and mode of delivery among cases

		Mean	±SD	Minimum	Maximum
Actual birth weight		3.03	0.45	2.00	4.70
APGAR Score		7.82	0.81	3.70	9.10
Gender	Male	110	50.0%		
	Female	110	50.0%		
Delivery mode	A.V.D	6	2.7%		
	S.V.D	89	40.5%		
	LSCS	125	56.8%		

Table (3) summarizes the outcomes, where the mean birth weight was 3.03 ± 0.45 Kg with 50% were males and 50% females. 125 (56.8%) had been delivered by cesarean section, 89 (40.5%) delivered spontaneous vaginal delivery and 6 (2.7%) by assisted vaginal delivery. The mean APGAR score was 7.82 ± 0.81.

Table (4): Correlations between each of BPD, FL, AC, HC, EFW (1) using Hadlock's formula and actual birth weight and umbilical cord diameter, umbilical arteries, umbilical vein, Wharton's jelly, EFW (2) using regression equation and actual birth weight.

		Actual birth weight
BPD	R*	.407**
	P	0.0001
	Sig	HS
FL	R*	.356**
	P	0.0001
	Sig	HS
AC	R*	.456**
	P	0.0001
	Sig	HS
HC	R*	.410**
		0.0001
	Sig	HS
EFW1	R*	.524**
	P	0.0001
	Sig	HS
A1	R*	.701**
	P	0.0001
	Sig	HS
A2	R*	.450**
		0.0001
	Sig	HS
A3	R*	.320**
	P	0.0001
	Sig	HS
A4	R*	.350**
	P	0.0001
	Sig	HS
Wharton's jelly area	R*	.562
	P	0.0001
	Sig	HS
EFW2	R*	.702**
	P	0.0001
	Sig	HS

*Correlation coefficient

In correlation between the neonatal birth weight and prenatal EFW, Table (4) demonstrates a significant moderate positive correlation using BPD, FL, AC, HC, and Hadlock's formula r= 0.407, 0.356, 0.456, 0.410, 0.524 respectively (P< 0.001). While umbilical cord diameter and regression equation for calculation of EFW shows a significant strong correlation with neonatal birth weight r= 0.701, 0.702 respectively (P<0.001). But moderate correlation with umbilical arteries, umbilical vein and Wharton's jelly r= 0.450, 0.320, 0.562 (P<0.001).

Figure (3) illustrates the correlation of neonatal birth weight with their prenatal estimated body weight by Hadlock's formula. While Figure (4) illustrates the correlation using EFW by regression formula of umbilical cord.

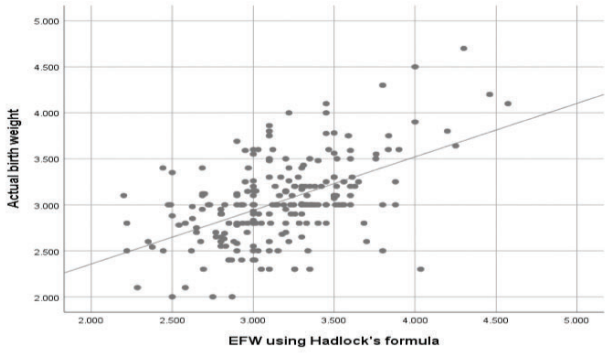

Figure (3): Correlation of neonatal birth weight with their prenatal estimated body weight by Hadlock's formula.

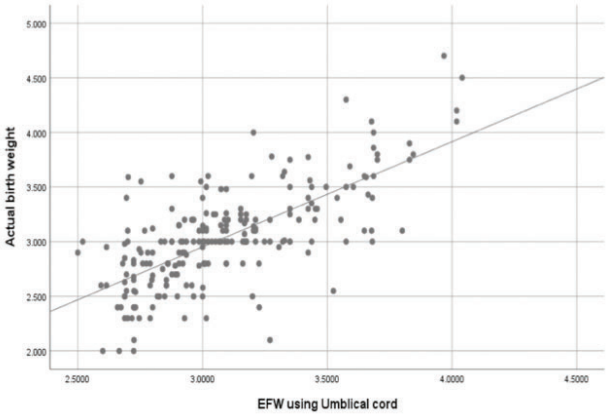

Figure (4): Correlation of neonatal birth weight with their prenatal estimated body weight by regression formula using umbilical cord.

Table (5): Correlations coefficients and Coefficient of determinant for each of BPD, FL, AC, HC, EFW(1) using Hadlock formula and umbilical cord diameter, umbilical arteries, umbilical vein, Wharton's jelly, EFW (2) using regression equation.

	Correlation coefficient (r)	Coefficient of determinant (R2)
BPD	0.407*	0.165*
FL	0.356*	0.127*
AC	0.456*	0.208*
HC	0.410*	0.168*
EFW(1)	**0.524***	0.274*
A0	0.701*	0.492*
A1	0.450*	0.202*
A2	0.320*	0.102*
A3	0.350*	0.122*
Wharton`s jelly area	0.555*	0.315*
EFW(2)	**0.702***	0.493*

*p<0.001

Table (5) shows that the correlation strength of the umbilical cord with the birth weight was higher than that by Hadlock's formula with the value of coefficient of determinant R2= 0.493 for umbilical cord that means 49% of the change in birth weight can be predicted using umbilical cord area versus R2= 0.274 for Hadlock's that's means that 27% of the change in birth weight can be predicted using Hadlock's formula.

DISCUSSION

One of the most important indicators of newborn survival is birth weight. Furthermore, the estimated fetal weight at term influences the timing and route of delivery. However, there is no agreement on acceptable clinical or acoustic measurements. As a result, researchers have tried a variety of strategies to enhance ultrasound-based fetal weight prediction (13).

Fetal biometric measures are the most often used approach for estimating birth weight. Despite extensive study into the most precise ultrasonography formula for determining estimated fetal weight, current evidence shows high error levels (14). Previously, sonographic examinations of the umbilical cord were confined to determining the number of arteries and assessing blood flow using Doppler. Heavier neonates have a bigger umbilical cord circumference at birth, according to research (11). The purpose of this study was to examine the effectiveness and accuracy of ultrasonography assessment of umbilical cord cross-sectional area with Hadlock's formula in predicting newborn birth weight at term gestation.

The current study found a significant moderate positive correlation of actual neonatal birth weight with prenatal EFW using Hadlock's formula (r=0.524, P 0.001), with the value of coefficient of determinant (R2) being 0.274, implying that Hadlock's formula can predict 27.4% of the actual birthweight. On the other hand, there was a significant strong positive correlation with EFW using the regression equation of umbilical cord area (r= 0.702, P0.001) with the value of the coefficient of determinant (R2) being 0.493, implying that umbilical cord area can predict 49.3% of the actual birth weight. That is, predicting birth weight using prenatal U/S measured umbilical cord cross sectional area is more accurate than Hadlock's algorithm.

This is consistent with other investigations. Henan et al. (11) studied 113 fetuses over 37 weeks and discovered that fetuses with umbilical cord areas less than the 10th percentile (lean umbilical cord) were more likely to have a low birth weight, confirming the existence of a correlation between umbilical cord area and fetal birth weight. Elghazaly et al. (10) shown a clear link between gestational age, fetal weight, and the amount of Wharton's jelly in the umbilical cord.

Furthermore, Morteza et al. (15), Rakesh et al. (16), and Sarah et al. (17) found a strong relationship between umbilical cord cross sectional area and birth weight. In contrast to

small cords, large cords are connected with high birth weight. Because Wharton's jelly improves cord diameter and blood vessel size, which enhances blood flow and nutrients, fetal weight gain increases. on addition to Ghezzi et al. (18), who discovered that a lean umbilical cord, particularly when accompanied by diminished Wharton's jelly on ultrasound, was related with an increased chance of delivering a child that was undersized for gestational age at birth. According to Afroze et al. (19), umbilical cords with a short cross-sectional area or a sparse amount of Wharton's jelly may be associated with the occurrence of oligohydramnios and fetal distress during delivery, resulting in a higher incidence of Cesarean sections and low birth weight.

While Morteza et al. (15) discovered that a big umbilical cord cross sectional area on ultrasound examination was considerably higher in the macrocosmic fetus population than in the non-macrocosmic fetus population. In addition to Benjamin et al., (9), there is a strong association between a large cross-sectional area of umbilical cord and the presence of metabolic diseases such as diabetes and macrocosmic fetuses, and that a thin umbilical cord is associated with a higher incidence of low birth weight.

Unlike Barbieri et al. (20), who discovered that the umbilical cord cross sectional area is a poor predictor of actual body weight. This discrepancy could be attributed to differences in gestational age (20-40) weeks and criteria covered in this study of low-risk pregnancy; they also categorised the umbilical cord according to their percentile curve.

There was no significant relationship between maternal age, height, parity, and fetal gender with estimated body weight (EFW) by Hadlock's formula in the current study, but there was a significant relationship between fetal gestational age (r=0.32 p value 0.001) and maternal weight (r=0.40 p value 0.001) with EFW, which means that the EFW changes with the mother's weight and gestational age of pregnancy.

The same was true for the umbilical cord cross sectional area, where there was no significant relationship with maternal age, height, parity, or fetal gender, but a significant relationship with maternal weight (r=0.61 p value 0.001) and fetal gestational age (r=0.27 p = 0.003), indicating that the umbilical cord cross sectional area changes as the mother's weight and fetal gestational age change.

When compared to other research, Raio et al. (21) found no significant relationship between age, parity, and gestational age at time of delivery and umbilical cord parameter in an ultrasound investigation. Furthermore, Rakesh et al. (16) found a significant relationship between umbilical cord parameter and maternal age and fetal gestational age without taking into account maternal weight or fetal gender. In contrast to Afroze et al., 2017, who discovered a strong link between umbilical cord parameters in an ultrasonography research and maternal age, parity, and fetal gestational age.

The mean real neonatal birth weight and Apgar score in the current study were 3.030.45 and 7.82 0.81, respectively. This was consistent with Tahmasebi's (22) study, which found that the average birth weight was 3372.12440.7 g (range: 1950-4350 g). The majority of babies had normal 5-minute Apgar scores, with a range of 4:10.

According to Raio et al. (21), the diameter of the umbilical cord is altered by a decrease in Wharton jelly around the umbilical arteries in cases of segmental thinning. Furthermore, because the cross-section of the cord may not be precisely circular, a modest reduction in the quantity of Wharton jelly with no modification in the artery lumen may be underestimated when only diameter estimates are employed, according to these authors.

The current study's strength is the large sample size of the study population and the use of this new method, regardless of maternal decubitus, parities, fetal presentation, position, and lie, which can provide a more predictive

method of estimating fetal weight than the standard Hadlock's formula. The link of the measurement with maternal medical problems like as diabetes mellitus or hypertension, in addition to amniotic fluid abnormalities, and correlation with earlier gestational age are areas for further research.

CONCLUSION

For the current sample, it is obvious that the umbilical cord area is a good predictor of birth weight at term gestation, which may provide support for future use of the umbilical cord formula for birth weight prediction. The current investigation demonstrates that measuring umbilical cord thickness and cross-sectional area in a free loop of umbilical chord is simple. The cross-sectional areas of the umbilical cord components can be determined to be crucial parameters to consider when evaluating fetal growth. This study's normalcy metrics might be used as a reference for future studies that may associate such characteristics with fetal growth abnormalities and pregnancy disorders such as diabetes mellitus and hypertension.

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Helicobacter Pylori Infection in Pregnant Women with Hyperemesis Gravidarum and Its Effect on Pregnancy Outcome

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Abstract

Background: Numerous studies established a significant positive correlation between HG and the presence of H. pylori.

Aim: This study aimed to assess the effects of helicobacter pylori infection among pregnant women with hyperemesis gravidarum on pregnancy outcome.

Patients and Methods: This cross-sectional study was conducted on 180 pregnant females with hyperemesis gravidarum. Women were assigned to one of two groups: Group A: pregnant women with hyperemesis gravidarum, who were tested positive for the presence of H. pylori infection and group B: pregnant women with hyperemesis gravidarum, who were tested negative for the presence of H. pylori infection.

Results: Group A had significantly higher percentage of abortion, past history of HG and family history of HG than group B with statistically significant differences as $p<0.05$. Group A had significantly lower mean of hemoglobin than group B with statistically significant differences as $p<0.001$. While group A had higher mean of random blood sugar than group B with statistically significant differences as $p=0.014$. Women in group B showed significantly higher resolution of HG than group A ($p<0.001$). Women in group B showed significantly higher resolution of HG and weight gain than group A ($p<0.001$). Group A had higher incidence of preterm labor and neonates with low birth weight than group B with statistically significant differences.

Conclusion: Although a link between H. pylori and HG has previously been established, this paper makes an important contribution to the literature by confirming this relationship among Egyptian women.

Keywords: H. pylori, Pregnancy, Hyperemesis.

Introduction

In a comprehensive study, Golberg et al. discovered that pregnant women with H. pylori infection had a greater

frequency of HG than women who were not infected. However, several research found no connection between HG and H. pylori [1].

Helicobacter pylori affects the health of both the mother and the fetus, and there is no recommended method for getting rid of it in pregnant women. When an H. pylori infection is discovered during pregnancy, it is typically advised to postpone eradication until after birth [2].

The most severe form of pregnancy-related nausea and vomiting, known as hyperemesis gravidarum, can result in weight loss, nutritional deficiencies, and metabolic disturbances like dehydration, acidosis from starvation, hypokalemia, and temporary hepatic dysfunction. As a result, it frequently necessitates hospitalization and medical care to prevent potentially fatal complications. It is second only to premature labor as the most frequent reason for hospitalization during the first half of pregnancy [3].

Since there is no recognized cause of hyperemesis gravidarum, a number of processes, including immunologic and endocrine variables such human chorionic gonadotropin, estrogen, and progesterone, may contribute to this condition. The link between Helicobacter pylori (H. pylori) infection and the risk of hyperemesis gravidarum has been highlighted in several research [4].

In Egypt, 75% of instances of HG were found to have Helicobacter pylori in stool samples, as opposed to 37.50% of healthy pregnant women, according to Elmahdy et al. The stomach is colonized by this bacteria. It usually develops throughout childhood and results in an asymptomatic chronic infection. Peptic ulcers and stomach cancer can occur in a tiny percentage of H. pylori-infected people, often in late adulthood [5].

The association between H. pylori and thrombocytopenia has been shown in a non-pregnant population, and the etiology of thrombocytopenia may be due to cross-molecular mimicry between specific H. pylori protein (CagA) and platelet antigens. Thrombocytopenia is also one of the maternal complications of H. Pylori [6].

Fetal problems including abortion might result from H. pylori infection. According to several research, H. Pylori infection is linked to a greater probability of miscarriage (seropositivity in the abortion group reached 66.7%, compared to 8% in the control group) [3].

Fetal growth retardation is another H. Pylori late fetal problem. The characteristic symptoms of H. Pylori infection in pregnant women include nausea, vomiting, anemia, fetal abnormalities, as well as fetal growth restriction and low birth weight. Pregnant women are one of the most sensitive populations to infection with H. Pylori. According to Graham et al. [7], intrauterine growth restriction affected 13.5% more H. pylori seropositive women than H. pylori-seronegative women.

According to several studies, persons with H. pylori infection had lower plasma levels of vitamin B12 and folate than subjects who are not infected, which is concerning since H. pylori may contribute to neural tube defects.

In this study, helicobacter pylori infection was found in pregnant women with hyperemesis gravidarum, and its impact on maternal and fetal outcomes was assessed.

Aim

The study aimed to improve general health and quality of life of pregnant women.

Patients and methods:

This is a prospective observational study was carried out in Obstetrics and Gynecology department of Suez Canal University hospital from June 2021 to April 2022. Patients attending Obstetrics and Gynecology clinic of Suez Canal University hospital complaining of hyperemesis gravidarum diagnosed by urine analysis, dehydration, vomiting cause > 5% loss of body weight were fulfilling the following criteria:

Inclusion criteria:

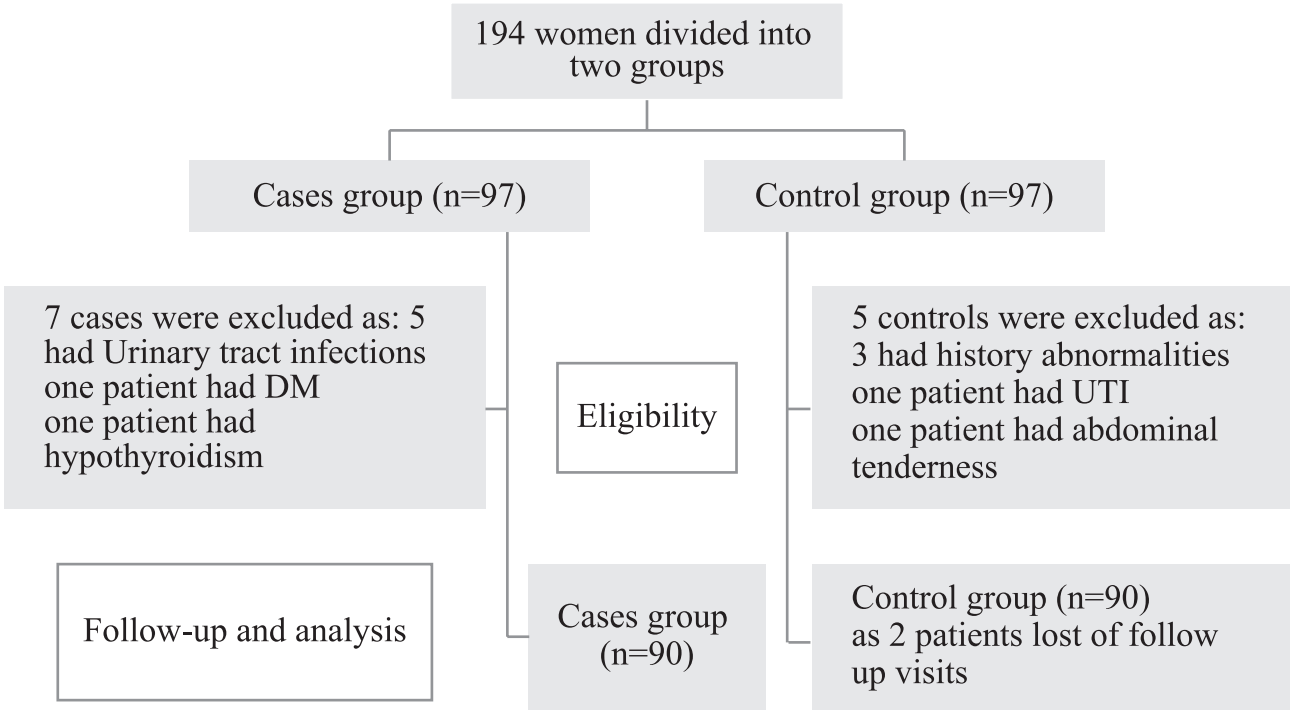
1. Gestational age ranging from 6 to 14 weeks.
2. They should previously have visited the antenatal care clinic of Suez Canal University hospital.
3. Singleton ongoing pregnancy.
4. The Patient was diagnosed and admitted as hyperemesis gravidarum, either clinically (severe vomiting (≥4 times a day) not responding to traditional treatments, weight loss (≥5% of body weight) or laboratory (ketones in urine, electrolyte disturbance).

- Exclusion criteria

1. History of peptic ulcer before pregnancy.
2. History of chronic drug administration "e.g., nonsteroidal anti-inflammatory drugs (NSAIDs).
3. Thyroid disorders
4. Psychiatric problems
5. Liver or renal disorders
6. Urinary tract infections
7. Diabetes Mellitus
8. Multiple gestations
9. Molar pregnancy
10. Smoking

Sampling Technique: Convenient sampling of pregnant women with hyperemesis gravidarum seeking medical care in the study setting was taken.

Figure 1: Flow chart of the study groups.



Methods

Study procedure

1. A thorough medical history and examination were conducted, covering any illnesses affecting the mother or ailments associated with nausea and vomiting, along with a clinical evaluation for indicators of dehydration and the phone number of each patient.
2. The last menstrual cycle was used to calculate the gestational age.
3. The presence of a live fetus, the gestational age, and the exclusion of any obstetric reasons of hyperemesis, such as multiple pregnancies and gestational trophoblastic illness, were all confirmed by ultrasound.

4. The following criteria were used to diagnose hyperemesis:
   - severe vomiting (more than four times per day) with no discernible reason other than pregnancy
   - A positive ketonuria test result.
5. For every case, comprehensive laboratory testing was performed to determine the extent of HG and rule out other medical conditions. This included serum electrolytes, TSH-free T3, and free T4 levels (CBC, FBS, kidney, and liver function tests). Iron supplements were used as a treatment for anemia in women.
6. Urine was analyzed in order to rule out urinary tract infections and to look for ketone bodies.
7. A stool antigen test for H. pylori was conducted. The results of the H. pylori test will determine which of the following two categories the women are placed in:
   - Group A: pregnant patients with hyperemesis gravidarum who had an H. pylori infection and had positive tests.
   - Group B: women experiencing hyperemesis gravidarum during pregnancy who did not have an H. pylori infection.Standard treatment for hyperemesis gravidarum:
   - Diet instructions such as eating small meals all over the day, avoiding spicy, greasy or fried food or food with strong odors, avoiding tea and coffee [8].
   - IV fluids and Electrolyte replacement as:

     I. Ringer lactate IV 8 hourly (500 ml three times daily).

     II. isotonic saline IV 8 hourly (500 ml three times daily) [9].
   - Antiemetics, according to Royal College of Obstetricians and Gynecologists (RCOG) green-top guideline No. 69 (The management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum), such as:

     I. Cyclizine (first line): 50 mg PO, IM or IV 8 hourly.
   - Metoclopramide and Ondansetron (Primperan and Danset) Metoclopramide: 5–10 mg 8 hourly PO, IV or IM (maximum 5 days' duration) and/or Ondansetron: 4- 8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV.
   - Vitamin supplementation specially (Vitamin B6 and B12) available as multivitamin combination such as (Becozyme) [8].
8. The clinical response was determined by the improvement of nausea and vomiting, and the increase in body weight in both groups two weeks after the start of management.
9. At every follow up visit weight, blood pressure, Pulse, Hb, HCT, and Platelets were measured. Women who didn`t attend follow up visits were excluded from the study.
10. Evaluation in both groups was done two weeks after intervention, 18th week, 23-24th week via:

    a. Recovery of hyperemesis gravidarum (hospitalization duration and improvement of symptoms).

    b. Persistence of GIT symptoms along pregnancy as: heartburn, nausea, vomiting, dyspepsia, loss of appetite, constipation and diarrhea

    c. Maternal Complications as: maternal iron deficiency anemia and pre-eclampsia and thrombocytopenia

    d. Fetal Complications as: miscarriage, fetal growth restriction and neural tube defects.
11. Patients of both groups (A and B) were followed up clinically at the Obstetrics and Gynecology department.

12. After that, both (group A) and (group B) were followed up after discharge till the end of the pregnancy (either delivery or abortion) to assess the maternal and fetal complications occurred in both groups at least five times as one prenatal visit per month to evaluate:
    - The symptoms of GIT
    - Fetal kicks.
    - Fetal Growth profile by ultrasound.
    - Maternal weight
    - Measure blood pressure to assess preeclampsia
    - CBC to assess the iron deficiency anemia
    - Last visit after delivery to follow up the newborn to assess any fetal complications.
13. The dropout rate was calculated from patients who come for follow up less than 3 prenatal visits.

Data Management & Statistical Analysis

- The data was entered into a Microsoft Excel sheet and then analyzed using the Statistical Package for Social Sciences (SPSS) software program version 25.0 (2017) or higher.
- Data was presented as tables and graphs, as suitable.
- For descriptive analysis, continuous data was expressed as mean ± standard deviation, whereas categorical data was expressed as frequencies and percentages.
- Chi-square test or Fisher exact test were used to compare the baseline characteristics between the two groups, whereas Student t- test was used to compare numerical variables, including the durations, different scores, and weight.
- Results were considered statistically significant at a p-value less than 0.05 and highly significant at p-value less than 0.001.

Results

This cross-sectional study was conducted on 180 pregnant females with hyperemesis gravidarum. According to the H. pylori testing results, women were assigned to one of two groups:

- Group A: pregnant women with hyperemesis gravidarum, who were tested positive for the presence of H. pylori infection.
- Group B: pregnant women with hyperemesis gravidarum, who were tested negative for the presence of H. pylori infection.

Table 1 shows the distribution of maternal characteristics of the study groups. There were statistical insignificant differences between study groups as regard age, parity and BMI as $p>0.05$. Group A had significantly higher percentage of abortion, past history of HG and family history of HG than group B with statistically significant differences as $p<0.05$.

Table 2 shows the distribution of maternal baseline measurements in the study groups. Group A had significantly higher mean of systolic and diastolic blood pressure than group B with statistically significant differences as $p<0.001$.

Table 3 shows the laboratory results in the study groups. Group A had significantly lower mean hemoglobin level than group B with statistically significant differences as $p=0.009$. While group A had higher mean random blood sugar level than group B with statistically significant differences as $p=0.014$.

Table 4 shows the serum electrolyte results in the study groups. Group A had significantly lower mean of potassium than group B with statistically significant differences as $p=0.037$.

Table 5 shows the outcomes after two weeks of intervention among the study groups. Women in group B showed significantly higher resolution of HG than group A ($p<0.001$). Group A had lower weight gain than group B but with statistical insignificant difference.

Table 6 shows the collected data by the end of the first trimester follow-up visit of intervention among the study groups. Women in group B showed significantly higher resolution of HG and weight gain than group A ($p<0.001$). Group A had higher mean of systolic and diastolic blood pressure than group B with statistically significant difference. Group A had lower mean of hemoglobin than group B with statistically significant difference.

Table 7 shows the collected data by the end of the second trimester follow-up visit of intervention among the study groups. Women in group B showed significantly higher resolution of persistent vomiting of pregnancy and weight gain than group A ($p<0.001$). Group A had higher mean of systolic and diastolic blood pressure than group B with statistically significant difference. Group A had lower mean of hemoglobin than group B with statistically significant difference.

Table 8 shows the collected data on the third follow-up visit of intervention among the study groups. Women in group B showed significantly higher resolution of persistent vomiting in pregnancy and weight gain than group A ($p<0.001$). Group A had higher mean of systolic and diastolic blood pressure than group B with statistically significant difference. Group A had lower mean of hemoglobin than group B with statistically significant difference.

Table 9 shows the maternal and neonatal outcomes among the study groups. Women in group A showed significantly higher women with anemia than group A ($p=0.003$). Group A had higher incidence of preterm labor and neonates with low birth weight than group B with statistically significant differences.

Discussion

This cross-sectional study evaluated the effects of helicobacter pylori infection among pregnant women with hyperemesis gravidarum on pregnancy outcome in terms of hyperemesis gravidarum severity, abortion rate, intrauterine growth retardation rate, iron deficiency anemia, thrombocytopenia, and preeclampsia. Its goal was to improve the general health and quality of life of pregnant women. 180 pregnant women with hyperemesis gravidarum participated in this study. The H. pylori testing outcomes placed the ladies in one of two groups: Pregnant women with hyperemesis gravidarum who tested positive for H. pylori infection were placed in group A, whereas those with hyperemesis gravidarum who tested negative for the infection were placed in group B.

According to the research's findings, there was no difference between the analyzed groups in terms of maternal age, body mass index, parity, or fetal gestational age at the beginning of the study. This concurs with a recent research from Egypt [10].

In the current study, women who tested positive for H. pylori had a statistically significant greater frequency of anemia than those who tested negative (p 0.001). With statistically significant differences, preterm labor and low birth weight babies are more common in H. pylori positive women than in H. pylori negative women.

According to another study, pregnant women with H. pylori infection were shown to have low Hb levels from the beginning of pregnancy [11].

Similar to this, Muhsen [12] recommended H. pylori testing and hypothesized that it could be a contributing cause to anemia in pregnant women. This advice is based on several research showing a link between H. pylori and anemia. Muhsen and Cohen conducted

a meta-analysis of epidemiological studies, interventional trials, case reports, and series.

Hb content was found to be considerably lower in cases compared to controls in a recent investigation. Hb was considerably lower in pregnant women with H. pylori infection than in instances without the infection [4]. Anemia was a side effect of H. pylori infection that was noted, and there is positive evidence linking the two conditions in expecting women.

In early pregnancy, women with H. pylori had lower Hb levels than those without it, according to Weyermann et al. (-0.25 g/dl; 95% CI: -0.49 to -0.003). This decrease in Hb level was worse as the pregnancy went on (-0.14 g/dl; 95% CI: -0.38 to 0.10) [13].

According to the findings of the current investigation, there were no appreciable variations in the blood levels of AST and ALT between women who tested positive for h. H. pylori and women who tested negative.

One of the organs that may be impacted by H. pylori infection is the liver, albeit the precise consequences of the bacterial infection and the underlying processes are yet unknown. Given the high prevalence of H. pylori infection in the general population and certain data linking the illness with a certain level of liver damage [14].

The question of whether H. pylori has any impact on the level of liver enzymes in the pregnant women tested was investigated in Hussein's study [4]. The findings showed that HG-affected women had considerably higher mean levels of liver enzymes than control women. Findings showed that the activity of AST was substantially higher in instances testing positively than in cases testing negatively. Previous research introduced two hypotheses: that there is an extrahepatic source for increased AST level and/or that there is a host genetic predisposition to both H. pylori infection and increased levels of liver enzymes [15]. This is because there is no association between H. pylori and ALT level, which is more specific than AST.

In the current investigation, group A had a statistically significant difference (p=0.037) lower mean potassium level than group B.

In accordance, Hussein's study [4] discovered that women with HG had considerably lower mean potassium levels than the controls.

According to McCarthy et al., hyperemesis gravidarum (HG), a condition marked by persistent, severe nausea and vomiting, 0.3–2% of pregnant women experience the ensuing ketosis [16].

According to the Azami et al. study, pregnant women with H. pylori infection had lower potassium levels than pregnant women with hyperemesis [11].

In the current investigation, there were 2 (2.2%) women with preeclampsia who also had H. pylori.

In line with a recent comprehensive study, which found that some negative consequences during pregnancy may have an independent link with H pylori infection. Contrary to H pylori infection negative, H pylori infection positive during pregnancy was substantially associated with a greater risk of preeclampsia, foetal growth restriction, gestational diabetes mellitus, and hyperemesis gravidarum [17].

In this study, women in group A experienced greater rates of preterm labor and low birth weight babies than women in group B, with statistically significant differences.

A substantial positive association between HG and the presence of H. pylori and poor newborn outcomes has been confirmed by several research [6].

Alwahed et al. [18] discovered in their research of pregnant women with HG that these women had a considerably greater prevalence of H. pylori than those who do not have HG (69 vs. 15%; P 0.001).

Li et al. looked at publications that were published in multiple databases before

March 20, 2014 for another meta-analysis of the H. pylori-HG connection. According to their data, expecting women with HG have a considerably greater incidence of H. pylori infection (P 0.001). According to this systematic review, H. pylori is one of the risk factors for HG and is associated with an increased risk of miscarriage, low birth weight, and premature labor [19].

Utilizing the stool antigen test is this study's main area of strength. Of course, this study's primary weakness is its tiny sample size. The power of this result is poor, which suggests that although the current study identified a significant link between HG and H. pylori, there may still be sociodemographic differences between women with HG and those without that did not reach the level of significance. Additionally, additional possible variables like socioeconomic status and gestational age were left unadjusted.

Conclusion

Investigations into HG should include H. pylori testing, particularly when the disease does not improve with therapy and in instances that last through the first trimester. It is necessary to conduct further study on H. pylori infection in the community of pregnant women who suffer from severe vomiting and nausea. To validate the findings of the current study, more prospective studies with bigger sample sizes are required.

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Tables and Figures

Table 1: Maternal characteristics of the study population

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Maternal age (years) mean±SD	29.6 ± 6.0	30.3 ± 6.01	0.817	0.440[1]
Parity (n,%) Nulliparous Multipara	 42(46.7%) 48(53.3%)	 37(41.1%) 53(58.9%)	 0.643	0.523[2]
Abortion No Yes	 24(26.7%) 66(73.3%)	 60(66.7%) 30(33.3%)	4.62	**<0.001**[*2]
BMI (kg/m^2) mean±SD	29.1 ± 5.0	27.8 ± 4.5	1.098	0.069[1]
Past history of HG (n,%)	13(14.4%)	3(3.3%)	3.99	**0.001**[*3]
Family history of HG (n,%)	9(9.9%)	1(1.1%)	3.61	**0.018**[*3]

Table 2: Maternal baseline measurements among the study group.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Gestational age (weeks) mean±SD	8.6 ± 2.5	8.4 ± 2.6	0.752	0.762[1]
Systolic Bl.P (mmHg) mean±SD	105.1± 4.3	95.03 ± 6.1	5.23	**<0.001**[*1]
Diastolic Bl.P (mmHg) mean±SD	75.0 ± 3.2	60.2 ± 9.7	4.72	**<0.001**[*1]
Respiratory rate (breath/minute) mean±SD	26.1 ± 5.0	24.8 ± 4.5	1.66	0.069[1]
Pulse (beat/minute) mean±SD	80.4 ± 6.4	80.4 ± 6.6	0.091	0.982[1]

Table 3: Laboratory investigations results among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Hb (g/dl) mean±SD	9.6 ± 1.89	10.5 ± 2.11	3.62	**0.009**[*1]
HCT (%) mean±SD	26.7± 3.5	33.9 ± 3.1	2.88	**0.017**[*1]
3 Platelets (*10) mean±SD	189 ± 32	198 ± 33	1.54	0.065[1]
PT (seconds) mean±SD	12.3 ± 1.1	12.4 ± 1.2	0.541	0.683[1]
INR (seconds) mean±SD	1.3 ± 0.2	1.2 ± 0.2	0.650	0.597[1]
ALT (U/L) mean±SD	33.7 ± 3.0	33.9 ± 3.5	0.508	0.653[1]
AST (U/L) mean±SD	34.4 ± 3.1	34.9 ± 3.3	0.871	0.312[1]
Creatinine (mg/dl) mean±SD	0.62 ± 0.05	0.69 ± 0.04	1.34	0.082[1]
RBS (mg/dl) mean±SD	101.0 ± 16.6	79.6 ± 16.0	3.01	**0.014**[*1]

Table 4: Serum electrolyte and ABG results among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Sodium (mEq/L) mean±SD	134.1 ± 3.1	134.2 ± 3.6	0.091	0.841[1]
Potassium (mEq/L) mean±SD	3.7 ± 0.9	4.6 ± 0.8	2.96	**0.037**[*1]
PH mean±SD	7.42 ± 0.04	7.43 ± 0.03	0.112	0.800[1]

CO2 (mmHg) mean±SD	54.4 ± 2.2	54.6 ± 2.4	0.503	0.650[1]
HCO3 (mEq/L) mean±SD	26.6 ± 1.1	26.7 ± 1.2	0.342	0.400[1]

Table 5: Comparison of outcomes after two weeks of intervention among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Body weight gain (n,%) No Yes	 88(97.8%) 2(2.2%)	 83(92.2%) 7(7.8%)	0.891	0.169[1]
Resolution of HG (n,%) No Yes	 88(97.8%) 2(2.2%)	 88(97.8%) 2(2.2%)	5.25	**<0.001**[*1]
Duration of hospitalization (days) mean±SD	6.0± 2.2	7.1 ± 2.3	0.603	0.594[2]

Table 6: Comparison of collected data by the end of first trimester follow-up visit among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Gestational age (weeks) mean±SD	15.2± 0.3	15.5 ± 0.5	0.008	0.991[1]
Persistent GIT symptoms (n,%) No Yes	 2(2.2%) 88(97.8%)	 19(21.1%) 71(78.9%)	4.67	**<0.001**[*1]
Weight gain (n,%) **Normal** **Abnormal**	 82(91.1%) 8(8.9%)	 59(65.6%) 31(34.4%)	5.61	<0.001[*1]
Systolic Bl.P (mmHg) mean±SD	119.7± 9.1	99.8 ± 8.5	4.78	**<0.001**[*2]
Diastolic Bl.P (mmHg) mean±SD	70.5± 4.3	65.3 ± 5.5	3.89	**<0.001**[*2]
Pulse (beat/minute) mean±SD	79.0± 5.5	80.09 ± 6.1	0.992	0.229[2]
Hb (g/dl) mean±SD	9.9 ± 1.0	10.8 ± 0.8	1.99	**0.042**[*1]
HCT (%) mean±SD	27.5± 2.9	32.6 ± 2.5	2.42	**0.023**[*2]
3 **Platelets (*10) mean±SD**	188.5 ± 32.3	201.2± 31.2	1.05	0.065[1]
IUGR (n,%)	0(0%)	0(0%)	--	1.00[1]
IUGR (n,%)	0(0%)	0(0%)	--	1.00[1]

Table 7: Comparison of collected data by the end of the second trimester follow-up visit among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Gestational age (weeks) mean±SD	26.2± 0.3	26 ± 0.5	0.021	0.981[1]
Persistent GIT symptoms (n,%) No Yes	30(33.3%) 60(66.7%)	54(60.0%) 36(40.0%)	5.76	**0.001**[*1]
Weight gain (n,%) No Yes	82(91.1%) 8(8.9%)	56(62.2%) 34(37.8%)	4.5	**<0.001**[*1]
Proteinuria (n,%) +	2(2.2%)	0(0.0%)	0.728	0.104[1]
Number of fetal Kicks mean±SD	5.4± 1.9	8.5 ± 1.5	6.17	**<0.001**[*2]
Systolic Bl.P (mmHg) mean±SD	123.7± 10.2	103.4 ± 9.2	7.87	**<0.001**[*2]
Diastolic Bl.P (mmHg) mean±SD	71.3± 3.9	67.4 ± 6.1	3.66	**<0.001**[*2]
Pulse (beat/minute) mean±SD	80.2± 4.3	78.4 ± 5.5	0.524	0.371[2]
Hb (g/dl) mean±SD	9.1± 1.4	10.5± 1.5	2.15	**0.039**[*1]
HCT (%) mean±SD	39.5± 3.2	39.8 ± 4.5	0.092	0.825[2]
Platelets (*10^3) mean±SD	191.5 ± 29.5	200.5± 30.3	1.02	0.065[1]
Asymmetrical IUGR (n,%)	2(2.2%)	0(0%)	--	0.526[1]
IUFD (n,%)	0(0%)	0(0%)	--	1.00[1]

Table 8: Comparison of collected data by the end of 36th week visit among the study groups.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Gestational age (weeks) mean±SD	36± 0.3	36.1 ± 0.3	0.014	0.992
Persistent GIT symptoms (n,%) No Yes	45(50%) 45(50%)	62(68.9%) 28(31.1%)	4.88	**<0.001**[*1]
Weight gain (n,%) No yes	73(91.1%) 17(8.9%)	39(43.3%) 51(56.7%)	5.11	**<0.001**[*1]

Proteinuria (n,%) + ++	86(95.5%) 4(4.5%)	90(100.0%) 0(0.0%)	0.651	0.104[1]
Number of fetal Kicks mean±SD	9.2± 0.6	11.5 ± 1.2	0.998	0.082[2]
Systolic Bl.P (mmHg) mean±SD	119.3± 9.5	105.3±8.2	5.46	**0.008**[*2]
Diastolic Bl.P (mmHg) mean±SD	79.7± 5.4	70.3 ± 5.2	3.18	**<0.001**[*2]
Pulse (beat/minute) mean±SD	79.4± 5.1	76.4 ± 3.4	0.413	0.534[2]
Hb (g/dl) mean±SD	9.8± 0.8	10.8± 1.2	2.00	**0.047**[*1]
HCT (%) mean±SD	39.1± 4.2	40.1 ± 3.6	0.102	0.877[2]
3 Platelets (*10) mean±SD	190.8 ± 30.1	201.2± 29.8	1.12	0.224[1]
IUGR (n,%)	3(3.3%)	1(1.1%)	0.423	0.526[1]
IUFD (n,%)	0(0%)	0(0%)	--	1.00[1]

Table 9: Comparison of maternal and neonatal outcomes among the study groups at delivery.

Variables	Group A (n=90)	Group B (n=90)	Test value	P-value
Anaemia (n,%)	30(33.3%)	14(15.6%)	4.27	**0.003**[*1]
Preeclampsia (n,%)	2(2.2%)	0(0.0%)	0.712	0.208[1]
Preterm labour (n,%)	8(8.9%)	2(2.2%)	3.01	**0.034**[*1]
Low birth weight (n,%)	22(24.4%)	4(4.5%)	4.22	**0.016**[*1]

Long-Term Complications of Caesarean Section, the Niche in the Scar: A Prospective Cohort Study on Niche Prevalence and its Relation to Abnormal Uterine Bleeding

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Abstract

Background: There have been several reports of an association between abnormal bleeding and a niche in particular, postmenstrual spotting seems to be a predominant symptom in women with a niche.

Aim of the Work: To study the prevalence of niches in the caesarean scar in a random population, and the relationship with postmenstrual spotting.

Patients and Methods: This prospective cohort study was performed on a total of 80 patients who underwent at least 1 lower segment caesarean section of single full-term pregnancy and conducted at Ain Shams University Hospital from April 2021 to December 2022. During this study, 100 patients were assessed for eligibility and 80 patients were included in the study. Of all eligible patients, 14 patients were excluded from the study based on the inclusion criteria and 6 patients refused to participate in of the study.

Results: Regarding TVUS and 3D findings of scar niche at weeks 6-12 and at month 6, our results revealed that there were no statistically significant differences according to scar niche regarding menstruation, premenstrual spotting, while Menstrual irregularity, BAC score, durations of menstruation, intermenstrual bleeding and postmenstrual spotting statistically were significantly higher among cases with scar niche. Our study results revealed that menstrual abnormalities and postmenstrual bleeding were statistically significantly found in cases with higher niche depth. Our study results revealed that there were no statistically significant differences according to menstrual abnormalities at week 6-12 regarding residual myometrium thickness with significantly lower ratio of residual myometrium thickness in cases with menstrual abnormalities except in intermenstrual spotting.

Conclusion: caesarean section scar was visible in all women at 6–12 weeks after caesarean section. The prevalence of niches detected by 3D is high after caesarean section (56.6%), and more niches are detected than using TVUS (41.3%), with a larger observed niche size and

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reduced residual myometrial thickness. The presence of a niche is significantly related to postmenstrual spotting.

Keywords: Caesarean Section; Niche; Abnormal Uterine Bleeding.

Introduction

Over the past few years, the rate of caesarean delivery has dramatically increased throughout the world. Nonetheless, about one-third of all deliveries are caesarean, a remarkable increase from even 20 years ago. In large part, this is because modern caesareans are quite safe with rare serious morbidity [1].

There is a downside to the increased rate of caesareans, however, that is just now becoming apparent. There is rare but serious morbidity for the mother and common but relatively minor respiratory morbidity for the neonate in the short term. In the long-term, there is a substantial increase in the risk for major maternal, fetal, and neonatal morbidity, primarily because of the consequences of abnormal placentation and placenta accreta. Only recently, gynecological symptoms such as painful menstruations and postmenstrual spotting have been associated with CSs [2].

The long-term complications of caesarean section in relation to future reproduction have been comprehensively examined in the previous few years. In the past decade several articles have described a defect that can be seen on ultrasound at the site of the caesarean section scar, known as a 'niche' The term CS niche (defect) describes the presence of a hypoechoic area within the myometrium in the isthmus (lower uterine segment) with discontinuation of myometrium at the site of previous CS. A niche has been described as the indentation of myometrium of at least 2 mm. Large niches are uncommon with reported varying incidence of 11-45% depending on the definition used. A significant niche is defined as involving a depth of at least 50-80% of anterior myometrium or the remaining myometrial thickness less than 2.2 mm when evaluated by transvaginal ultrasound scanning (TVS). Small niches may indeed be quite common but would be clinically unimportant. The large niches are most likely to give rise to long-term sequelae [3].

Presumably a lack of coordinated muscular contractions occurs around the cesarean scar, allowing the defect to collect menstrual debris. Subsequently, the debris leaches out through the cervix for several days after the majority of menstrual flow has ceased. There have been several reports of an association between abnormal bleeding and a niche in particular, postmenstrual spotting seems to be a predominant symptom in women with a niche [4].

With ultrasonographic higher frequency and proximity to the pelvic organ, transvaginal ultrasonography has offered unprecedentedly clear images of the female pelvic organs. Its value for the visualization of the lower uterine segment and cervix had been emphasized. This makes it particularly useful in observing previous section scars in the lower uterine segment [5].

The aim of this work is to study the prevalence of niches in the caesarean scar in a random population, and the relationship with postmenstrual spotting.

Patients and Methods

This prospective cohort study was performed on a total of 80 patients who underwent at least 1 lower segment caesarean section of single full-term pregnancy and conducted at Ain Shams University Hospital from April 2021 to December 2022. During this study, 100 patients were assessed for eligibility and 80 patients were included in the study. Of all eligible patients, 14 patients were excluded from the study based on the inclusion criteria and 6 patients refused to participate in of the study. Ultimately, the analysis was based on the data of 80 patients who underwent at least

1 lower segment caesarean section of single full-term pregnancy.

The patient should be medically and surgically free. She was evaluated by both transvaginal ultrasound and 3D ultrasound after 6-12 weeks of uneventful lower segment CS followed by evaluation of her menstrual regularity and pattern. After 6 months of the CS, she is reevaluated for her menstrual pattern and regularity. The menstrual pattern is evaluated by questionnaire and validated menstrual score chart: The Pictorial Blood Assessment Chart (PBAC).

Statistical analysis

The data was collected, reviewed, coded and entered into an excel sheet. Data will be analyzed by using SPSS software. Descriptive statistics were done in terms of frequency and percentages for categorical variables. Mean (±SD) or median (interquartile range) was used for continuous variables. Statistical tests for comparing groups were used according to type of data. Differences were considered significant at a p-value less than or equal to 0.05.

Results

Table (1): Demographic characteristics among the studied cases

		Mean±SD	Range
Age (years)		27.1±3.4	21.0–35.0
BMI (Kg/m^2)		27.8±3.1	20.6–34.8
Number of previous sections		1.6±0.7	1.0–3.0
Time from last CS (weeks)		8.8±1.7	6.0–12.0
Gestational age at last section (weeks)		38.8±0.8	37.0–40.0
		n	**%**
Current breast feeding		78	97.5%
Current contraception	**None**	66	82.5%
	IUD	7	8.8%
	Hormonal	7	8.8%

Table (2): Comparison according to scar niche regarding demographic characteristics

		Niche	No niche	p-value
TVUS diagnosis				
		Total=34	**Total=46**	
Age (years)		27.0±3.3	27.1±3.5	^0.895
BMI (Kg/m²)		29.1±3.0	26.8±2.8	**^<0.001***
Number of previous sections		2.0±0.7	1.3±0.5	**^<0.001***
Time from last CS (weeks)		8.7±1.8	8.9±1.7	^0.654
Gestational age at last section (weeks)		38.7±0.8	38.9±0.8	^0.277
Current breast feeding		32 (94.1%)	46 (100.0%)	§0.178
Current contraception	**None**	29 (85.3%)	37 (80.4%)	§0.905
	IUD	3 (8.8%)	4 (8.7%)	
	Hormonal	2 (5.9%)	5 (10.9%)	
3DS diagnosis				
		Total=46	**Total=34**	
Age (years)		26.8±3.3	27.4±3.5	^0.422
BMI (Kg/m²)		28.4±3.3	26.9±2.6	**^0.027***
Number of previous sections		1.9±0.7	1.2±0.4	**^<0.001***
Time from last CS (weeks)		8.9±1.8	8.7±1.7	^0.564
Gestational age at last section (weeks)		38.7±0.9	38.9±0.8	^0.290
Current breast feeding		44 (95.7%)	34 (100.0%)	§0.505
Current contraception	**None**	38 (82.6%)	28 (82.4%)	§0.999
	IUD	4 (8.7%)	3 (8.8%)	
	Hormonal	4 (8.7%)	3 (8.8%)	

Table (3): Comparison according to scar niche regarding uterine characteristics

Findings		**Niche**	**No niche**	**p-value**
TVUS diagnosis				
		Total=34	**Total=46**	
Uterine position	**AVF**	24 (70.6%)	42 (91.3%)	**#0.016***
	RVF	10 (29.4%)	4 (8.7%)	
Uterine length (mm)		71.7±2.4	73.1±4.4	^0.115
Uterine width (mm)		42.3±2.4	41.7±4.1	^0.466
Endometrial thickness (mm)		6.0±1.1	6.1±0.9	^0.766
Anterior wall thickness (mm)		10.5±1.9	10.3±2.7	^0.700

3DS diagnosis				
		Total=46	**Total=34**	
Uterine position	**AVF**	34 (73.9%)	32 (94.1%)	**#0.019***
	RVF	12 (26.1%)	2 (5.9%)	
Uterine length (mm)		72.5±3.3	72.4±4.3	^0.904
Uterine width (mm)		42.5±3.4	41.1±3.5	^0.077
Endometrial thickness (mm)		6.0±1.1	6.1±0.8	^0.525
Anterior wall thickness (mm)		10.3±2.1	10.4±2.7	^0.771

Table (4): Comparison according to scar niche (TVUS) regarding abnormalities findings at weeks 6-12

Findings	Niche	No niche	p-value
	Total=34	**Total=46**	
Menstruation	31 (91.2%)	43 (93.5%)	§0.695
	Total=31	**Total=43**	
Menstrual duration (day)	5.8±2.0	4.2±1.1	**^<0.001***
PBAC score	161.3±28.4	135.8±30.0	**^<0.001***
Menstrual irregularity	14 (45.2%)	3 (7.0%)	**#<0.001***
Premenstrual spotting	0 (0.0%)	1 (2.3%)	§0.999
Intermenstrual bleeding	4 (12.9%)	0 (0.0%)	**§0.027***
Postmenstrual spotting	11 (35.5%)	3 (7.0%)	**#0.002***
	Total=0	**Total=1**	
Premenstrual spotting days		4.0	NA
	Total=4	**Total=0**	
Intermenstrual spotting days	2.8±0.5		NA
	Total=11	**Total=3**	
Postmenstrual spotting days	6.2±1.3	2.3±0.6	**^<0.001***

NA: Not applicable. ^Independent t-test. #Chi square test. §Fisher's Exact test. *Significant

Table (4) showed that: No statistically significant differences according to scar niche regarding menstruation and premenstrual spotting. Menstrual irregularity, Intermenstrual bleeding and Postmenstrual spotting statistically was significantly more frequent among cases with scar niche. PBAC score as well as durations of menstruation, Postmenstrual spotting were significantly higher among cases with scar niche.

Table (5): Comparison according to scar niche (3DS) regarding abnormalities findings at month-6

Findings	Niche	No niche	p-value
	Total=22	**Total=15**	
Menstruation	22 (100.0%)	15 (100.0%)	NA
	Total=22	**Total=15**	
Menstrual duration (day)	6.1±1.9	4.3±0.6	^<0.001*
PBAC score	160.4±31.7	140.5±20.5	^0.040*
Menstrual irregularity	12 (54.5%)	2 (13.3%)	#0.011*
Premenstrual spotting	0 (0.0%)	0 (0.0%)	NA
Intermenstrual bleeding	5 (22.7%)	1 (6.7%)	§0.368
Postmenstrual spotting	11 (50.0%)	2 (13.3%)	#0.022*
	Total=5	**Total=1**	
Intermenstrual spotting days	3.4±0.5	3.0	¤0.541
	Total=11	**Total=2**	
Postmenstrual spotting days	5.6±1.1	3.0±1.4	^0.012*

Table (6): Comparison according to menstrual abnormalities at week 6-12 regarding scar niche depth (mm)

Abnormalities	Findings	TVUS		3DS	
		Total	Mean±SD	Total	Mean±SD
Menstrual irregularity	**Present**	14	5.5±0.9	15	5.7±1.3
	Absent	17	3.3±0.9	28	3.3±1.3
	p-value	**<0.001***		**<0.001***	
Intermenstrual bleeding	**Present**	4	5.0±0.8	4	5.3±0.5
	Absent	27	4.2±1.5	39	4.0±1.8
	p-value	0.299		0.176	
Postmenstrual spotting	**Present**	11	5.6±0.9	12	5.8±1.5
	Absent	20	3.6±1.1	31	3.5±1.4
	p-value	**<0.001***		**<0.001***	

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

Discussion

Different studies were done evaluating the prevalence of niches in the caesarean scar with the relationship with postmenstrual spotting, some of them agree and others differ from our results.

The current study revealed that Cesarean section scar niche found by transvaginal ultrasonography in 42.5% of the studied cases and was in 57.5% by 3D.

According to the demographic characteristics, BMI and the Number of previous sections were significantly higher among cases with scar niche. Using TVUS; BMI was (29.1±3.0, p value = <0.001) and the Number of previous sections was (2.0±0.7, p value = <0.001). While using 3D; BMI was (28.4±3.3, p value = 0.027) and the Number of previous sections was (1.9±0.7, p value = <0.001). Age, Time from last CS, Gestational age at last CS, Current breast feeding, and current contraception were insignificant.

Also, according to uterine characteristics the current study revealed that Cesarean section scar niche was significantly more frequent in RVF uterus. Using TVUS; RVF uterus was (29.4%, p value = 0.016). While using 3D; it was (26.1%, p value = 0.019). Uterine length, Uterine width, Endometrial thickness, and Anterior wall thickness were insignificant.

Regarding TVUS and 3D findings of scar niche at weeks 6-12 and at 6 months, our results revealed that there were no statistically significant differences according to scar niche regarding menstruation, premenstrual spotting, and intermenstrual bleeding.

While Menstrual irregularity, PBAC score, durations of menstruation, and postmenstrual spotting statistically were significantly higher among cases with scar niche.

At weeks 6-12, using TVUS; Menstrual irregularity was (45.2%, p value = <0.001), PBAC score was (161.3±28.4, p value = <0.001), duration of menstruation was (5.8±2.0, p value = <0.001), and postmenstrual spotting was (35.5%, p value = 0.002). While using 3D; Menstrual irregularity was (34.9%, p value = 0.004), PBAC score was (153.0±31.2, p value = 0.038), duration of menstruation was (5.3±1.9, p value = 0.017), and postmenstrual spotting was (27.9%, p value = 0.020).

At 6 months, using TVUS; Menstrual irregularity was (70.6%, p value = <0.001), PBAC score was (163.7±31.5, p value = 0.027), duration of menstruation was (6.6±1.8, p value = <0.001), and postmenstrual spotting was (64.7%, p value = <0.001). While using 3D; Menstrual irregularity was (54.5%, p value = 0.011), PBAC score was (160.4±31.7, p value = 0.040), duration of menstruation was (6.1±1.9, p value = <0.001), and postmenstrual spotting was (50.0%, p value = 0.022).

These findings are in agreement with previous studies. Van der Voet et al., [2] conducted a prospective cohort study that enrolled 263 non-pregnant women delivered by caesarean section to study the prevalence of niches in the caesarean scar in a random population, and the relationship with postmenstrual spotting.

In agreement with our results, Van der Voet et al., [2] reported that Niche prevalence was 49.6% when evaluated by TVU and 64.5% when evaluated by Sono hysterography (3D) and number of previous sections were significantly correlated with higher prevalence of scar niche as in women with one caesarean section, 62% who underwent 3D had a niche, compared with 68.2% of women with two caesarean sections and 77.8% of women with three caesarean sections which is in harmony with our results.

In a study conducted by Bij de Vaate et al. [6], on 225 patients with a previous history of cesarean section examined for disorders of menstruation, CS niche was detected by TVS in 54 women (24%), and the definition of the niche was an anechoic region at the line of the CS scar with at least 1mm depth.

On the contrary, another prospective study, in which the examination was conducted six months after a cesarean section, showed the incidence of the niche of 22.4% with TVS [7]. The difference in prevalence percentage was dependent of different sample sizes.

At week 6-12, according to menstrual abnormalities, our study results revealed that there were no statistically significant differences regarding residual myometrium thickness with significantly lower ratio of residual myometrium thickness in cases with menstrual abnormalities like Menstrual irregularity by using both TVUS and 3D (p value = <0.001) and Postmenstrual spotting using TVUS (p value = <0.002) and using 3D (p value = <0.001) but not in intermenstrual spotting which was not significant statistically.

Consequently, our study results revealed that there were statistically significant positive correlations between scar depth and each PBAC score; TVUS (p value = <0.002) and 3D (p value = <0.001) as well as durations of Menstrual duration; TVUS (p value = <0.001) and 3D (p value = <0.001) and Postmenstrual spotting; TVUS (p value = <0.014) and 3D (p value = <0.001). While there were no statistically significant correlations between Residual myometrium thickness and menstrual bleeding durations, PBAC score or postmenstrual spotting. Yet, there was statistically significant negative correlations between Ratio of residual myometrium thickness and each PBAC score; TVUS (r = -0.462, p value = 0.009) and 3D (r = -0.644, p value = <0.001) score as well as Menstrual duration; TVUS (r = -0.424, p value = 0.018) and 3D (r = -0.463, p value = 0.002) and Postmenstrual spotting duration; TVUS (r = -0.691, p value = 0.018) and 3D (r = -0.686, p value = 0.014).

At 6 months, according to menstrual abnormalities, our study results revealed that there were no statistically significant differences regarding residual myometrium thickness with significantly lower ratio of residual myometrium thickness in cases with menstrual abnormalities like Menstrual irregularity by using both TVUS (p value<0.007) and 3D (p value<0.008) and Postmenstrual spotting using TVUS (p value<0.019) and using 3D (p value<0.031) but not in intermenstrual spotting which was not significant statistically.

Consequently, our study results revealed that there were statistically significant positive correlations between scar depth and each PBAC score; TVUS (p value = <0.001) and 3D (p value = 0.003) as well as durations of Menstrual duration; TVUS (p value = <0.001) and 3D (p value = <0.001) and Postmenstrual spotting; TVUS (p value = <0.001) and 3D (p value = <0.026).While there were no statistically significant correlations between Residual myometrium thickness and menstrual bleeding durations, PBAC score or postmenstrual spotting. Yet, there was statistically significant negative correlations between Ratio of residual myometrium thickness and each PBAC score; TVUS (r = -0.704, p value = 0.002) and 3D (r = -0.388, p value = 0.044) score as well as Menstrual duration; TVUS (r = -0.579, p value = 0.015) and 3D (r = -0.547, p value = 0.008) and Postmenstrual spotting duration; TVUS (r = -0.771, p value = 0.005) and 3D (r = -0.545, p value = 0.043).

In agreement with our results, El-Samie et al. [8] conducted a prospective study that enrolled 100 Patients, who had a previous cesarean section and complained of unexplained abnormal uterine bleeding to evaluate the prevalence of uterine niche after CS in women with abnormal uterine bleeding and revealed that there was a statistically significant difference (P<0.05) as regards the type of abnormal uterine bleeding and associated pain with a higher percentage of postmenstrual spotting pattern of abnormal bleeding (65.2%) and dysmenorrhea (60.9%).

In a previous study on 207 women with prior CS performed by Wang et al. [9], to evaluate the prevalence of clinical symptoms

related to niches within the cesarean scar, the most common clinical presentation was postmenstrual spotting found in 63.8% (131/207) of patients (P< 0.001). That agreed with the results of our study which was statistically significant and reveals an association between CS niche and postmenstrual spotting.

In agreement with our results, Van der Voet et al. [2] compared the results of 3D with TVU and revealed that women with a ratio of residual myometrium of less than half of the adjacent myometrium (ratio <0.5) measured by TVU or GIS reported postmenstrual spotting more often than women with a ratio of >0.5.

Also, niche prevalence was higher, measured niche depth was greater, and residual myometrium was thinner when detected by SIS and postmenstrual spotting 1 year after caesarean section was strongly related to the presence of a niche detected by both TVU and 3D [2].

Bij de Vaate et al. [6] findings were in agreement with our results in that postmenstrual spotting was reported by 33.6% of women with a niche and 15.2% of women without a niche (P = 0.002) that indicated significant correlation between niche and postmenstrual bleeding. The niche size was significantly different between women with and without postmenstrual spotting (P = 0.02) that was larger in women with postmenstrual bleeding.

Several previous studies agreed with our results and indicated a positive relationship between large niches and postmenstrual spotting. Large niches (those with a residual myometrium with thickness of <50% of that of the adjacent myometrium) was significantly related to postmenstrual spotting [2].

This parameter and cut-off level were also used by Ofilli-Yebovi et al. [10] who reported a high prevalence of women with a ratio of less of than 50% in a population with gynecological symptoms. A potential relationship between niche size and postmenstrual spotting is in line with the hypothesis that spotting is induced by the accumulation of blood inside the niche. A depth of more than half the myometrial thickness makes the anterior part of the niche possibly large enough to obstruct the direct outflow of menstrual blood. This, in combination with lower contractility as a result of fibrosis, may induce the accumulation of blood in a niche [2].

Conclusion

Caesarean section scar was visible in all women at 6–12 weeks and 6 months after caesarean section. The prevalence of niches detected by 3D is high after caesarean section (56.6%). More niches are detected than using TVUS (41.3%), with a larger observed niche size and reduced residual myometrial thickness. The presence of a niche is significantly related to intermenstrual and postmenstrual spotting.

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Effect of women's Obesity on the outcome of In Vitro Fertilization (Comparative study)

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Abstract

Background: Obesity is a major problem of public health, intervenes at different levels on the reproductive function such as: increase conception time and decreased fecundity.

Aim of the Work: to assess the impact of women's obesity on the outcome of ICSI and embryo transfer by measuring the number of clinical pregnancies in groups of patients with different BMI, also by measuring total FSH dose required for follicular stimulation, The duration required for stimulation, Serum estradiol level on the day of hCG administration, number of oocytes collected, number of normally fertilized oocytes, fertilization rate, positive serum β-hCG rate, ongoing pregnancy rate.

Patients and Methods: Retrospective comparative cohort study, conducted in IVF unit in maternity hospital of Ain Shams university, from January 2016 to December 2021, all the patients underwent ICSI and embryo transfer in the given period their record will be revised and included regardless sample size. With at least 132 patients will be enrolled divided into 3 groups: normal weight patients with BMI from 18.5kg/m2 to 24.9 kg/m2, overweight patients with BMI from 25kg/m2 to 29.9 kg/m2, and obese patients with BMI ≥ 30kg/m^2.

Results: The starting dose of FSH showed no significant differences (p=0.240), and likewise, the total dose exhibited no significant variations (p=0.370). However, certain trends emerged. Group C had a slightly longer duration of stimulation (p=0.091), potentially indicating a more robust approach, notably, the number of oocytes collected significantly differed among the groups (p=0.019*), with Group A having the highest mean count (13.17±8.28), followed by Group B (11.05±6.78), and then Group C (9.48±6.37). This disparity might imply differences in ovarian response or treatment effectiveness. The number of oocytes fertilized did not significantly differ (p=0.630).

Conclusions: The comprehensive analysis of demographic and fertility-related parameters across three distinct groups (Group A, Group B, and Group C) undergoing in vitro fertilization (IVF) treatment reveals that there are statistically significant differences in the ovarian response

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to the stimulation in the form of the duration and the number of oocytes retrieval, while in the in most of the measured variables there is no statistically significant difference. These include age, parity, infertility status, hormone levels, antral follicle counts, type and dosage of follicle-stimulating hormone (FSH), and numerous IVF outcome measures such as the number of good quality embryos, embryos obtained, fresh transferred embryos, biochemical and clinical pregnancy test results, and live birth outcomes. These findings suggest that, on average, the studied groups exhibit comparable demographic characteristics, ovarian function, and IVF treatment outcomes, highlighting the consistency in various aspects of IVF protocols and reproductive outcomes among these groups.

Keywords: Women's Obesity, Vitro Fertilization.

INTRODUCTION

Obesity is a major problem of public health, intervenes at different levels on the reproductive function such as: increase conception time and decreased fecundity. The number of obese women in demand of ART is unknown **(Brunet et al., 2020)**.

According to the National Institute for Health and Care Excellence (NICE) guidance on fertility problems, women should be informed that body mass index (BMI) has to be in the range of 19–30 kg/m2 before starting assisted reproduction. Higher BMI is likely to reduce ART procedures success. A BMI more than 35 kg/m2 is likely to be considered as a contraindication to ART, and many centers around the world are prohibit access to ART program for obese women, in particular IVF **(Brunet et al.,2020)**

Studies on the potential effects of the increased BMI on fertility treatment outcomes have shown conflicting results. Surprisingly, multiple studies and two systematic reviews reported insignificant adverse effects of elevated BMI on IVF outcomes **(Kudesia et al., 2018)**.

Other studies, however, including a systematic-analysis have associated elevated BMI with higher gonadotropin requirement, fewer oocytes collected, higher cancellation rates, reduced pregnancy and live birth rates, as well as higher miscarriage rates **(Sarais et al., 2016)**.

Given the limited access of obese women to IVF, few studies included women with a BMI greater than 35 kg/m2. Most studies considered only fresh embryo transfer (Provost et al., 2016; Kawwass et al., 2016) or only the first stimulation attempt (Ding et al., 2019). Thus, the impact of obesity on IVF outcomes remains unclear, especially the grade of obesity, and studies taking into account both the entire embryonic cohort (fresh and frozen or vitrified embryos) and all stimulation attempts are lacking **(Brunet et al.,2020)**.

AS it is common for overweight and obese women to seek fertility treatment, such as IVF. Many studies have found that the excess in the maternal adipose tissue is linked to a number of important adverse outcomes in spontaneous pregnancies (Liu et al., 2020).

After ART, pregnant women have a higher risk to experience pregnancy-related complications (i.e., high blood pressure, gestational diabetes, placenta previa, placental abruption, postpartum hemorrhage, hydramnios, small for gestational age (SGA), premature birth, and cesarean) compared with those who conceive naturally **(Luke, 2017 ;Szymusik et al., 2019)**.

In an analysis of nearly 500,000 cycles reported to the Society for Assisted Reproductive Technologies (SART), both obese and underweight women had lower rates of clinical pregnancy and live birth after fresh autologous transfers (adjusted RR 0.97 and 0.95 for underweight, 0.94 and 0.87 for obese women, respectively), as well as higher rates of low birth weight and premature deliveries. Meanwhile, in the study, only obese women had a higher miscarriage rate **(Kawwass et al., 2016)**.

Some studies have tried to identify the mechanisms by which excess weight might affect IVF outcomes by exploring associations with oocyte quality, embryo quality, or uterine function. For example, preliminary data has associated maternal obesity with decreased oocyte size or deformities in meiotic spindle formation **(Kudesia et al., 2018)**.

Given these results and the higher spontaneous miscarriage rates that have been observed in obese women, some researchers have speculated that increased meiotic errors might underlie these pregnancy losses. However, higher miscarriage rates were also observed in one study of women who had pre-implantation screened embryos transferred after IVF **(Tremellen et al., 2016)**.

It has long been hypothesized that environments of excessive adipose tissues may negatively impact implantation. Ovum donation cycles considered as a way to study the possible impact of obesity on implantation in a more well-controlled way **(Kudesia et al., 2018)**.

AIM OF THE WORK

The aim of this study is to assess the impact of women's obesity on the outcome of ICSI and embryo transfer by measuring the number of clinical pregnancies in groups of patients with different BMI.

Also by measuring total FSH dose required for follicular stimulation, The duration required for stimulation, Serum estradiol level on the day of hCG administration, number of oocytes collected, number of normally fertilized oocytes, fertilization rate, positive serum β-hCG rate, ongoing pregnancy rate.

PATIENTS AND METHODS

Study Design: Retrospective comparative cohort study

Study setting: IVF unit in maternity hospital of Ain Shams university

Period of study: From January 2016 to December 2021

Population of the study: All the patients underwent ICSI and embryo transfer in the given period their record will be revised and included regardless sample size. With at least 132 patients will be enrolled divided into 3 groups: normal weight patients with BMI from 18.5kg/m2 to 24.9 kg/m2, overweight patients with BMI from 25kg/m2 to 29.9 kg/m2, and obese patients with BMI ≥ 30kg/m2.

Inclusion Criteria: Patients age between 18 years old to 35 years old, and patients with BMI ≥ 18.5 kg/m^2.

Women will be divided into 3 groups according to the World Health Organization (WHO) classification cut-points: (Brunet et al., 2020) Normal-weight (18.5–24.9 kg/m^2), Overweight (25–29.9 kg/m^2), and obesity (≥ 30 kg/m) and all participants underwent induction of ovulation using long gonadotropin agonist protocol.

Exclusion Criteria: Whose BMI wasn't recorded in their files (Because of the lack of the information), those undergoing IVF for pre-implantation genetic diagnosis, (To minimize the factors that may affect the result), and those for who cycles were cancelled before oocyte pickup, (Because of not completing the IVF process).

Ethical Consideration: the study will be approved by research ethical committee of the faculty of medicine of Ain Shams University. The data will be anonymously analyzed so the confidentiality of the patients will be preserved.

Study procedure: collecting data from records of the patients who underwent induction of ovulation using long gonadotropin agonist protocol:

History taking: including

Personal history: Name, age and married for…., previous marriage, any children, parity, type of infertility whether primary

or secondary, husband history, occupation, special habits of medical importance, and previous marriage: any children

Complaint: Failure of conception

Present history: History suggestive of ovarian factor (irregular cycle- hirsutism-galactorrea- change in body weight), history of virilization (irregular cycle- facial hair-deepening of voice), history suggestive of PID (lower abdominal and pelvic pain-heavy vaginal discharge- pain or bleeding during intercourse), and history suggestive of thyroid abnormality (Abnormal menstrual periods numbness or tingling in hands-appetite change- insomnia).

Menstrual history: Menarche age, rhythm (regular, irregular), menstrual cycle (average- polymenorrhea - oligomenorrea), Intermenstrual (pain- bleed- discharge), Dysmenorrhea (No-congestive- spasmodic), and first day of LMP.

Obstetric history: Data of all previous pregnancies (including miscamiages and terminations), Length of gestation, date and place of delivery, onset of labor (including details of induction of labor), mode of delivery, sex and birth weight, fetal and neonatal lie, and clear details of complications or adverse outcomes (Shoulder dystocia. post-partum hemorrhage, stillbirth)

Contraceptive history: What method-duration- complication.

Sexual history: Frequency- dyspareunia.

Past history: Medical disorders (DM-HTN.), previous operations, allergy, and medications.

Clinical examination including: General exam: include, blood, temperature, height, and weight to calculate BMI body, pressure-pulse-weight (kg) /height (m2), Breast examination: for any discharge, mas, and change in color of skin, Pelvic exemption: Inspection of the vulva, perineum, vaginal examination of bleeding or discharge if any (amount, color, odor), vaginal walls, fornices, and cervical mobility and os direction, MOCK test for assessment of cervical canal by pass catheter through the cervix till internal os to asses for easy embryo transfer if difficult MOCK refer to do hysteroscopy assessment, Bimanual examination for size, mobility, and direction of the uterus- adnexa, Speculum for inspection of the vaginal walls, and fornices and cervix for detection of any adnexal mass or any pelvic pathology.

Infertility evaluation including:

Male partner: Semen analysis of the husband.

Female partner: Hysterosalpingogram (HSG) or laparoscopy of the patients, hormonal profile: basal serum (FSH, LH, TSH, basal estradiol), and baseline transvaginal ultrasound which include; Uterus (position, size .....X…..X...mm- myometrium-cervix), RT ovary (size ....x....x...mm- site-follicles-any pathology), left ovary (size ....x....x... mm- site-follicles-any pathology), and douglas pouch

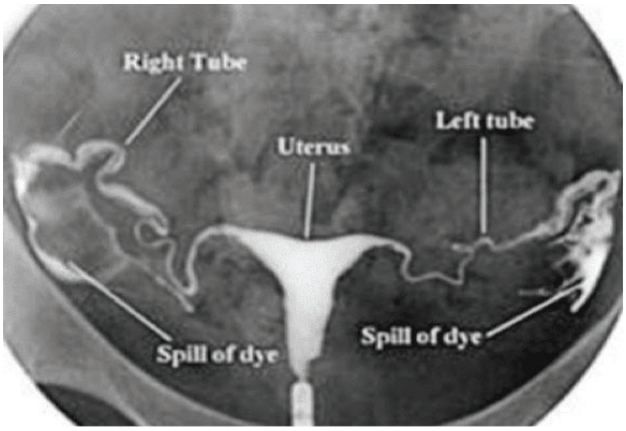

Figure 1: Normal Hysterosalpingogram **(Ain shams maternity hospital)**

Figure 2: Normal ovarian size with multiple follicles **(Ain shams maternity hospital)**

Induction of ovulation: On day 3 of spontaneous cycles, all patients Had basal Hormonal profile (FSH, LH, E2, TSH and prolactin), transvaginal (TV) ultrasound (U/S) on day 3 of Non- Stimulated Cycles was done by transvaginal probe of 5-9 MHZ. Any patient found to have uterine Abnormalities Was excluded, and controlled ovarian hyper stimulation protocol was held according to a long GnRH agonist protocol starting from 21" day of cycle midluteal phase by daily subcutaneous injection of triptoreline acetate (Decapeptyl 0.05 mg.Ferring Pharmaceutical, Kid, Germany). On day 2 of next Cycle Patient did serum E2 level if E2≤ 50pg/ml or Decapeptyl was taken for 12-14 days for comple down regulation. Then on day 3 of cycle ovarian hyper stimulation was started by daily injection of HMG (Menogon 75 IU/ amp "FerringPharmceutical. Kid,Germany" Merional 75 IU/ amp IBSA, Switzerland") or rFSH (Gonapure 75 IU/amp MINAPHARM, Egypt) or Urofollitropin (fostimon 75IU/ amp IBSA, Switzerland)

The Starting dose of gonadotropins was prescribed **According to:** Age, BMI, AFC, hormonal profile, and previous response to induction.

Then the dose was adjusted according the ovarian Response that was assessed Transvaginal folliculometry which was done on day Six stimulation for ovarian response and endometrial pattern and thickness. According to The ovarian response, every other day TV U/S was performed and at the moment when the leading follicle reaches14mm, Daily TV U/S was Performed till the largest follicle reached a Diameter Of>18mm.

HCG (Choriomon 10,000 du/n1 "IBSA, Switzerland") was administered for triggering ovulation when at least 3 Follicles >18mm diameter.

The endometrium pattern was classified as: Proliferative when echogenicity is hypo echoic in relation to the myometrium, peri-ovulatory when it is trilaminar, and secretory when it is hyper echoic.

Figure 3: Monitoring of endometrial development during ovulation induction preovulatory **(Ain shams maternity hospital)**

Ovum Pick up: 34-36 hours After HCG injection, the transducer was connected to the ultrasound system. The direction of the Guide Beam was checked. The puncturing needle was connected to an aspiration apparatus attached by a fixation Ring To The front and rear ends of the vaginal transducer, there by defining the direction of puncture corresponding to the guide beam on the ultrasound image.

The aspiration was checked using test tubes. The uterus, both ovaries and iliac vessels were identified by the Visualization in Both planes. The distance between the Upper pole of the vagina and the ovary was closely Evaluated (care was taken to Avoid intestinal or Vascular Interposition).

Depth localization of the closest accessible follicle (distance from the upper vaginal pole the center of the follicle) was done. Needle was pushed forcefully to the center of the Follicle (Aspiration pressure 90-100mmHg).

IVF-ICSI: Intracytoplasmic sperm injection was performed on Metaphase II oocytes using the direct penetration Technique, fertilization results were assessed 16-19 Hours after ICSI. Fertilization was considered normal by the presence of two pronuclear and or 2nd polar body. Oocyte degeneration was identified by collapse of cytoplasmic contents and separation from the zona. Failed fertilization was defined the absence pronuclei.

Embryo transfer: Embryo transfer was done on day 3 or 5 using cook or labotect soft catheter under ultrasound guide at a distance about 1-1.5 cm from the fundus by the same gynecologist number maximum embryos transferred 3 embryos on day 3 and maximum 2 embryos on day 5.

Luteal phase support and assessment of: This may involve oral, vaginal or intramuscular progesterone, and assessment of pregnancy by serum βhCG was performed after 12 days on day 3 embryo transfer and after 9 days on day 5 embryo transfer followed Transvaginal US 4 weeks after pregnancy test for clinical pregnancy assessment either fetal echo or pulsation of heart.

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

The following tests were done: One way ANOVA test of significance was used when comparing between more than two means, the Comparison between groups with qualitative data was done by using Chi-square test and the confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

Probability (P-value): P-value <0.05 was considered significant, P-value <0.01 was considered as highly significant, and P-value >0.05 was considered insignificant.

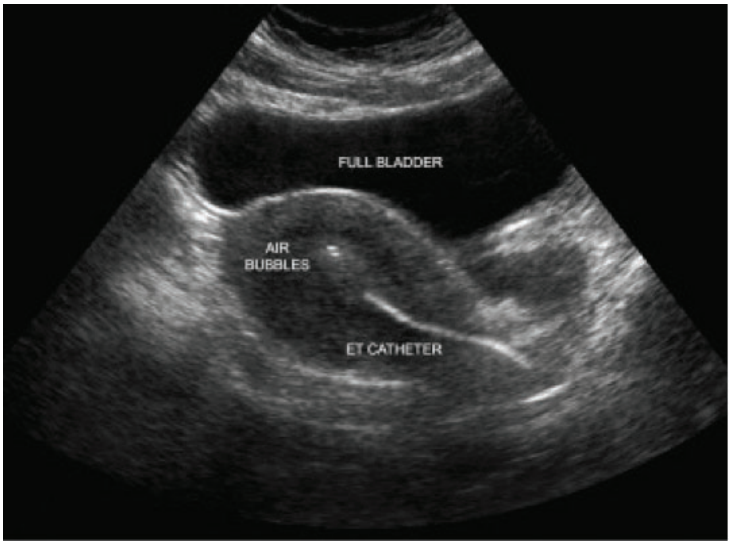

Figure 4: Embryo transfer by soft catheter

RESULTS

The aim of the study was to assess the impact of women's obesity on the outcome of ICSI and embryo transfer by measuring the number of clinical pregnancies in groups of patients with different BMI

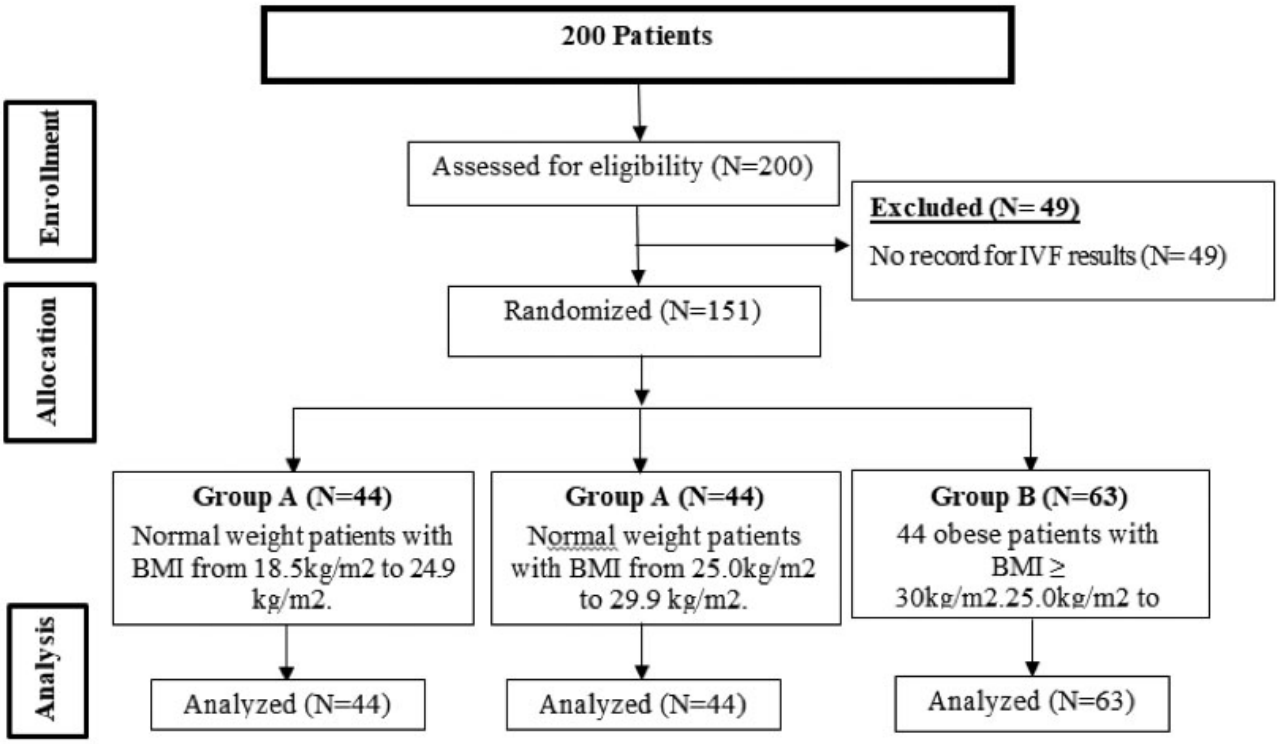

Figure (5): Study consort

Table 1: Comparison of Demographic Data in Groups (A, B, and C).

		Group A (n=44)	Group B (n=44)	Group C (n=63)
Age	**Range**	19 - 35	20 - 35	21 - 35
BMI	**Range**	**18 – 24.9**	**25 – 29.9**	**30 - 35**

Using: One way ANOVA test for Mean±SD (§); p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.01 is highly significant.

The study compared three groups (A, B, and C), Group A and B consisting of 44 participants and Group C consisting of 63, based on age and BMI.

Table 2: Distribution of Parity and Infertility Factors among Participant Groups (A, B, and C).

		Group A (n=44)		Group B (n=44)		Group C (n=63)		Test value	P-value
		N	%	N	%	N	%		
Parity	**Null Para**	32	72.6%	25	56.8%	39	61.9%	0.323	0.729
	Multipara with living offspring	6	13.7%	12	27.3%	17	26.9%		
	Multipara with no living offspring	6	13.7%	7	15.9%	7	11.2%		
Infertility	**NR**	14	32.0%	17	38.3%	24	38.3%	0.423	0.644
	Male factors	18	40.9%	15	34.3%	21	33.4%		
	PCO	2	4.5%	2	4.5%	9	14.3%		
	Tubal factor	4	9.1%	5	11.2%	6	9.2%		
	Poor ovarian reserve	3	6.8%	2	4.5%	1	1.6%		
	Endometriosis	3	6.8%	1	2.3%	1	1.6%		
	Hypogonadotrophic	0	0%	1	2.3%	1	1.6%		
	Small uterus	0	0%	1	2.3%	0	0%		

-NR: no recorded cause for the infertility -PCO: polycystic ovarian syndrome.

Using: X2= Chi- Square test, p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.01 is highly significant.

This table analyzed three groups (A, B, and C), with respect to parity and infertility factors. Parity distribution demonstrated no significant differences (p=0.729), where Group A had 72.6%, Group B had 56.8%, and Group C had 61.4% null gravid women. Similarly, infertility factors exhibited no significant distinctions (p=0.644).

Table 3: Comparison of Reproductive Hormone Levels and Antral Follicle Counts among Participant Groups (A, B, and C).

		Group A (n=44)	Group B (n=44)	Group C (n=63)	Test value	P-value
AMH	**Mean ±SD**	3.0±2.06	2.89±1.71	3.39±2.17	0.547	0.581
	Range	0.85 – 10.0	0.61 – 8.33	0.72 – 8.33		
FSH	**Mean ±SD**	6.33±1.78	6.74±2.30	6.98±2.49	0.745	0.477
	Range	3.7 – 11.0	0.10 – 13.60	3.70 – 11.0		
LH	**Mean ±SD**	6.27±2.36	5.63±2.52	5.94±2.63	0.572	0.566
	Range	3.0 – 12.80	0.10 – 13.35	0.65 – 13.70		
Antral follicular count	**Mean ±SD**	13.23±4.4	12.26±4.19	13.66±6.09	0.873	0.421
	Range	7.0 – 23.0	4.0 – 22.0	2.0 – 24.0		

Using: One way ANOVA test for Mean±SD (§); p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.01 is highly significant.

This table analyzed three groups (A, B, and C) in terms of various reproductive parameters. No significant differences were found among the groups for anti-Mullerian hormone (AMH) levels (p=0.581), follicle-stimulating hormone (FSH) levels (p=0.477), luteinizing hormone (LH) levels (p=0.566), and antral follicular count (p=0.421) Despite variations in means, the lack of statistically significant differences suggests that these reproductive parameters are relatively comparable among the three groups.

Table 4: Comparison of Treatment Protocol and Oocyte Outcomes among Participant Groups (A, B, and C).

		Group A (n=44)		Group B (n=44)		Group C (n=63)		Test value	P-value
		N	%	N	%	N	%		
Type of FSH	NR	12	27.3%	14	31.8%	19	30.2%	5.369	0.497
	rFSH	18	40.9%	23	52.3%	30	47.6%		
	Human menopausal gonadotrophin	13	29.5%	5	11.4%	13	20.6%		
	Urofollitropin	1	2.3%	2	4.5%	1	1.6%		
Starting dose (amp)	Mean ±SD	2.93±0.83		3.0±0.73		3.20±0.95		1.082	0.240
	Range	2 - 5		2 - 4		2 - 6			
Total dose (amp)	Mean ±SD	36.13±15.76		41.0±13.73		42.0±16.06		1.002	0.370
	Range	12 - 68		12 - 68		18 - 80			
Duration of stimulation (days)	Mean ±SD	12.56±2.02		12.95±2.33		13.34±2.51		2.444	0.091
	Range	9 - 16		9 - 18		10 - 21			
No. oocytes collected	Mean ±SD	**13.17±8.28**		**11.05±6.78**		**9.48±6.37**		**4.120**	**0.019***
	Range	**2 - 31**		**1 - 31**		**1 - 27**			
No. oocytes fertilized	Mean ±SD	10.73±6.58		8.72±5.59		7.05±4.30		0.463	0.630
	Range	1 - 26		1 - 23		1 - 17			

Using: One way ANOVA test for Mean±SD (§), X2= Chi- Square test; p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.01 is highly significant.

This table evaluated three groups (A, B, and C) based on the type and dosage of follicle-stimulating hormone (FSH) used during stimulation for assisted reproduction. No significant differences were observed in the type of FSH used (p=0.497), with each group having varying proportions of participants using different types. The starting dose of FSH showed no significant differences (p=0.240), and likewise, the total dose exhibited no significant variations (p=0.370).

However, certain trends emerged. Group C had a slightly longer duration of stimulation (p=0.091), potentially indicating a more robust approach.
Notably, the number of oocytes collected significantly differed among the groups (p=0.019*), with Group A having the highest mean count (13.17±8.28), followed by Group B (11.05±6.78), and then Group C (9.48±6.37). This disparity might imply differences in ovarian response or treatment effectiveness. The number of oocytes fertilized did not significantly differ (p=0.630).

Table 5: Comparison of Embryo Quality, Transfer Outcomes, and Pregnancy Measures among Participant Groups (A, B, and C).

		Group A (n=44)		Group B (n=44)		Group C (n=63)		Test value	P-value
		N	%	N	%	N	%		
No. of good quality embryo	**Mean ±SD**	3.66 ± 3.31		3.50 ± 3.35		3.25 ± 3.18		0.586	0.532
	Range	1 - 7		2 - 7		1 - 6			
No. of embryo obtained at day 2	**Mean ±SD**	5.83±4.77		5.26±4.71		4.18±3.07		1.517	0.224
	Range	1 - 19		1 - 21		1 - 13			
No. of fresh transferred embryos	**1**	6	13.7%	7	16.2%	11	17.5%	3.055	0.802
	2	18	40.9%	11	25.6%	21	33.3%		
	3	18	40.9%	23	51.2%	29	46.0%		
	4	2	4.5%	3	7.0%	2	3.2%		
Biochemical pregnancy test	**Positive**	21	47.7%	24	54.5%	37	58.7%	1.145	0.564
	Negative	23	52.3%	20	45.5%	26	41.3%		
Clinical pregnancy test	**Mean ±SD**	0.76±0.89		0.59±0.79		0.59±0.87		0.462	0.631
	Range	0 - 3		0 - 2		0 – 3			
live birth	**Mean ±SD**	0.72±0.88		0.51±0.71		0.60±0.88		0.565	0.570
	Range	0 - 3		0 - 2		0 – 3			

Using: One way ANOVA test for Mean±SD (§), X2= Chi- Square test; p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.01 is highly significant.

This table analysis of three groups (A, B, and C) the outcomes of assisted reproductive procedures were assessed. The number of good quality embryos displayed no significant differences (p=0.532), with Group A having a mean of 3.66, Group B with 3.50, and Group C with 3.25. Likewise, the number of embryos obtained at day 2 showed no significant variation (p=0.224), with Group A having a mean of 5.83, Group B with 5.26, and Group C with 4.18.

When it comes to fresh transferred embryos, the distribution did not significantly differ (p=0.802), with different groups having similar percentages for 1, 2, 3, and 4 embryos transferred. Biochemical pregnancy tests yielded no significant distinctions (p=0.564), with positive results for 47.7%, 54.5%, and 58.7% of Groups A, B, and C respectively.

Clinical pregnancy tests exhibited a non-significant difference (p=0.564), the number of live births did not significantly differ (p=0.630).

DISCUSSION

Obesity is a prevalent global health concern, and its impact on various aspects of reproductive health has garnered significant attention. Among the critical areas of interest is the influence of obesity on the outcomes of in vitro fertilization (IVF). In recent years, obesity has been recognized as a complex factor that can potentially affect the success rates of IVF treatments. This introduction explores the multifaceted relationship between women's obesity and IVF outcomes, shedding light on the challenges and considerations that healthcare providers and researchers must address in the realm of fertility treatments(Tauqeer et al., 2018).

This study is a retrospective cohort study aimed to assess the impact of women's obesity on the outcome of ICSI and embryo transfer by measuring the number of clinical pregnancies in groups of patients with different BMI. All the files of the patients attended to the ART unit in the period of the study were revised with total number 2000.The patients, underwent long agonist gonadotropin ovarian stimulation , divided in to three groups as group (A) of 44 women of normal weight with BMI between 18kg/m2 to 24.9kg/m2, group (B) with 44women of over-weight with BMI from 25kg/m2 to 29.9kg/m2 and group (C)of 63 women obese patients with BMI $\geq$ 30kg/m2.

The current study data presents a comparison of demographic information among the three groups labeled as Group A, Group B, and Group C. The data includes information on age and BMI (Body Mass Index) for each group.

The mean age for Group A is 27.97 years, for Group B is 29.42 years, and for Group C it is 29.17 years. Group B has the highest mean age, while Group A has the lowest .The age range for all groups' spans from 19 to 35 years to have a good response during the ovarian stimulation, suggesting that the participants in all three groups are within a similar age range.

Sneed ML et al.,(2008) in their retrospective study to show the impact of both the age and BMI on the IVF revealed that although BMI did not have a major effect on IVF outcome, but there was a significant BMI x Age interaction. Younger ages, a high BMI had a pronounced negative influence on fertility, but this effect decreased as the patient age increased. Clinical pregnancy rates decreased with increasing BMI and increasing Age. So the impacts of BMI on fertility change in relation to the Age of the patient.

In cohert study in china (Xiang Liu et al (2023)) to evaluate the influence of male / female over-weight and obesity combined .They found that combined male/female overweight/obesity groups had much lower numbers of available embryos and high-quality embryos .

In the current study a comparative analysis of demographic information among the three groups. The data includes information on two variables: parity and infertility cause, with the associated test values and p-values. Let's discuss the findings in paragraphs:

The data reveals the distribution of parity among the three groups. It is interesting to note that the majority of participants in all three groups fall into the "NG" category, which typically represents women who have not given birth. Group A has 72.6% in this category, Group B has 56.8%, and Group C has 61.9%. The differences in parity among the groups do not appear to be statistically significant, as indicated by the p-value of 0.729. This suggests that the distribution of parity is relatively similar across the groups.

In the same line Vural et al., (2015) revealed that the mean parity values among three groups.. While there are slight differences in mean parity values, these variations are not statistically significant (p=0.228). This suggests that, on average, the parity levels are relatively similar among the three groups, with no substantial differences observed.

The infertility status of the participants, categorized into various types of infertility conditions. The most common infertility type in group A appears to be the male factor with 40.9% while in group B and C was "NR" (No Reason Specified), with approximately 38.3% in Group B, and 38.3% in Group C. Other infertility types such as tubal and endometriosis are also present across the groups.

Pandey et al., (2010) revealed that the provided information categorizes infertility factors and suggests diagnostic tests and treatments. Participants' infertility status can be assessed and managed accordingly. Categories include ovulatory dysfunction, tubal occlusion, endometriosis, diminished ovarian reserve, uterine factors, and male factors, each requiring specific evaluation and interventions for improved fertility outcomes.

In the current study the basil hormonal levels AMH (Anti-Müllerian Hormone) levels, FSH (Follicle-Stimulating Hormone) levels, LH (Luteinizing Hormone) levels were measured in the second day of the cycle , and antral follicle counts for both the right and left ovaries, a comparative analysis was done and their associated test values and p-values.

AMH is an important marker for ovarian reserve, reflecting a woman's remaining egg supply. The mean AMH levels are quite similar among the three groups, with Group A having mean of 3.0, Group B with 2.89, and Group C with the highest mean of 3.39. The test value and p-value for AMH levels (0.547 and 0.581, respectively) indicate that there is no statistically significant difference in AMH levels among the three groups. This suggests that the ovarian reserve, as indicated by AMH levels, is comparable across these groups.

FSH is another hormone that plays a role in ovarian function. The mean FSH levels are also quite similar among the three groups, with Group A having a mean of 6.33, Group B with 6.74, and Group C with 6.98. The test value and p-value for FSH levels (0.745 and 0.477, respectively) indicate that there is no statistically significant difference in FSH levels among the groups. Similar to AMH, this suggests that ovarian function, as measured by FSH, is comparable across the groups.

LH is a hormone that, along with FSH, regulates the menstrual cycle and ovulation. The mean LH levels are again quite similar among the three groups, with Group A having a mean of 6.27, Group B with 5.63, and Group C with 5.94. The test value and p-value for LH levels (0.572 and 0.566, respectively) also indicate no statistically significant difference in LH levels among the groups. This suggests that LH levels are comparable across the groups, which is important for normal menstrual and ovulatory function.

Antral follicle counts , indicative of the number of small, growing follicles in the ovaries and can provide insights into ovarian reserve, show similar patterns among the groups. The test values and p-values for these counts also indicate no statistically significant differences among the groups. This suggests that the number of antral follicles in the ovaries, which can influence fertility potential, is comparable across the groups.

The same results was obtained by Vural et al., (2015) who revealed that the provided data compares basal hormonal and ultrasonography characteristics among three groups (Group A, Group B, and Group C). While there are some numerical differences in FSH, LH, E2, AMH, and antral follicle count, most of these variations are not statistically significant ($p>0.05$). The only significant difference is in LH levels ($p=0.015$), where Group C has lower levels compared to the other groups. These findings indicate relatively similar baseline characteristics among the groups, with the exception of LH levels in Group C.

In contrary to Alexis L Oldfield et al.,(2023) who showed that although obese and non-obese women has similar level of gonadotropins, but obese women had a lower AMH .

They also had a fewer antral follicles, fewer follicles progressed to >10 mm. Luteal phase defects were also more common in obese women compared to those with normal weight.

In the current study a comparative analysis of various aspects related to in vitro fertilization (IVF) treatment among the three groups. These aspects include the type of FSH (Follicle-Stimulating Hormone) used, the starting dose of FSH, total dose of FSH, duration of stimulation, number of oocytes collected, and number of oocytes fertilized, along with their associated test values and p-values. Let's discuss the findings in paragraphs:

The data indicates the distribution of the type of FSH used in each group, which includes NR (Not Reported), rFSH (recombinant FSH), Human Menopausal Gonadotrophin, and Urofollitropin. The percentages of each type are provided for each group. The test value and p-value (5.369 and 0.497, respectively) indicate that there is no statistically significant difference in the type of FSH used among the three groups. This suggests that the choice of FSH type is similar across the groups.

The mean starting dose of FSH in ampoules for each group, along with the range of doses. While there are differences in the mean starting doses as the obese women(3.20) need higher dose than the normal weight (2.93)and overweight women (3.0), the test value and p-value (1.082 and 0.240, respectively) suggest that these differences are not statistically significant. This implies that, on average, the starting dose of FSH is comparable among the groups.

Similarly, the data provides information on the mean total dose of FSH in ampoules for each group, along with the range of doses. The test value and p-value (1.002 and 0.370, respectively) indicate that there is no statistically significant difference in the total dose of FSH among the groups. This suggests that, on average, the total amount of FSH administered during IVF treatment is similar across the groups.

The duration of stimulation is presented as the mean number of days of FSH administration, along with the range. It was notable that Group C had a slightly longer duration of stimulation than the other two groups but the test value and p-value (2.444 and 0.091, respectively) suggest that these differences are not statistically significant.

Similar results obtained by Rafique M et al.,(2021)As there was slight increase in gonadotropin requirement in the overweight and obese group, but this had not achieve statistical significance. This is because protocols modify dosage based on the BMI for the IVF cycle.

In contrary to Ozekinci M et al ., (2015) who revealed that Higher gonadotropin consumption and longer stimulation durations were observed in the obese females, when compared with the normal weight women.

The current study show the mean number of oocytes collected and the mean number of oocytes fertilized for each group, along with the range. The test values and p-values for these variables that indicate statistically significant differences among the groups. This suggests that the number of oocytes collected were higher in the normal weight group that to the over-weight and obese (p=0.019*), with Group A having the highest mean count (13.17±8.28), which may indicate to the effect of obesity on the ovaries and their respond to the stimulation while fertilized oocytes show no statistically significant during IVF treatment among the groups.

The same results obtained by Yuval Atzmon et al.,(2017) who conduct a prospective cohort study to evaluate the effect of body

mass index (BMI) (kg/m2) on oocyte diameter and treatment. Their result was that more mature oocytes (MII) were retrieved from normal weight than from obese women .Mature oocytes from women in the obese group were significantly smaller than those in the normal weight group were, including diameter (157.9 ± 7.9 vs. 164.3 ± 5.1 μm).

In contrary to Ozekinci M et al.,(2015) who found insignificant differences between the BMI categories in the number of retrieved oocytes, number of MII oocytes, proportion of oocytes fertilized.

The current study show a comparative analysis of various outcomes related to in vitro fertilization (IVF) treatment among the different BMI groups. These outcomes include the number of good quality embryos, the number of embryos obtained at day 2, the number of fresh transferred embryos, biochemical pregnancy test results, clinical pregnancy test results, and live birth outcomes, along with their associated test values and p-values.

The data presents the mean number of good quality embryos for each group, along with the range. The test value and p-value (0.586 and 0.532, respectively) suggest that there is statistically insignificant difference in the number of good quality embryos among the three groups. This implies that, on average, the quality of embryos obtained during IVF treatment is comparable across the groups.

Similarly, the mean number of embryos obtained at day 2, along with the range. The test value and p-value (1.517 and 0.224, respectively) do not indicate statistically significant differences among the groups. Suggesting that, on average, the number of embryos obtained at day 2 during IVF treatment is relatively similar across the groups.

Also the distribution of the number of fresh transferred embryos for each group. The percentages of each category (1, 2, 3, and 4 embryos) are provided. The test value and p-value (3.055 and 0.802, respectively) indicate that there is no statistically significant difference in the distribution of the number of fresh transferred embryos among the groups. This suggests that the choice of the number of embryos for transfer is similar across the groups.

As for the results of both biochemical pregnancy tests and clinical pregnancy tests for each group, along with the associated percentages. The test values and p-values for these variables do not indicate statistically significant differences among the groups. This suggests that the outcomes of biochemical and clinical pregnancy tests are comparable among the groups, with similar percentages of positive and negative results.

The mean number of live births for each group, along with the range. The test value and p-value (0.565 and 0.570, respectively) suggest that there is no statistically significant difference in the number of live births among the three groups. This implies that, on average, the live birth outcomes following IVF treatment are relatively similar across the groups.

In the same line Sathya et al.,(2010) revealed that Increase in body mass index in women does not appear to have an adverse effect on IVF outcome. Also Martinuzzi et al., (2008) revealed that obesity in young women does not adversely affect clinical pregnancy rates in patients treated with in vitro fertilization.

In contrast Vural et al., (2015) revealed that similar counts of recruited mature oocytes, obese POR women had decreased fertilization and clinical pregnancy rates.

In a retrospective cohort study included 11,191 couples undergoing IVF. Per the Chinese BMI standard showed that overweight/obesity does not affect the CPR, LBR or abortion rate after IVF. There was no significant difference in the number of harvested oocytes between the overweight/ obesity group and the normal weight group.(Liu X et al.,(2023))

On contrary to a large meta-analysis on almost 48000 treatment cycles from 33 studies, concluded that overweight or obese women had significantly lower clinical pregnancy and live-birth rates (LBR) and significantly higher miscarriage rates compared with women with a BMI <25 kg/m2 (Rittenberg V et al.,(2011)) .although in the analysis , they did not adjust for the effect of other potentials such as age and polycystic ovary syndrome (PCOS), which both are strongly associated with obesity, as well as other factors, such as smoking. (M Khairy et al.,(2017).

CONCLUSION

In conclusion, the comprehensive analysis of demographic and fertility-related parameters across three distinct groups (Group A, Group B, and Group C) undergoing in vitro fertilization (IVF) treatment reveals that there are statistically significant differences in the ovarian response to the stimulation in the form of the duration and the number of oocytes retrieval, while in the in most of the measured variables there is no statistically significant difference . These include age, parity, infertility status, hormone levels, antral follicle counts, type and dosage of follicle-stimulating hormone (FSH), and numerous IVF outcome measures such as the number of good quality embryos, embryos obtained, fresh transferred embryos, biochemical and clinical pregnancy test results, and live birth outcomes. These findings suggest that, on average, the studied groups exhibit comparable demographic characteristics, ovarian function, and IVF treatment outcomes, highlighting the consistency in various aspects of IVF protocols and reproductive outcomes among these groups.

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Postpartum Twelve-hour Magnesium Sulphate for Preeclamptic Patients versus Twenty four-hour: A Randomized Controlled Trial

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Abstract

Background& aim: Eclampsia is one of the major complications for patients with severe pre-eclampsia. Magnesium sulphate has been used as gold standard preventive treatment for a long time. Currently there is no consensus on the optimum duration of administration with maximum efficacy and less adverse events. In postpartum women with severe pre-eclampsia, the effectiveness of taking magnesium sulphate for 12 hours versus 24 hours was compared in this research. The objective was to maximize anticonvulsant action effectiveness while reducing magnesium sulphate adverse effect exposure.

Patients and Methods: A total of 280 women with severe preeclampsia were enrolled in the study. Those patients were randomly subdivided into group 1): received Mgso4 12- hour after delivery maintained at 1g per hour for 12 h and group 2): received Mgso4 24-hour after delivery maintained at 1g per hour for 24 h. All participants were subjected to thorough evaluation with recording demographic, obstetric and peripartum data.

Results: Both groups had insignificant differences as regard demographic, obstetric, clinical, laboratory, antepartum and intrapartum data. Administration of 12-hour magnesium sulfate as much as 24-hour magnesium sulfate was effective regard occurrence of eclampsia. Postpartum 12 hours group had significantly shorter duration of urinary catheter insertion (15.07 ± 11.01 vs. 28.11 ± 11.49 (h); $p< 0.001$) and length of hospital stay (2.52 ± 1.57 vs. 3.56 ± 1.69 (day); $p< 0.001$). Only one woman in 12 hours group had oliguria. There were three women in 12 hours group required prolongation of magnesium sulphate intake beyond the planned time.

Conclusion: twelve hours postpartum magnesium sulphate intake could be beneficial in women with severe preeclampsia as regard prevention of eclampsia with fewer side effects.

Keyword: preeclampsia, magnesium sulphate, postpartum seizure, eclampsia, fits.

Introduction

Preeclampsia, a pathological condition of pregnancy, is typified by the onset of hypertension that typically arises after the 20th week of gestation and often near term (1). The advent of eclampsia represents a perilous outcome of preeclampsia. For the prevention of eclampsia, the utilization of magnesium sulphate has been deemed the quintessential method (2).

Although it is recommended to administer magnesium sulphate to women with severe preeclampsia, there no consensus regarding the optimal duration of preventive postpartum anticonvulsant treatment. A proposition has been put forth suggesting the administration of magnesium sulphate for a period of 24 hours after childbirth, as this timeframe is believed to encompass the highest vulnerability period for the onset of eclampsia (3).

There are multiple protocols, including 12-hour and 6-hour regimens, for the administration of magnesium sulphate therapy. However, it is crucial to acknowledge that prolonged usage of this therapy may lead to adverse effects, particularly magnesium toxicity, which can manifest as respiratory depression, renal impairment, and neuromuscular dysfunction (4).Given the inherent risks associated with these complications, constant monitoring becomes a necessity. Consequently, it becomes imperative to ascertain the minimum duration of therapy that is both effective and safe (5).

At women Health Hospital, Assiut University, Egypt our policy is using magnesium sulphate as first line but there is paucity in the literature about comparison between the different regimens of magnesium sulphate. The present study conducted a comparison between the utilization of magnesium sulphate for a duration of 12 hours as opposed to 24 hours in postpartum women with severe pre-eclampsia. This was done to ensure the attainment of optimal efficacy in terms of anticonvulsant activity, while simultaneously minimizing the potential adverse effects associated with magnesium sulphate exposure.

Patients and Methods

Study design and setting

A prospective Randomized controlled trial study was conducted at The Department of Obstetrics and Gynecology (Women's Health Hospital), Assiut University, Assiut, Egypt. It was performed in the period between October 2020 to November 2022

Ethical approval

The study protocol was approved by Assiut School Ethical Review Board (IRB No17101300). Informed written consent was obtained from all participants according to the declaration of Helsinki. The study protocol is registered at Clinicaltrails.gov with NCT04576364.

Inclusion criteria:

Any patient who clinically diagnosed as antepartum or intrapartum pre-eclampsia with severe features as classified by ACOG guidelines (6) and accepted to participate the study was recruited.

Exclusion criteria:

Any patient with one or more of the following criteria was excluded; eclampsia, nervous system disorders as epilepsy or convulsions due to metabolic disturbances, neurological lesions, intracranial neoplasia or intra cerebral infections and comorbidities as chronic kidney or cardiac diseases.

Sample Size Calculation

Sample size based on the outcome of number of patients needed to prolong treatment duration in both groups. The total number of scheduled patients to be recruited was 280 patients 140 in each group. (Sample size was calculated using Epi-info 7 Version 3) with confidence level 95 % and power of 85%, alpha error 0.05, based on expected difference of 5.4% need to prolong treatment (7).

Randomization and allocation:

Randomization was conducted using a computer-generated table of random numbers with allocation concealment.

Allocation concealment: the details of the series were contained in a set of sequentially numbered, opaque sealed envelopes, each bearing on the outside only the name of the hospital and a number. The envelope wasn't opened till the moment of assignment.

Blinding: both medical service provider & patient couldn't be blinded because there was difference in duration of treatment of both groups.

Methodology

All enrolled women were diagnosed based on diagnostic criteria for preeclampsia defined by ACOG 2019(6). All women were subjected to;

- Complete history taking and clinical evaluation.
- Clinical examination: pulse, blood pressure measurement (two blood pressure readings at least 4 h apart were obtained).
- Chest examination to exclude pulmonary edema, heart examination to exclude cardiac problems.
- The following investigations were done; complete blood count, coagulation profile, liver function tests, renal function tests and urine analysis.in addition to, ultrasound evaluation to assess state of the fetus and placenta.

Intervention

All recruited participants received a loading dose of 4 g of intravenous drip MgSO4 over 30 minutes, followed by a maintenance dose of 1g per hour before and during delivery. After delivery patients were Randomly assigned to one of two groups:

- Group (1): received IV drip of Mgso4 after delivery maintained at 1g per hour for 12 hours.
- Group (2): received IV drip of Mgso4 after delivery maintained at 1g per hour for 24 hours.

Follow up as following:

Patients of both groups assessed hourly for;

- pulse and blood pressure
- urine output, tendon reflexes in form of knee jerk and respiratory rate for early detection of symptoms of magnesium sulphate toxicity

As a safety measure, need to prolong treatment was considered if there were signs of imminent eclampsia as defined by RCOG 2019 (ongoing or recurring severe headaches, visual scotomata, nausea or vomiting, epigastric pain), And /or, she had very high blood pressure (systolic blood pressure of 180 mm Hg or more and/or a diastolic blood pressure of 120 mm after completion of sulphate. These patients were managed according to local protocol.

Complication and toxicity of MgSO4 are considered as loss of the patellar reflex at concentrations between 3.5 and 5 mmol/L. Respiratory paralysis and cardiac arrest may occur at supratherapeutic concentrations beyond 5 mmol/L (8). Patients were managed based on local hospital protocol. Patients of both groups were assessed for their neonatal outcomes including gestational age at delivery, fetal birth weight, Apgar score and neonatal ICU admission.

Outcome of study:

- **Primary outcome:** compare efficacy of 12-hour vs 24-hour postpartum Mgso4 patients who needed to prolong treatment in each group.
- **Secondary (subsidiary):**

  a. to compare efficacy of 12-hour vs 24-hour postpartum Mgso4 to prevent occurrence of eclampsia.

  b. Duration of Hospital stay.

  c. Time from delivery to beginning of Ambulation.

  d. Maternal and fetal outcomes.

Statistical analysis

Data was collected and analyzed through the utilization of SPSS (Statistical Package for the Social Science), version 20, developed by IBM and headquartered in Armonk, New York. The Shapiro test was employed to ascertain the adherence of the data to a normal distribution. For quantitative data that exhibited a normal distribution, the mean ± standard deviation (SD) was employed as a means of expression and subsequently compared using the Student t test. On the other hand, quantitative data that deviated from a normal distribution were expressed as the median (minimum-maximum) and compared using the Mann-Whitney U test.

Nominal data were presented as a number (n) and percentage (%), and the Chi2 test was performed on such data. The level of confidence was set at 95%, and therefore, a P value of less than 0.05 was considered to be significant.

Results

Baseline data of the studied groups (table 1)

Both groups had insignificant differences as regard baseline data (p> 0.5).

Risk factors for preeclampsia among the studied groups (table 2):

Both groups had insignificant differences as regard risk factors for preeclampsia either as regard previous obstetric and medical history or during the current pregnancy (p> 0.05). The most frequent risk factors in previous obstetric and medical history were miscarriage and preeclampsia followed by chronic hypertension. Meanwhile, the most frequent risk factors in the current pregnancy were, first pregnancy followed by gestational hypertension.

Clinical and laboratory assessment of the studied groups (table 3):

Both studied groups had insignificant differences as regard clinical and laboratory data (p> 0.05).

Intrapartum and antepartum data among the studied groups (table 4):

Antepartum MgSo4 was used in most patients (92.1% vs. 97.1%; p= 0.06) with mean dose (16.74 ± 2.45 vs. 14.57 ± 4.87 (mg); p= 0.11) and mean duration was (12.85 ± 9.77 vs. 10.86 ± 8.77 (h); p= 0.19).

Postpartum follow up among studied groups (table 5):

No case developed eclampsia in both groups. Postpartum magnesium 12-hours group had significantly shorter duration of urinary catheter insertion (15.07 ± 11.01 vs. 28.11 ± 11.49 (h); p< 0.001) and length of hospital stay (2.52 ± 1.57 vs. 3.56 ± 1.69 (day); p< 0.001).

Only one patient developed MgSo4 toxicity in the form of oliguria in the 24 hours group. Three women, from the 12-hours group; required prolongation of MgSo4 versus none in 24 hours group secondary to nausea and vomiting (one patient), epigastric pain (3 patients), systolic blood pressure≥ 180 mmHg (3 patients) and diastolic blood pressure ≥ 120 mmHg (2patients).

Discussion

Preeclampsia associated with maternal and fetal morbidities. Eclampsia is one of the risky complications. Mgso4 is the gold standard preventive measure for occurrence of eclampsia in patients with preeclampsia. In our study we compare shortened protocol versus 24-hour protocol for intravenous MGSO4 administration. 280 participants were enrolled in this study, 140 in each group.

In the current study, no patient in the studied groups developed eclampsia. This finding goes in accordance with many authors (7-17) who also compare 12 hours versus 24 hours with different patient samples with zero incidence of eclampsia,

while maintaining a high safety margin. in addition to being safe and cost-effective, short term administration was as effective as long-term administration of this drug(17).

In the other hand many studies reported insignificant difference between both groups; Yifu et al., observed that only two eclampsia episodes were documented across the seven trials, both in the shorter regimen arm (risk difference 0.00, 95% CI -0.01-0.01, P = 0.49) (18). Titus K Beyuo and colleagues, no distinct disparity was observed in the incidence of seizures following the completion of the designated regimen in the 24-hour group (n = 5, 0.9%) as opposed to the 12-hour group (n = 2, 0.3%), yielding a p-value of 0.29 (19).

The contrasting findings between the current study and Beyuo et al.'s study regarding the development of eclampsia can be attributed to several factors. These include differences in sample size (1176 participants) and differences in treatment regimens. Also, Kashanian et al. stated that one out of 79 patients had convulsions, and that to avoid this one incident of convulsion, they gave MgSO4 to 78 women for an extra 12 hours with no apparent effect. To avert one occurrence of convulsion, 78 women must be given MgSO4 for 24 hours (20). Moreover, Quist-Nelson et al. reported a negligible elevation in the occurrence of eclampsia within the early cessation cohort (5 out of 1,088 compared to 2 out of 1,095) (0.5% versus 0.2%) in the 24-hour group. Utilizing this proportion (with an absolute risk reduction of 0.0027) to determine the needed number to treat(NNT), it is estimated that 370 women would need to undergo the conventional 24-hour regimen to avert a single case of eclampsia (21).

In our study, three women, from the 12-hours groups; required prolongation of MgSo4 usage secondary to nausea vomiting (one patient), epigastric pain (3 patients), systolic blood pressure ≥ 180 mmHg (3 patients) and diastolic blood pressure ≥ 120 mmHg (2 patients).

In Ehrenberg and colleagues' study, the application of magnesium sulphate treatment was prolonged in seven individuals (6.9%) within the 12-hour group due to a progress of their condition to a severe features, whereas only one individual (1.1%) within the 24-hour group experienced a similar progression (P=.07) (24). In contrast, Maia et al. and Leal et al. reported that, there was no need to re-initiate treatment after completing the scheduled magnesium sulfate therapy in either group (7, 22).

In our study, 12-hours group had significantly shorter duration of urinary catheter insertion. This is supported by many studies with similar shorter duration of bladder indwelling (16,19,22,24). With less risk for urinary tract infection, less patient discomfort, and early ambulation.

In our study, there is no significant difference in the time it takes for women to ambulate or have contact with their baby, regardless of whether they receive magnesium sulfate therapy for 12 hours or 24 hours.

Maia et al. revealed that the length of postpartum magnesium sulfate medication may be reduced, reducing the time for ambulation. The time between delivery and engaging with the infant was shortened

in the 12 hours group as women had been discharged from the intensive care unit and immediately placed in a rooming-in arrangement after discontinuing their anticonvulsant medication(7). Also, (Leal et al., 2014) reported that, in the 12-hour group, significant time reductions were found concerning time until the start of deambulation, and the interval between delivery and the mother's contact with her newborn.

In our study, 12-hours group had significantly shorter length of hospital stay, This agrees with previous studies (16,19,24) that is explained by early ambulation and discharge from intensive care unit.

In our study, in 24-hours group only one patient developed suspected MgSo4 toxicity in form of oliguria that was managed according to local protocol. In general there is no significant difference between both groups regarding side effects and toxicity which cope with previous studies (7,9,19)

The study had some limitations, it was conducted at a single site, which might confine the applicability of the findings to other localities and demographic cohorts.

The study did not examine long term outcomes for mothers or newborns, rather it concentrated on immediate consequences and adverse reactions. As well as the study did not evaluate the impact of MgSO4 regimens on the initiation and success of breastfeeding.

In conclusion, compared to continuation of magnesium for 24-hour postpartum, 12-hours magnesium postpartum therapy does not significantly increase the rate of prolongation of magnesium therapy or postpartum eclampsia. Additional benefits of shorter postpartum regimen may include reduction of the risk of drug toxicity, and side effects of more injections.

Recommendation for Further Studies:

The cost-benefit analysis of such medication should be conducted, and it should be noted that this number of convulsions can also occur within 24 h following MgSO4 delivery.

Larger sample sizes, multi-center settings, and longer-term follow-up are required to validate our findings and provide more comprehensive data regarding the appropriate duration of MgSO4 treatment in postpartum women with severe pre-eclampsia.

Ethics approval:

The study was approved by the ethical committee of faculty.

Availability and data material:

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

Competing interests:

The authors report there are no competing interests to declare.

Funding:

This study received no financial support.

Acknowledgments: none

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Table 1: Baseline data of the studied groups

	12 hours group (n= 140)	**24 hours group (n= 140)**	**P value**
Age (years)	28.29 ± 6.38	29.31 ± 6.51	0.18
Residence Rural Urban	 125 (89.3%) 15 (10.7%)	 126 (90%) 14 (10%)	0.50
Gestational age (week)	34.80 ± 3.06	34.90 ± 3.09	0.35
Number of deliveries	2 (0-8)	1 (0-9)	0.07
Number of abortions	1 (0-4)	2 (0-6)	0.90
Number of living children	2 (0-8)	1 (0-9)	0.10

Data expressed as frequency (percentage), mean (SD), median (range). P value was significant if < 0.05.

Table 2: Risk factors for preeclampsia among the studied groups

	12 hours group (n= 140)	24 hours group (n= 140)	P value
Previous obstetric and medical history			
Preeclampsia	22 (15.7%)	29 (20.7%)	0.17
Preterm labour	3 (2.1%)	6 (4.3%)	0.25
IUFD	6 (4.3%)	6 (4.3%)	0.61
Chronic HTN	16 (11.4%)	21 (15%)	0.24
Pregestational DM	5 (3.6%)	4 (2.9%)	0.50
Current pregnancy			
Multiple pregnancy	7 (5%)	18 (12.9%)	0.17
Pgda	44 (31.4%)	37 (26.4%)	0.21
Assisted reproductive technique	7 (5%)	6 (4.3%)	0.50
Inter-pregnancy interval > 10 years	5 (3.6%)	6 (4.3%)	0.50
Overweight/obese	120 (85.7%)	132 (94.3%)	0.05
Vaginal bleeding in early pregnancy	5 (3.6%)	4 (2.9%)	0.50
Gestational HTN	20 (14.3%)	18 (12.9%)	0.43

Data expressed as frequency (percentage). P value was significant if < 0.05. IUFD: intrauterine fetal death; HTN: hypertension; DM: diabetes mellitus

Table 3: Clinical and laboratory data of the studied groups

	12 hours group (n= 140)	24 hours group (n= 140)	P value
Systolic blood pressure (mmHg)			
1st measure	155.87 ± 10.19	158.89 ± 9.87	0.65
2nd measure	160.11 ± 16.56	159.89 ± 6.78	0.39
Diastolic blood pressure (mmHg)			
1st measure	89.11 ± 8.01	88.88 ± 8.17	0.09
2nd measure	90.17 ± 10.10	89.12 ± 5.44	0.33
Hemoglobin (g/dl)	11.52 ± 1.78	11.38 ± 1.60	0.48
Hematocrit value (%)	34.85 ± 4.69	34.22 ± 4.51	0.24
Platelets (10^3/ul)	211.89 ± 7.60	201.56 ± 6.87	0.34
Prothrombin time (s)	11.37 ± 1.58	11.31 ± 1.58	0.70
Prothrombin concentration (%)	111.44 ± 19.01	110.45 ± 19.85	0.67
INR	0.96 ± 0.13	0.96 ± 0.10	0.93
Urea (mg/dl)	4.47 ± 2.67	5.11 ± 2.47	0.27
Creatinine (mg/dl)	0.52 ± 0.12	0.56 ± 0.23	0.21
AST (u/l)	58.11 ± 23.87	60.68 ± 22.19	0.07
ALT (u/l)	60.88 ± 12.98	62.87 ± 13.87	0.07
Bilirubin (mg/dl)	1.24 ± 0.13	1.23 ± 0.12	0.40
Albumin (mg/dl)	3.22 ± 0.98	3.30 ± 0.45	0.50

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05. INR: international randomized ratio; AST: alanine transaminase; ALT: alanine transaminase.

Table 4: Intrapartum and antepartum data among the studied groups

	12 hours group (n= 140)	24 hours group (n= 140)	P value
Usage of antepartum $MgSo_4$	129 (92.1%)	136 (97.1%)	0.06
Dose (gm)	16.74 ± 2.45	14.57 ± 4.87	0.11
Duration (h)	12.85 ± 9.77	10.86 ± 8.77	0.19
Mode of delivery			0.50
Cesarean section	129 (92.1%)	128 (91.4%)	
Vaginal delivery	11 (7.9%)	12 (8.6%)	
Intraoperative complications	0	2 (1.5%)	0.24
Fetal outcome			
One-minute Apgar score	5.87 ± 2.22	6.01 ± 1.98	0.11
Five-minutes Apgar score	8.12 ± 2.45	8 ± 2.01	0.13
Fetal weight (kg)	2.22 ± 0.63	2.09 ± 0.54	0.10
Respiratory distress	74 (52.8%)	76 (54.3%)	0.33
Need to Ambu	11 (7.9%)	12 (8.6%)	0.42
Need to MV	4 (2.9%)	1 (0.70%)	0.18
Admission to NICU	16 (11.4%)	11 (11.4%)	0.61

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05.
MV: mechanical ventilation; NICU: neonatal intensive care unit

Table 5: Postpartum follow up among studied groups.

	12 hours group (n= 140)	24 hours group (n= 140)	P value
Development of eclampsia	0	0	---
$MgSo_4$ toxicity	0	1 (0.70)	0.50
Prolongation of $MgSo_4$ usage	3 (2.1%)	0	0.12
Causes of prolongation			
Nausea/vomiting	1 (0.70)	0	0.50
Epigastric pain	3 (2.1%)	0	0.12
SBP ≥ 180 mmHg	3 (2.1%)	0	0.12
DBP ≥ 120 mmHg	2 (1.4%)	0	0.24
Duration of urinary catheter (h)	15.07 ± 11.01	28.11 ± 11.49	**< 0.001**
Duration till ambulation	7.64 ± 1.36	8.10 ± 1.48	0.10
Length of hospital stay (day)	2.52 ± 1.57	3.56 ± 1.69	**< 0.001**

Data expressed as frequency (percentage), mean (SD). P value was significant if < 0.05.SBP: systolic blood pressure; DBP: diastolic blood pressure

Progesterone versus combined estrogen and progesterone for luteal phase support (LPS) in women with unexplained infertility undergoing ICSI cycle: A randomized controlled, double-blinded study

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Abstract

Background : This study aims to determine the effectiveness and safety of adding estrogen and progesterone for luteal phase support to improve the live birth rate in women with unexplained infertility undergoing ICSI cycles using the long ovarian hyperstimulation protocol over the study period.

Methodology: This randomized, controlled, double-blinded study was conducted at the ART unit of Ain Shams University Maternity Hospital (ASUMH) from July 2020 till June 2021.It included 182 women, all of whom are suffering from unexplained infertility and underwent ICSI using the long protocol. Patients were randomly assigned into two groups: **Group A** ***(control): which*** consisted of patients who received vaginal progesterone supplementation (400mg twice a day), and **Group B** ***(study-estradiol group)*****:**2 mg of estradiol valerate were initiated orally along with progesterone, starting on the day of oocyte retrieval and continued until the end of first trimester. **Antenatal follow-up:** Patients with clinical conception did their antenatal care in the Ain Shams University Maternity Hospital outpatient clinic with follow-up of their outcome using a phone number.

Results: Regarding **main outcome measures,** statistical analysis of current results showed that the biochemical, clinical pregnancy, and live birth rates were all comparable in both groups. In group A, 34 (37.4%) had positive biochemical and clinical pregnancy compared with 40 (44.0%) patients in group B (p-value = 0.365). Twenty-six (28.6%) patients in Group A had live birth compared with 29 (31.9%) patients in Group B (p-value = 0.628). There was no statistically significant difference between both groups as regards the rate of twin pregnancy or CS delivery (p-value >0.999 and 0.628, respectively).

Conclusion: In women with unexplained infertility undergoing long protocol in assisted reproduction cycles, there were no significant differences between the relative effectiveness and safety of administering progesterone

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versus progesterone combined with estrogen for luteal phase support regarding biochemical, clinical pregnancy and live birth rates.

Key Words: luteal phase support, unexplained infertility, ICSI.

Background

The endometrium constitutes the inner layer of the uterus; it prevents adhesions between the opposed walls of the uterus, thereby maintaining its patency(1).The decidualized endometrium protects the embryo from maternal immunological rejection and provides nutrition before placental formation(2).

Even with high-quality embryos, the implantation rates in ART are still low, demonstrating the importance of impaired decidualization as a major cause of pregnancy failure (3).

In vitro fertilization (IVF) treatment usually involves ovarian stimulation (OS) with gonadotropins in addition to GnRH analogs to prevent premature luteinization and ovulation, as it is known that the use of GnRH analogs during OS may impair corpus luteum function, which results to suboptimal endometrial receptivity.Thus, using progesterone for LPS is an essential part of IVF treatment and is necessary to support implantation and increase pregnancy rates after fresh embryo transfer (4).

Still, there is a debate about what is best for LPS during IVF/ICSI cycle;. At the same time, some use progesterone-only protocols, and others prefer estrogen and progesterone protocols, which is still controversial.

Ceyhan et al.2008 (5) experienced higher pregnancy rates(56.5% vs. 61.9%) in their randomized study, which was performed on 60 patients, all of which are regular responders, and they demonstrated that in IVF cycles with antagonist protocol using estradiol in addition to progesterone led to better outcomes. Kwon et al.2013 (6) presented a randomized prospective study on 110 patients using antagonist protocol on IVF/ICSI cycles. They compared the use of progesterone-only versus estrogen and progesterone for LPS, and they demonstrated higher pregnancy rates with the combined approach (2.0% vs. 15.8%, p=0.035) and Also, this supplemental use significantly reduced the incidence of vaginal bleeding (7.4% vs. 27.8%, p=0.010).

Ismail Madkour et al. 2016 (7), in a recent prospective randomized study on 259 patients, showed no benefits from the additional use of estrogen to progesterone for luteal phase support in ICSI cycles. They demonstrated that ongoing pregnancy rates per embryo transfer conferred no significant difference in Group 1, with 32.7% and 32.7% in Group 2 (p=0.1). Also, there was no significant difference in implantation rates and abortion rates. In agreement with that, Pinheiro et al. 2017 (8) in his review comparing studies assessing the addition of estradiol to progesterone for LPS and its effects on pregnancy rates in IVF cycles using an antagonist protocol. They stated that only one study shows more successful embryo implantation in patients receiving estrogen progesterone combination. However, this success was not confirmed in any of the selected studies on pregnancy rate. Therefore, they emphasize the importance of further studies to clarify the role of estradiol in the luteal phase support in IVF cycles.

This study aims to determine the effectiveness and safety of adding estrogen and progesterone for luteal phase support to improve the live birth rate in women with unexplained infertility undergoing ICSI cycles using the long ovarian hyperstimulation protocol over the study period.

Patients and methods

This study was conducted at the ART unit of Ain Shams University Maternity Hospital

(ASUMH) from July 2020 to June 2021. This is a randomized, controlled (double-blinded) study. The Department of Obstetrics and Gynecology Council approved the study protocol and gained ethical approval from the Faculty of Medicine, Ain Shams University no (FWA 000017585).

The study was registered in the Pan-African Clinical Trial registry PACTR with ID 25717

Inclusion criteria are Couples with a diagnosis of unexplained infertility, planned treatment is the long protocol of ovarian stimulation in the context of ART, age group ranging between 18 years to 37 years, BMI ranging between 18.5 – 35, and every woman participating in the study signed an informed consent and had the right of withdrawal from the study at any time.

The following exclusion criteria were applied: previous uterine surgery, e.g., myomectomy, polypectomy, hydrosalpinx, uterine malformations, endometrial line < 8mm and/or not tri-laminar in sonography, endometriosis diagnosed by previous laparoscopy or ultrasound findings, previous preterm labor, recurrent pregnancy loss, HT, pre-eclampsia, eclampsia, unexplained IUFD, hypersensitivity to the used drugs, canceled cycles for poor or over response and failed fertilization, and withdrawal of the consent.

Primary outcome:

Live birth rate. number of births of neonates who showed any sign of life per 100 embryo transfer.

Secondary outcome:

Biochemical pregnancy: A pregnancy test was performed two weeks after the ICSI technique (Serum HCG).

Clinical pregnancy: The rate of clinical conception was confirmed with the presence of an intrauterine gestational sac with living embryo four weeks after embryo transfer.

Antenatal-care outcomes: side effects of estrogen as nausea, breast tenderness, headache, hypertension, venous thrombosis, predicted hyperstimulation syndrome during follow-up, spontaneous abortion rate, stillbirth, congenital anomalies, complication during pregnancy, e.g., hypertension, ectopic pregnancy, rupture membranes, DVT and delivery outcome were recorded.

Sample size justification:

The sample size was calculated using G*Power software version 3.1.2 for MS Windows, Franz Faul, Kiel University, Germany. Reviewing the literature, the available studies (10-12) addressed ongoing pregnancy rate as the primary outcome, and no studies addressed live birth rate as the primary outcome. Assuming a 5% difference between the two groups, a birth rate of 21% in group **A and 25%** in group **B**, a sample of 91 patients in each group would be enough to detect such a difference, if accurate, of 0.05 alpha errors & 0.80 power of the test.

Study interventions and procedures: All cases were subjected to detailed history taking, including age, parity, duration, and type of infertility, either primary or secondary, previous induction of ovulation, previous IVF, and previous ICSI in detail, i.e., when, how many times, age and outcomes, obstetric history, complications during pregnancy, and mode of delivery, general examination: weight, height, and body mass index (BMI).

Baseline evaluation:

The infertility workup was revised, including semen analysis, hormonal profile, hysterosalpingography, previous infertility treatment, and ART procedures.

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) were measured on day 2 of the cycle.

All participants underwent trans-vaginal sonography for endometrial lining assessment and antral follicle count (AFC).

Controlled ovarian hyperstimulation:

The long protocol was used for ovarian stimulation. In this protocol, the women were downregulated with a GnRH analog (Decapeptyl, Ferring, Egypt) administered 0.1 mg subcutaneously from day 21 of the previous menstrual cycle.

(E2) was analyzed on the second day of the menstrual cycle to assess pituitary suppression. If E2 was below 50 pg/ml, ovarian stimulation was done with human menopausal gonadotrophin hormone in the form of (Menogon®, Ferring, Egypt) 75IU vials from the second day of the menstrual cycle daily. The dose was calculated by the consultant in the IVF unit according to age, BMI, AFC, and response to previous IVF cycles.

Patients were followed by ultrasound folliculometry using trans-vaginal sonography (SONOACE X4) 7.5MHz on the 6th day of the menstrual cycle. Follow-up folliculometry was done according to follicle size with a further dose adjustment of the gonadotrophin dose according to the response calculated by the consultant in the IVF unit.

Triggering was done using HCG 10,000 units in the form of Choriomon®, IBSA, Egypt) when at least two follicles are exceeding 17mm in diameter.

Oocyte retrieval: The Oocytes were aspirated trans-vaginally under ultrasound guidance under general anesthesia 34 hours after triggering; fertilization was carried out by intra-cytoplasmic sperm injection (ICSI) technique, then embryo transfer of high-quality embryos guided by ultrasound 3 or 5 days after oocyte retrieval. The number of transferred embryos was determined by the IVF consultant; usually, two or three embryos were transferred or as available.

The Luteal support was started on the same day of oocyte retrieval. Patients were randomly assigned into two groups: **Group A** ***(control)***: consisted of patients who received vaginal progesterone supplementation (400mg twice a day) using (Prontogest®; Marcyrl, Egypt) combined with an identical placebo to the white tablets of Cycloprogynova tablets that were made at faculty of pharmacy Ain shams University starting on the day of oocyte retrieval and continued until the end of first trimester.

Group B ***(study-estradiol group)***:2 mg of estradiol valerate in the form of the white tablets of (CycloProgynova®; Bayer, Egypt) were initiated orally along with progesterone, starting on the day of oocyte retrieval and continued until the end of the first trimester.

Randomization was done by computer-generated random number sequence method into two groups, either group **(A)** or group **(B)**. We performed allocation concealment by sealed, opaque, sequentially numbered envelopes. This method was suitable for the current study.

Antenatal follow-up for patients with clinical conception did their antenatal care in Ain Shams University Maternity Hospital out-patient clinic with follow-up of their outcome using their phone numbers.

Blinding of patient and personnel:

For blinding, we used placebo preparation identical to the white tablets of Cycloprogynova made at the faculty of Pharmacy Ain Shams University prepared by the pharmacist in sealed opaque envelopes with serial numbers. The coding was kept with the pharmacist and revealed at the end of the study.

Statistical Analysis:

The collected data were revised, coded, tabulated, and introduced to a PC using the Statistical Package for Social Science

(SPSS 20.0.1 for Windows; Chicago, IL, 2001). Descriptive statistics for measured variables were expressed as a range, mean, and standard deviation (for metric data); range, median, inter-quarter range (for discrete data); number and proportion (for categorical data). The demographic data, primary and secondary outcomes of all patients were compared using a T-test (for quantitative parametric measures), Mann-Whitney's U-test (for quantitative non-parametric measures), Chi-square and Fisher exact test for categorical measures, sensitivity, specificity, positive predictive value, negative predictive value were calculated.

Results

Table 1 illustrates the demographic characteristics of both groups:

Table (1): Baseline evaluation among the studied cases

			Difference		95% CI		
Variable	Group A (n=91)	Group B (n=91)	Mean	SE	Lower	Upper	p-value†
Age (years), mean ± SD	30.3 ± 3.9	31.4 ± 4.4	-1.1	0.6	-2.3	0.1	0.076
BMI (kg/m^2), mean ± SD	28.6 ± 4.8	29.9 ± 3.9	-1.3	0.6	-2.6	0.0	0.043
Duration of infertility (years), mean ± SD	5.3 ± 3.2	5.2 ± 2.8	0.03	0.4	-0.8	0.9	0.941
Variable	Group A (n=91)		Group B (n=91)			P-value†	
Type of infertility, n (%)						0.048†	
Primary	62 (68.1%)		49 (53.8%)				
Secondary	29 (31.9%)		42 (46.2%)				
Parity, n (%)						0.003‡	
P0	83 (91.2%)		70 (76.9%)				
P1	8 (8.8%)		16 (17.6%)				
P2	0 (0.0%)		5 (5.5%)				
Abortions, n (%)						0.464†	
Nil	62 (68.1%)		52 (57.1%)				
1 Miscarriage	17 (18.7%)		26 (28.6%)				
2 Miscarriages	4 (4.4%)		7 (7.7%)				
≥3 Miscarriages	8 (8.8%)		6 (6.6%)				

†. Independent-samples t-test.

SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.

basal hormonal work up, ovarian reserve and semen analysis"). There was no statistically significant difference between both groups as regards baseline FSH (p-value = 0.557), LH (p-value = 0.346), TSH (p-value = 0.219), E2 (p-value = 0.650) or AMH (p-value = 0.234). Likewise, endometrial thickness, AFC, and the number of retrieved oocytes were comparable in both groups (p-value = 0.351, 0.537 and 0.300, respectively). Both groups were comparable regarding semen volume, sperm count and sperm motility (p-value = 0.195, 0.083 and 0.377, respectively). Mean abnormal forms was 90.4% (SD, 19.4%) versus 81.5% (SD, 27.8%) in Group A or Group B, respectively (p-value = 0.013).

Controlled ovarian stimulation data of the study participants: Table 2 illustrates induction characteristics, ovulation characteristics, fertilization characteristics, and embryo transfer characteristics among studied cases.

Induction Characteristics	Group A	Group B	P-value
Long Protocol	Group A (n=91)	Group B (n=91)	
Stimulation duration (days) **Mean±SD** **Range**	13.2±2.8 8.0–21.0	13.2±2.8 8.0–21.0	<0.999
Total dose (IU) **Mean±SD** **Range**	3392.6±1322.3 750.0–7200	3392.6±1322.3 750.0–7200	<0.999
AFC **Mean±SD** **Range**	13.7±6.3 4.0–39.0	13.7±6.3 4.0–39.0	<0.999
Ovulation characteristics:			
Variable	**Group A**	**Group B**	**P-value**
Ovulation	N 86	N 84	
Day of ovum pickup Mean±SD **Range**	15.2±2.9 10.0–23.0	15.1±2.6 10.0–22.0	0.911
Number of expected ovum pickup **Mean±SD** **Range**	10.1±6.5 2.0–31.0	10.0±6.3 2.0–30.0	0.922
Number of oocytes retrievedMean±SD **Range**	9.3±6.1 1.0–27.0	9.2±6.0 1.0–26.0	0.981
Number of M2 oocytes **Mean±SD** **Range**	7.5±5.1 1.0–24.0	7.5±5.0 1.0–23.0	0.999
<u>Fertilization characteristics:</u>			
Variable	**Group A**	**Group B**	**P-value**
Fertilization	83	84	
Number of fertilized oocytes Mean±SD range	5.0±3.4 1.0–19.0	5.1±3.6 1.0–20.0	0.982
Fertilization rate **Mean±SD** **Range**	71.4±23.0 14.1–99.0	71.6±23.1 14.3–100.0	0.971
<u>Embryo transfer characteristics:</u>			
Variable	**Group A**	**Group B**	**P-value**
Embryo transfer	82	81	
Day of embryo transfer **Mean±SD** **Range**	3.9±1.0 3.0–5.0	3.9±1.0 3.0–5.0	<0.999
Number of transferred embryos **Mean±SD** **Range**	2.2±0.7 1.0–4.0	2.2±0.7 1.0–4.0	<0.999

†. Independent-samples t-test.
SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.

Table 3: illustrated main outcomes , maternal complications and fetal complications:

Variable	Group A (n=91)	Group B (n=91)	P-value†
Biochemical pregnancy, n (%)	34 (37.4%)	40 (44.0%)	0.365
Clinical pregnancy, n (%)	34 (37.4%)	40 (44.0%)	0.365
Twin, n (%)	6 (6.6%)	6 (6.6%)	>0.999
Live birth, n (%)	26 (28.6%)	29 (31.9%)	0.628
CS delivery, n (%)	26 (28.6%)	29 (31.9%)	0.628
Incidence of maternal adverse outcomes in both groups:			
Nausea, n (%)	31 (34.1%)	34 (37.4%)	0.643†
Vomiting, n (%)	24 (26.4%)	22 (24.2%)	0.733†
Headache, n (%)	13 (14.3%)	24 (26.4%)	0.043†
Gestational DM, n (%)	4 (4.4%)	5 (5.5%)	>0.999‡
Gestational hypertension, n (%)	8 (8.8%)	10 (11.0%)	0.619†
Withdrawn because of adverse effects, n (%)	7 (7.7%)	4 (4.4%)	0.351†
DVT, n (%)	0 (0.0%)	0 (0.0%)	NC
APH, n (%)	0 (0.0%)	0 (0.0%)	NC
Complications	**Group A**	**Group B**	**p-value**
Ovarian hyperstimulation syndrome	8	8	<0.999
Hetero-tropic pregnancy	0	0.0	NC
Multiple pregnancy	6	6	<0.999
Mortality	0	0.0	NC
Fetal complications among the studied cases			
Early fetal loss (miscarriage), n (%)	8 (8.8%)	11 (12.1%)	0.467†
PTD, n (%)	2 (2.2%)	6 (6.6%)	0.278‡
IUGR, n (%)	1 (1.1%)	2 (2.2%)	>0.999‡
Macrosomia, n (%)	0 (0.0%)	1 (1.1%)	>0.999‡
PROM, n (%)	2 (2.2%)	4 (4.4%)	0.682‡

Chi-squared test for trend.

Discussion

We found that in women with unexplained infertility undergoing long protocol in assisted reproduction cycles, there were no significant differences between the relative effectiveness and safety of administering progesterone versus progesterone combined with estrogen for luteal phase support regarding biochemical, clinical pregnancy, and live birth rates.

Regarding main outcome measures, statistical analysis of current results showed that the biochemical, clinical pregnancy, and live birth rates were all comparable in both groups. In group A, 34 (37.4%) had positive biochemical and clinical pregnancy compared with 40 (44.0%) patients in group B (p-value = 0.365). Twenty-six (28.6%) patients in Group A had live birth compared with 29 (31.9%) patients in Group B (p-value = 0.628). There was no statistically significant difference between both groups as regards the rate of twin pregnancy or CS delivery (p-value >0.999 and 0.628, respectively).

Regarding the incidence of maternal adverse outcomes, current results showed that significantly more patients in group B

complained of headaches (24 [26.4%] versus 13 [14.3%], p-value = 0.043). Otherwise, there was no statistically significant difference between both groups as regards the incidence of nausea (p-value = 0.643), vomiting (p-value = 0.733), gestational DM (p-value >0.999) or gestational hypertension (p-value = 0.619). None of the patients in either group had DVT or APH. The rate of withdrawal from the study because of medication-related adverse effects was comparable in both groups (7 [7.7%] versus 4 [4.4%] in Group A or Group B, respectively, p-value = 0.043).

Regarding the incidence of fetal adverse outcomes, statistical analysis of current results showed that there was no statistically significant difference between both groups as regards the incidence of early fetal loss (p-value = 0.467), PTD (p-value = 0.278), IUGR (p-value >0.999), macrosomia (p-value >0.999) or PROM (p-value = 0.682). None of the patients in either group had fetal anomalies.

Comparison of our results to similar studies

Çakar and his colleagues conducted a case-control study to evaluate the effect of combined use of oral estrogen (E2) and vaginal progesterone (P) for LPS in antagonist (ICSI) cycles. A total of 176 patients were enrolled. Once a day, progesterone 90mg vaginal gel and micronized E2 of 4 mg/day was started from the day of oocyte pick up and continued to the 12th day of embryo transfer. Group 1 (n=79) patients received E2 +P for luteal phase support. In group 2(n=97) patients, only P 90mg vaginal gel was used. They agreed with our study and stated that no significant difference existed between group 1 and group 2 in means of pregnancy rate (26.58% n = 21 vs. 24.74%n = 24) (p = .781), clinical pregnancy rate (26.58% n = 21 vs. 20.62%n = 20) (p = .352) and implantation rate (22.8% n = 21 vs. 16.9% n = 20) (p = .298), the incidence of luteal vaginal bleeding (8.86% n = 7 vs. 8.25% n = 8) (p =.885). They also agreed with our study and stated that no significant difference existed between group 1 and group 2 in means of early pregnancy loss rate (6.33% n = 5 vs. 6.19% n = 6) (p = .969) (9).

Madkour and his colleagues conducted a randomized controlled study to compare pregnancy outcomes in 220 patients undergoing antagonist (ICSI) cycles protocol. The patients were randomly assigned into two equal groups to receive either vaginal progesterone alone (90mg once daily) starting on the day of oocyte retrieval for up to 12 weeks if pregnancy occurred or estradiol addition (2mg twice daily) starting on the same day and continuing up to seven weeks (fetal viability scan). They agreed with the current study and stated that early pregnancy loss rates were comparable with 6.3% and 7.2% for groups 1 and 2, respectively (p value=0.4). They also agreed with the current study and stated that pregnancy rate per embryo transfer did not differ between group 1 (progesterone) (39.09%) compared to group 2 (progesterone/ E2 group) (43.63%) (p value=0.3). Similarly, both groups gave comparable ongoing pregnancy rates per embryo transfer with32.7% in group 1 compared to 36.3% in group 2(p value=0.1) (7)

Lin and his colleagues conducted a prospective randomized controlled study on 402 patients to explore whether oral oestradiol (E2) supplementation (6 mg) in the luteal phase is beneficial to the outcome of patients undergoing gonadotrophin-releasing hormone agonist (GnRHa)long protocol in vitro fertilization (IVF)/(ICSI) cycles. In total, 402 patients were prospectively randomized to receive either progesterone injection plus oral E2 supplementation (Group A, n = 202) or progesterone injection alone (Group B, n = 200) for LPS after oocyte retrieval. They agreed with our study and stated that the cycle outcomes, including clinical pregnancy rate, implantation rate, miscarriage rate, and moderate OHSS rate, were comparable between the groups. (10)

Engmannand his colleagues agreed with

current study and stated there were no significant differences in the implantation (56/210 [26.7%] vs. 64/203 [31.5%]), clinical pregnancy (42/84 [50%] vs. 52/82 [63.4%]), and ongoing pregnancy rates (40/84 [47.6%] vs. 46/82 [56.1%]) between the study and control groups, respectively. One hundred sixty-six patients undergoing their first IVF treatment cycle were enrolled in a prospective randomized controlled trial. Patients underwent three different protocols for controlled ovarian hyperstimulation for IVF treatment with long GnRH agonist suppression, use of GnRH antagonist, or a microdose GnRH agonist protocol. LPS was in the form of IM P. Patients randomized into the study group (n = 84) received E2 supplementation in the form of vaginal estrace 2 mg twice a day starting on the day of ET. Patients randomized to the control group (n = 82) received no E2 supplementation. (11)

Serna and his colleagues agreed with current study and stated that there were no statistically significant differences in terms of implantation rate (34.9% [51 of 146] vs. 28.9% [41 of 142]), ongoing pregnancy rate 42% ([34 of 81]vs. 41.8% [33 of 79]), early pregnancy loss (15% [6 of 40] vs. 13.2% [5 of 38]), or multiple pregnancy rate(28.6% [12 of 42] vs. 24.4% [10/41]) in patients receiving P versus E2 + P.(12)

Against the current study, Drakakis and his colleagues stated that estradiol supplementation during the luteal phase in women undergoing IVF/ICSI-ET benefits the outcome without adverse effects. In this prospective, randomized study, they studied patients undergoing IVF/ICSI with controlled ovarian hyperstimulation using a gonadotropin-releasing hormone agonist/ human recombinant gonadotropin long protocol. A total of 77 patients were included in the study. The first group received estrogen and progesterone supplementation from the day of oocyte retrieval (N=39), and the second group(N=38) took only progesterone supplementation during the luteal phase. From the 24 cases with successful outcomes, 75% were from Group 1 that received estradiol supplementation, and 25% were from Group 2 with no estradiol ($p<0.05$). but there was a tendency towards a higher abortion rate in Group 1 (10.3% vs.2.6%). The implantation and pregnancy rates were significantly increased in the group with estradiol supplementation (implantation rate: 10.2vs. 4.0%, pregnancy rate: 46.1 vs. 15.8%; $p<0.05$ for both) (13). These differences can be attributed to the small sample size included in Drakakis's study.

Strengths and limitations of our study

Our strength point is that all clinical assessment and assessment of study outcomes were done by the same team. Blinding of patients and personnel was achieved. The limitation of our study is the relatively small number of patients and it is a single and not multicenter study.

The clinical implication of this study is that we did not find evidence of the benefit of adding estrogen to progesterone for luteal phase support in women undergoing ICSI using the long protocol.

Recommendation for future research

We recommend further future studies with larger sample sizes to demonstrate what is best for luteal phase support in ICSI cycles with different ovulation induction protocols.

Conclusion

In women with unexplained infertility undergoing long protocol in assisted reproduction cycles, there were no significant differences between the relative effectiveness and safety of administering progesterone versus progesterone combined with estrogen for luteal phase support regarding biochemical, clinical pregnancy and live birth rates.

List of abbreviations

1. LPS : luteal phase support .
2. ICSI : intracytoplasmic sperm injection .
3. ART: assisted reproductive techniques .
4. ASUMH : Ain Shams university maternity hospital .
5. IVF: in vitro fertilization .
6. GnRH: gonadotrophin releasing hormone
7. BMI: body mass index .
8. FSH: follicle stimulating hormone.
9. LH: luteinizing hormone .
10. E2 : estradiol.
11. AFC: antral follicle count.
12. HCG: human chorionic gonadotrophin.
13. SD: standard deviation .
14. IU : international unit .
15. ET: embryo transfer .

Declarations

Ethical: The Obstetrics and Gynecology Department Council approved the study protocol and ethically was approved by the Ethical Research Committee (Faculty of Medicine, Ain Shams University). FMASU 000017585

Availability of data: data will be available from the corresponding author upon reasonable request.

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

Funding: not applicable.

Acknowledgments: not applicable.

Authors contributions

MH did the literature review, was participated in data collection and follow-up of cases

SS participated in the literature reviewand revision of the manuscript.

YA was responsible for data collection, statistics, and gathering scientific data.

WK was responsible for revising all data and writing the manuscript.

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Cabergoline, metformin and Clomiphene citrate therapy in infertile female with mild endometriosis: A Randomized Clinical Trial

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Ethical statement

Authors declare that there is no interest

No fund.

Accepted by the Ethical Research Committee of the Obstetrics and Gynecology Department and institutional review board (IRB) in the Faulty of Medicine (MS.21.12.1763)

Written informed consent was taken from the participants

Introduction

an urgent need for new medication without impeding the patient's fertility. cabergoline, Metformin, and Clomiphene citrate have been studied in experimental model in cases of endometriosis. however, there was still no evidence of its use with mild endometriosis. Our study's goal was to see if use these medications could help women with minimal to mild endometriosis.

Methods

Between November 2021 to November 2022, 150 Infertile women with minimal to mild endometriosis were recruited from outpatient Gynecology clinic for this study a prospective, randomized trial.

The cases will be randomly assigned to receive one of the four treatment modalities by using computer generate random table and sealed envelop

- Group A: they got cabergoline (0.25 mg twice weekly) for three months.
- Group B: they received metformin 500 mg three times daily for three months
- Group C: they received Clomiphene citrate (50mg twice daily for 5days) from second day of menstrual cycle for three months
- Group D: they got placebo once per day during the three months follow up period Serum prolactin (PRL), basal follicular stimulating hormone (FSH), basal

luteinizing hormone (LH), basal serum estradiol (E2) and midluteal serum progesterone (P) were measured before the start of the treatment.

After the three months, a clinical evaluation was conducted, which compromised clinical examination with assessment of dysmenorrhea, dyspareunia and pelvic pain, menorrhagia, and pregnancy. A second hormonal assessment was performed.

Results

For group A; 20 cases, for group B 22 cases, for group C 20 cases, and for group D 17 cases were analyzed. The mean prolactin level, mean FSH level, and mean estradiol level after treatment statistically significant difference between studied group and placebo. The pregnancy in studied groups were 8 out of 20 in Group A, 10 out of 22 in Group B, 8 out 20 in Group C, however, 2 out of 17.

Conclusion

We had encouraging results from the use of cabergoline, metformin, and clomiphene citrate in patient with mild to moderate endometriosis.

Introduction

Despite being one of the most prevalent gynecological disorders, endometriosis pathogenesis is still poorly understood. There is a pressing need for new medication without impeding the patient's fertility because the traditional medical treatments have this effect (1). Dopamine agonists as a molecule with antiangiogenic activity, have been studied in experimental model in cases of endometriosis with good results (2). Metformin, as an insulin sensitizer, studied in vitro and animal models and proved to be associated with the recession of endometriotic implants (3). However, the clinical data are insufficient to recommend the use of both (2,3). Clomiphene citrate, as antiestrogen for ovulation induction, had tried in infertile patients with endometriosis, however, still had no evidence of its use with mild endometriosis after laparoscopy (4). The aim of our study to try to use these drugs in the treatment of women with minimal to mild endometriosis.

Patients & Methods

This study a prospective randomized study conducted on a total of 150 Infertile women with endometriosis. Patients were collected from outpatient Gynecology clinic within the period from November 2021 to November 2022 after obtaining the approval our Institutional Research Board (MS.21.12.1763). Informed consent obtained from participants in study.

Our study included infertile woman aged between 25 and 35 years who had minimal to mild endometriosis according to the revised American fertility society classification diagnosed by previous laparoscopy (5). These patients should have normal tubal patency, within normal luteal phase progesterone levels, and normal seminal analysis of her husband.

All patients with any other causes of infertility and those with any renal, hepatic dearrangement, apparent endocrinopathy (hypothalamopituitary, diabetes mellitus and thyroid disorders), cardiac disorders, hypertension, or any medical condition were excluded from the study.

The cases will be randomly assigned to receive one of the four treatment modalities by using computer generate random table and sealed envelop

- Group A: they received cabergoline (0.25 mg twice weekly) for three months.
- Group B: they received metformin 500 mg three times daily for three months
- Group C: they received Clomiphene citrate (50mg twice daily for 5days) from

second day of menstrual cycle for three months

- Group D: they got placebo once per day throughout the three months follow up period

Before the treatment cases, full history taking, and physical examination were done. Ultrasound scan was done and laboratory Investigations: serum prolactin (PRL), basal follicular stimulating hormone (FSH), basal luteinizing hormone (LH), basal serum estradiol (E2) and midluteal serum progesterone (P) were done.

Clinical assessment was done after three months, this included clinical examination with assessment of dysmenorrhea, dyspareunia and pelvic pain, menorrhagia and pregnancy. Hormonal assessment was also repeated.

Statistical analysis:

Using the SPSS application (version 22) for windows, the gathered data were recorded, processed, and analyzed. When necessary, the relevant statistical tests will be applied. P values under 0.05(5%) were regarded as statistically significant.

Results

Consort flow chart showing study design in Figure 1. The number of cases finally remain for analysis were: For group A; 20 cases, for group B 22 cases, for group C 20 cases, and for group D 17 cases. Table 1 demonstrates that there is no statistically significant difference between studied groups as regard age, sex, weight, height and body mass index, duration of symptoms, infertility type, and Mean duration of infertility. Table 2 demonstrates that the mean prolactin level, mean FSH level, and mean estradiol level after treatment statistically significant difference between studied group and placebo. Table 3 shows that there is no statistically significant difference between studied groups as regard symptoms before nor after treatment except for menorrhagia alter treatment. The pregnancy in studied groups were 8 out of 20 in Group A, 10 out of 22 in Group B, 8 out 20 in Group C, however, 2 out of 17 in placebo as shown in Table (3)

Discussion

the new era in the medical treatment of infertile patients with endometriosis is to target the pathogenesis of this lesion either Targeting Angiogenesis, Neuroangiogenesis, Apoptotic, or Estrogens (6).

The dopamine agonist cabergoline acts as an anti-angiogenic drug interaction with dopamine receptors, causing general and local prolactin decreases and subsequent decrease in Vascular endothelial growth factor (VEGF) level (2). Metformin seems to regress endometriotic implants as anti-inflammatory and anti-proliferative agent by decreasing the levels of the VEGF through the activation of AMP-activated protein kinase (3). Clomiphene citrate can be used in the treatment of mild to moderate endometriosis because it may correct the ovarian dysfunction that is considered one of the reasons that endometriosis causes infertility (4).

Mean prolactin level that is decreased in the three drugs support the concept of their mechanism of action on prolactin and subsequent effect on VEGF. the decreased of FSH level and increase estradiol level may be explained by increase ovarian follicular activity and correction of ovarian dysfunction.

Our result showed symptomatic relief of heavy menstrual bleeding only with variable degree of relief of dyspareunia, dysmenorrhea, or pelvic pain for each drug without any firm conclusion which can be explained by the drugs did not inhibit the ovulation in contract with Yarmolinskaya et al who studied 227 patients of reproductive age with endometriosis I—III and found that Patients receiving cabergoline combined with

hormone therapy standard show considerable pain relief (7).

The pregnancy rate in our trial is promising and give a good hope for these patients in contrast with Zhou et al who studied ovulation induction with clomiphene citrate after laparoscopy for infertile women with minimal to mild endometriosis and showed significantly increases ovulation rate without a significant improving pregnancy rate when compared to laparoscopy alone (4).

To the best of our knowledge, all the experimental data of using these medications are positive and encouraging however, limited number of clinical trials aren't enough to confirm or reject this hypothesis. Limitation of our study is the bounded number of cases and limited duration of follow up. The promising results may motivate us more for further prospective multicenter trials. We concluded that we had promising results on the use of cabergoline, metformin, and clomiphene citrate in patient with mild to moderate endometriosis.

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Figure (1): consort flow chart showing study design

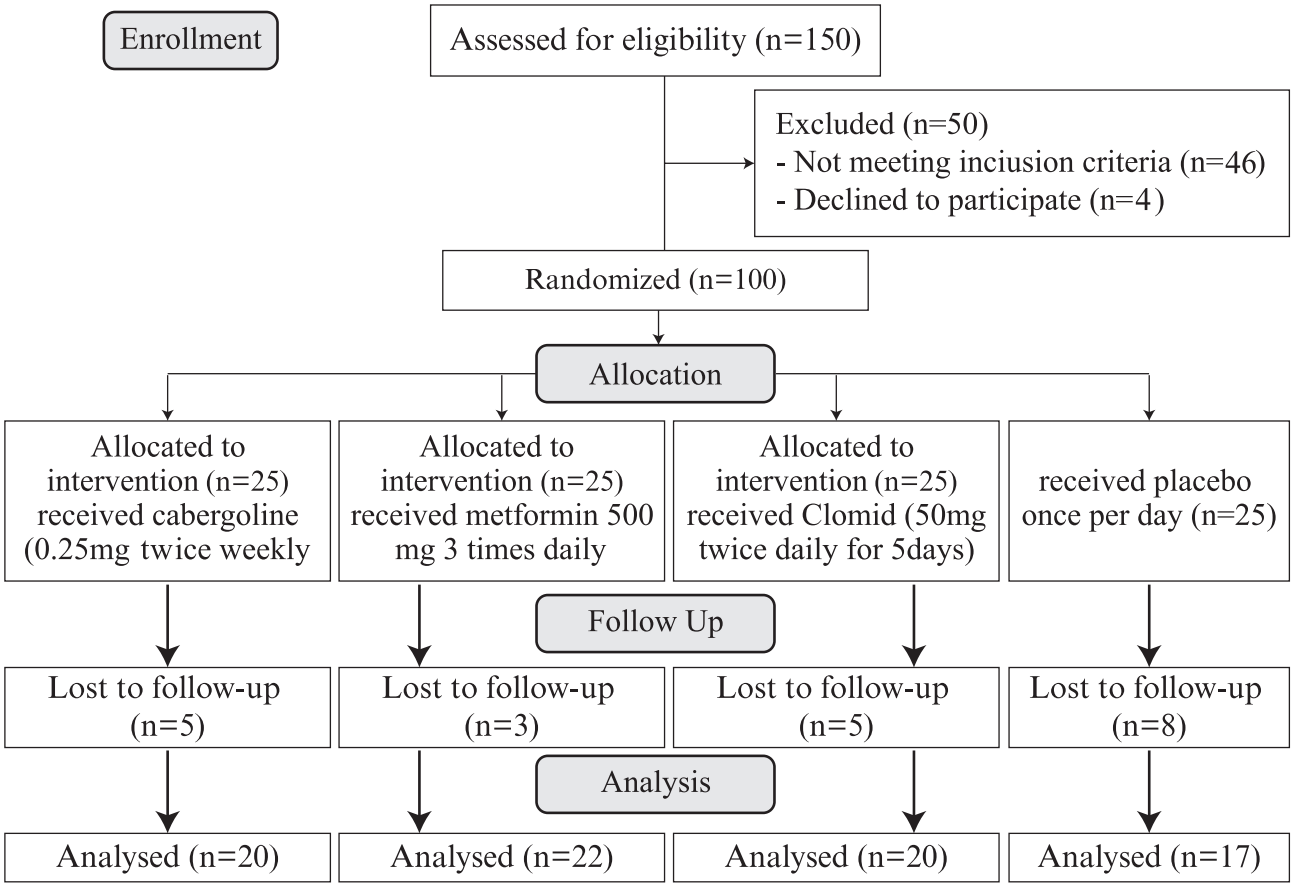

Table 1: Demographic characteristics of the studied groups:

	Group A (n=20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P-value
Age (years)	29.65±3.27	30.36±3.67	28.40±3.03	29.88±3.35	0.288
Weight (kg)	73.03±9.08	74.97±11.58	70.57±9.73	77.66±11.68	0.220
Height (m)	1.65±0.06	1.64±0.06	1.62±0.06	1.66±0.054	0.212
BMI (kg/m^2)	26.96±2.84	27.74±3.83	26.84±3.14	28.15±3.82	0.595
Duration of symptoms (months)	45.60±12.68	41.45±12.68	39.60±12.37	44.47±11.03	0.515
Infertility type	9(45.0)	14(63.6)	7(35)	9(52.9)	0.298
Primary					
Secondary	11(55.0)	8(36.4)	13(65)	8(47.1)	
Infertility duration (months)	23.40±7.26	24.55±9.25	21.30±6.59	24.71±7.31	0.490
Data is expressed as mean and standard deviation P is significant					

Table 2 Laboratory assessment of the studied groups before treatment:

		Group A (n= 20)	Group A (n= 20)	Group C (n=20)	Group D (n= 17)	P-value
Prolactin	before	22.48±1.16	22.07±1.30	23.23± 1.39	22.74±1.53	0.053
	After	18.64±1.22[a]	18.23±1.29[bc]	19.16±1.91[bd]	22.81±1.49[acd]	<0.001*
FSH	before	8.02±1.42	8.18±1.46	8.32± 1.98	8.29±1.65	0.936
	After	6.29±1.27a	6.26±1.33[b]	6.47± 1.55[c]	8.30±1.70[abc]	<0.001*
LH	before	3.14±1.31	3.63±1.79	2.61±1.17	2.59±1.82	0.135
	After	4.74±1.54	5.40±2.24[ab]	4.25±1.47a	3.61±1.84[b]	0.02*
Estradiol	before	144.13±75.21	182.96±62.23	182.35±56.44	159.90±93.05	0.253
	After	189.19±95.84[a]	238.94±81.74[b]	244.76±78.22[ac]	164.38±95.50[bc]	0.015*
Progesterone	before	9.16±3.69	8.19±3.51	8.06±3.75	9.06±5.48	0.766
	After	12.35±5.20	12.03±4.33	12.15±4.79	9.24±5.59	0.220

Data is expressed as mean and standard deviation. P is significant when < 0.05.

Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test

Table 3 Symptoms of endometriosis after treatment of the studied groups:

		Group A (n=20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P value
Dysmenorrhea	before	11(55)	13(59.1)	14(70)	9(52.9)	0.708
	After	9(45)	8(36.4)	10(50)	9(52.9)	0.733
p-value		0.157	0.025*	0.046*	1.0	
Pelvic pain	before	12(60)	15(68.2)	15(75.0)	10(58.8)	0.688
	After	10(50)	13(59.1)	12(60)	10(58.8)	0.911
p-value		0.157	0.157	0.083	1.0	
Dyspareunia	before	9(45)	11(50)	12(60)	10(58.8)	0.749
	After	6(30)	7(31.8)	9(45)	10(58.8)	0.247
p-value		0.083	0.046*	0.083	1.0	
Menorrhagia	before	13(65)	13(59.1)	13(65.0)	15(88.2)	0.242
	After	8(40)[c]	5(22.7)[bd]	11(55.0) [ad]	15(88.2) [abc]	**0.001***
p-value		0.025*	0.005*	0.157	1.0	

Data is expressed as percentage and frequency. P is significant when < 0.05. Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test.

Table 4 Pregnancy rate of the studied groups:

	Group A (n= 20)	Group B (n= 22)	Group C (n= 20)	Group D (n= 17)	P value
Pregnancy	8(40)[a]	10 (45.5) [b]	8(40)[c]	2 (11.8) [abc]	0.139

Data is expressed as percentage and frequency. P is significant when < 0.05.

Similar superscripted letters denote significant difference between groups within same row by Post Hoc Tukey test

High-Intensity Focused Electromagnetic Field (HIFEM) Technology Paves the Way for Incontinent Women to Better Quality of Life and Sexual Function

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Abstract

Objectives : The evaluation of efficacy and tolerability of flat magnetic stimulation (FMS) for pelvic floor muscle (PFM) training using the high-intensity focused electromagnetic field (HIFEM) technology for female urinary incontinence (UI).

Patients & Methods : 153 women, 60 with recurrent (Group R) and 93 with De Novo UI (Group D) were assessed at enrolment (Ass 1), at the end of sessions (Ass 2), and 6 weeks later (Ass 3) subjectively using the Pad-Usage Questionnaire (PUQ), the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), and the Female Sexual Function Index (FSFI), objectively using the International Continence Society-Uniform Cough Stress Test (ICS-UCST), and for satisfaction by the procedure outcomes. All patients received 2 sessions of 28 minutes weekly for 6 weeks. Procedure effectiveness was determined subjectively by achieving >50% reductions on the PUQ and ICIQ-SF questionnaires at Ass 3 concerning Ass 1 and objectively by a negative ICS-UCST. The frequency and severity of adverse events (AEs) were determined.

Results: At Ass 3, 99.4% and 61.4% of women achieved the procedure-effectiveness cutoff point for PUQ and ICIQ-SF scores, respectively. Objectively, 68.6%of women had negative ICS-UCST, and 60.1% of women were very satisfied-to-satisfied by the procedure outcomes. Thirty-one AEs were reported by 21 women, but all were transient and faded away in the next session. Procedure effectiveness variates were significantly better in (Group D) women, while the frequency of AEs and FSFI scores showed non-significant differences between both groups. Desire scorings were changed significantly at (Ass 3) with significantly higher scores for (Group D) women.

Conclusion: FMS of PFM using HIFEM technology is a promising efficient non-invasive therapeutic strategy for female UI with a high satisfaction rate, minimal AE, and improved sexual desire.

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Keywords: Female Urinary incontinence, Flat magnetic stimulation, Pelvic floor muscle, Pad Usage Questionnaire, Cough Stress Test, Adverse events, Satisfaction.

Introduction

Urinary incontinence (UI) is a common global condition, which affects both genders, especially elder people [1]. UI is mostly due to disturbed physiological urination-controlling factors: such as weak pelvic floor muscles, overactive or weak bladder muscles, and pelvic muscle or nerve injury [2]. However, a national survey suggested an association between urge urinary incontinence (UUI) and household income and assured that social inequity is perhaps the greatest driver of UUI [3]. The same survey detected lower oxidative balance scores in participants who experienced UI and the prevalence of UI showed an inverted U-shaped trend with increased oxidative stress [4]. Another study found that anxiety and depression are more prevalent in UUI and mixed UI (MUI) patients than in stress UI (SUI) patients and are more with increasing severity of incontinence [5]. Also, patients with obstructive sleep apnea syndrome showed worse urinary continence recovery than patients free of obstructive airways [6].

Lower urinary tract symptoms are prevalent in the female population and are increased in both frequency and severity with age. However, urgency and incontinence are the most bothersome symptoms [7]. SUI is defined as UI that occurs concomitantly with effort as physical exercise and even with coughing and sneezing, frequently affects women after middle age and harms their quality of life (QOL) and sexual function [8].

Multiple therapeutic lines were tried for female UI, and a recent survey study found pharmacotherapy was the most common UI intervention, and the most often treated women were those with more severe and longer duration of symptoms [1]. However, about 20% of UI female patients did not receive any therapeutic line and 23% were dependent on behavioral treatments (24%), while the minority receives either neuromodulation or onabotulinumtoxin-A therapy [9]. The standard mid-urethral sling for SUI showed an acceptable success rate, and the Altis single-incision sling was also found to be effective with low adverse event rates [10].

Objectives

The assessment of the efficacy of flat magnetic stimulation (FMS) for pelvic floor muscle (PFM) training using the High-intensity focused electromagnetic field (HIFEM) technology as a non-invasive therapy for female UI.

Design

Prospective comparative clinical trial

Setting

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University in conjunction with multiple private Gynecological centers.

Study Rational

The use of non-invasive modalities for the management of female USI, whenever surgical correction is indicated, may be advantageous for these patients in terms of regaining volitional control over the micturition process with subsequent functional and psychological improvement and sparing the psychological, physical, and financial impacts of surgery, especially for women in active life.

Blindness and authors' contributions

Preparatory evaluations (Ass 1) and the conduction of questionnaires for functional, sexual, and QOL evaluation were provided by an author (Dr. Abdelzaher YMA), who is also responsible for patients' evaluations

regarding inclusion and exclusion criteria. The assignment and provision of settings were the responsibility of another author (Dr. Elshirbeny MF) who was blinded by the results of the preparatory evaluation. At the end of the sessions (Ass 2), and 6 weeks later (Ass 3), another evaluation session was provided by an author (Amer WM) who was blinded by the results of the preparatory evaluation. Following complete case collection, the results of the evaluations were interpreted to determine the outcomes.

Patients' approval of the study protocol

The study rationale and protocol of sessions were discussed with the patients before the preparatory evaluations, and patients accepted to participate in the study were evaluated for inclusion and exclusion criteria, and those fulfilling the indications for enrolment were asked to sign the written fully informed consent according to the institutional rules.

Ethical considerations

The study protocol was approved by the departmental committee in June 2019 to allow case collection. In the end, after the completion of case collection and sessions, the final approval of the protocol and its outcomes was obtained by the Local Ethical Committee. RC:3-8-2023.

Initial evaluation

During Ass 1, age and body mass index (BMI), which was calculated as weight divided by height in square meters, were determined. An obstetric history concerning several pregnancies, labors, and living offspring, mode of delivery (spontaneous or instrumental vaginal delivery) need for episiotomy and efficacy of its repair, development of tears during delivery, and the quality of its repair and operative delivery was recorded. UI data including type and severity, previous evaluation, and treatment and its results were obtained. Full gynecological examination to determine the presence of pelvic prolapse, its type, degree, and associated symptoms other than UI. Urine analysis with bacteriological examination to exclude urinary tract infection was performed. Cystoscopic examination and urodynamic studies were undertaken if indicated.

Exclusion criteria

Women who had multiple recurrences after surgical corrections of their SUI, women who had recurrences after surgical procedures other than the trans-obturator tape (TOT) procedure, and women who had moderate or severe degrees of urogenital prolapse, were maintained on hormonal therapy, refused the study rationale, or missed sessions or follow-up visits were excluded from the study.

Inclusion criteria

Women who had UI either DE Novo or recurrent after the TOT procedure for the first time, accepted the study rationale, and completed the sessions and follow-up visits were included in the study.

Evaluation tools

These tools were applied at Ass 1 for the primary evaluation of the patient's problems and at Ass 2 and Ass 3 to assess the outcomes of the applied procedure. The used tools included:

1. Two-day Voiding Dairy (2-d VD): to assess the volume and frequency of voids by daytime and nighttime, the amount leaked, the relation of leak to activity and type of the triggering activities, and the presence of urgency [11]. These points have to be fulfilled by the patient herself for three days and registered in the provided printed form (Appendix I).
2. The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) consists of three items

regarding the average frequency and amount of leakage, the impact of leakage on QOL over the past four weeks for a score range of 0-21 with a higher score indicates greater impairment secondary to incontinence [12].

3. Pad usage questionnaire to evaluate the number of pads used per day [13].
4. The Female Sexual Function Index (FSFI) is a questionnaire consisting of 6 domains evaluating Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. Each item was rated from 1-5 with items concerning difficult function, and pain related in reverse according to its severity and the sum of points was calculated with the lower the score, the more sexual dysfunction [14].
5. The International Continence Society - Uniform Cough Stress Test (ICS-UCST) was performed at each assessment to objectively detect SUI, and its results were qualitatively evaluated as positive or negative tests. While the patient was in a lithotomy position with 200-400 ml of fluid in the bladder as judged by the US, the patient was asked to cough forcefully 1-4 times, and the examiner directly visualizes the urethral meatus for the presence of leakage coincident with/ simultaneous to the cough(s), which is considered a positive test [15].

Treatment Protocol

- The device rationale, the used device (BTL EMSELLA, BTL Medical Technologies Inc., Canada), as described by the manufacturer, depends on the generation of a rapidly changing electromagnetic field of high intensity reaching up to 2.5 T that was produced by a flat spiral-shaped coil, which is situated within a uniquely-designed seat for comfortable patient's seating position. The HIFEM interacts with motor neurons and triggers stimulation and toning of the pelvic floor area to help restoration of neuromuscular control. A single session of FMS causes thousands of supramaximal PFM contractions.
- Treatment protocol: each woman was assigned to receive 2 sessions of 28 mins weekly for 6 weeks. The patient was asked to sit straight in the center of the chair seat to ensure PFM stimulation. The author responsible for the provision of HIFEM sessions must confirm patients' posture during the session and adjust HIFEM intensity as high as tolerated by the patient

Study outcomes

- Effectiveness endpoints included subjective dryness, negative ICS-UCST, and adverse events (16).

- The primary effectiveness endpoint, as defined by the FDA, was a reduction of baseline (Ass-1) 2-d VD, ICIQ-SF, FSFI and PUQ by ≥50% at 6-w after the last session (Ass-3).
- The primary safety endpoint was the rate of related adverse events (AE) throughout the observation period. Local AE occurred locally to the treated area including muscle, joint or tendon pain, muscle spasm, local erythema or skin redness. AE was evaluated as frequency per patient, total number, and if temporary or persistent.

- The secondary effectiveness endpoint was patients' satisfaction scoring using a Likert scale of 1-5 items; very dissatisfactory, dissatisfactory, Neither dissatisfactory nor satisfactory, satisfactory or very satisfactory. Each item is given a score from 1 to 5 with a higher score indicating a higher satisfaction rate.

Results

Evaluation of patients attending the Gynecology outpatient clinic excluded 23

women; 7 were maintained on hormonal therapies for multiple indications, 5 had recurrent UI after surgical procedures than TOT, 8 had moderate-to-severe genitourinary prolapse, and three women had urolithiasis. Moreover, 11 women were missed during the study duration and were also excluded. Sixty women had recurrent UI after TOT (Group R), and 93 women had IU and did not receive any previous surgical intervention and were collected as De Novo UI group (Group D) as shown in Figure 1.

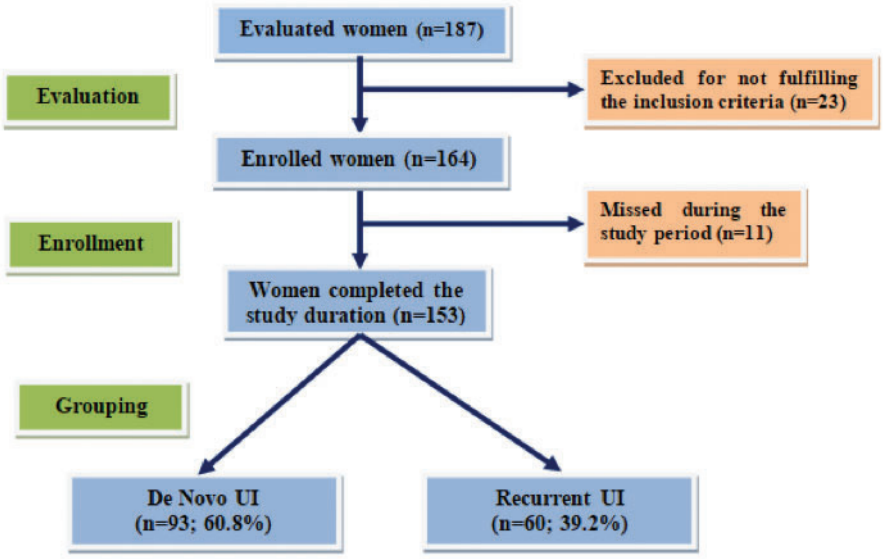

Figure 1: Study Flow Chart

Among (Group D) women, 26 patients (28%) did not receive any line treatment for their UI, while 67 patients (72%) received multiple lines of medical treatment that failed to control their UI. Duration since the start of compliance was non-significantly (P=0.056) shorter among (Group D) women, and the mean duration of recurrence of UI after TOT was 1.55 (±0.66) years. The constitutional data of the enrolled women were comparable, but (Group R) women had significantly (P=0.042) higher numbers of pregnancies and spontaneous vaginal delivery (P==0.042, 0.007, respectively). Also, the number of women who had perineal tears, and women who had badly repaired or not repaired perineal tears were significantly (P=0.024, 0.041, respectively) higher among (Group R) (Table 1).

Table 1: Constitutional and clinical data of enrolled women

Data		Group D	Group R	P
Treatment	Medical	67 (72%)	0	-
	Surgical	0	60 (100%)	-
	No	26 (28%)	0	-
Duration of UI (years)	Since the start of the complaint	3.6±1.9	4.2±1.9	**0.056**
	Since the recurrence of UI	-	1.55±0.66	-
	Average (±SD)	39.7±6.6	41±6.7	**0.251**

Age (years)	Strata	≤30	4 (4.3%)	4 (6.7%)	**0.221**
		31-35	27 (29%)	13 (21.6%)	
		36-40	20 (21.5%)	9 (15%)	
		41-45	27 (29%)	16 (26.7%)	
		46-50	15 (16.2%)	16 (26.7%)	
		>50	0	2 (3.3%)	
	Average (±SD)		30.5±2.3	30.95±2.6	**0.261**
BMI (kg/m²)	Strata	<25	1 (1%)	1 (1.6%)	**0.797**
		25-29.99	34 (36.6%)	19 (31.7%)	
		30-34.99	58 (62.4%)	40 (66.7%)	
Obstetric history	Previous pregnancies		2.6±0.95	2.9±1.08	**0.042**
	Previous labors		2.5±0.8	2.8±1.05	**0.058**
	Living offspring		2.3±0.8	2.5±0.98	**0.189**
	Mode of delivery	Spontaneous VD	55 (23.6%)	61 (36.3%)	**0.007**
		Instrumental VD	48 (20.6%)	38 (22.6%)	
		Cesarean section	130 (55.8%)	69 (41.1%)	
	Total number of deliveries		233 (100%)	168 (100%)	
Perineal examination	Vaginal delivery with	Episiotomy	72 (69.9%)	54 (54.5%)	**0.024**
		Perineal tear	31 (30.1%)	45 (44.5%)	
	Episiotomy (n=126)	Well-repaired	65 (90.3%)	44 (81.5%)	**0.153**
		Badly-repaired	7 (9.7%)	10 (18.5%)	
	Perineal tear (n=76)	Well-repaired	24 (77.4%)	22 (48.9%)	**0.041**
		Badly-repaired	4 (12.9%)	15 (33.3%)	
		Not repaired	3 (9.7%)	8 (17.8%)	

P indicates significance between both groups

At (Ass 1), subjective evaluation and ICS-UCST detected SUI, UUI, and MUI in 65 (42.5%), 43 (28.1%), and 45 women (29.4%), respectively with significantly (P=0.0084) higher frequency of MUI among (Group R) women. At (Ass 2), 50 (32.7%) women, and (Ass 3) 105 women (68.6%) stopped complaining of UI and showed negative ICS-UCST with a significant difference in comparison to (Ass 1) distribution in both groups. The difference in patient distribution between both groups was insignificant at (Ass 2), but at (Ass 3), it was significant (P=0.0036) in favor of (Group D) women (Table 2).

Table 2: Patients' distribution during assessments according to type of UI

Type of UI	Group-D			Group-R		
	Ass-1	Ass-2	Ass-3	Ass-1	Ass-2	Ass-3
Continent	0	32 (34.4%)	74 (79.6%)	0	18 (30%)	31 (51.7%)
Urge UI	28 (30.1%)	20 (21.5%)	6 (6.4%)	15 (25%)	10 (16.7%)	8 (13.3%)
Stress UI	46 (49.5%)	27 (29%)	8 (8.6%)	19 (31.7%)	15 (25%)	11 (18.3%)
Mixed UI	19 (20.4%)	14 (15.1%)	5 (5.4%)	26 (43.3%)	17 (28.3%)	10 (16.7%)
P	0.0084	0.754	0.0036			
P1		<0.001	<0.001		0.00001	<0.001
P2			<0.001			0.062

P indicates significant between both groups; P1: indicates significance of difference versus Ass-1; P2: indicates significance of difference versus Ass-2

All patients showed progressively decreasing number of daily voids and concomitantly increasing volume of urine per void at the Ass-2 and Ass-3 with significant differences concerning the numbers and volumes registered at Ass-1. Despite improvements, the number of daily voids and volume of urine per void were comparable at (Ass 2) and (-3). Rec UI is more tedious, as evidenced by detecting 10 of (Group R) women (16.7%) were still complaining of the high frequency of several daily voids at (Ass 3) (Table 3).

At Ass-3, 63 (41.2%) women had no leaks and 53 patients (34.6%) denied leaks with any type of activities, while 64 patients (41.8%) still had drops, especially on activities despite the decreased frequency and number of drops. Unfortunately, 26 women (17%) were still complaining of wetting, especially on activities with significantly higher frequency among women of (Group R). The frequency of patients who got rid of UI was significantly lower among (Group R) women both at (Ass 2) and at Ass-3, but this frequency was significantly increased in both groups at (Ass 3) than at Ass-2. Interestingly, the number of activities triggering leaks before treatment was significantly higher among Group-R women with nearly double the number of activities per woman to that reported by Group-D women. However, the number of activities causing leaks per woman decreased progressively in women of both groups with treatment and the decrease showed a non-significant difference in favor of D Group (Table 3).

Table 3: Two-day Voiding Dairy (2-d VD)

Items	Time	Group-D			Group-R		
		Ass-1	Ass-2	Ass-3	Ass-1	Ass-2	Ass-3
Number of voids/ day	Mean	6.4±1.9	5±1.5	4.7±1.1	7.65±3	6.1±2.6	5.2±2.1
	P	0.002	0.0012	0.038			
	P1		<0.001	<0.001		0.0037	<0.001
	P2			0.198			0.163
Urine volume (cc)/ voiding time	Mean	250±46	290±52	301±55	211.3±48	233.3±46	259±54
	P	<0.001	<0.001	<0.001			
	P1		<0.001	<0.001		0.042	<0.001
	P2			0.309			0.014
Daily urine output (cc)	Mean	1623±644	1463±561	1430±478	1528±490	1365±522	1303±475
	P	0.332	0.284	0.104			
	P1		0.131	0.053		0.164	0.033
	P2			0.916			0.765
Amount of leaked urine	No	0	48 (51.6%)	85 (91.4%)	0	15 (25%)	41 (68.3%)
	Wet	75 (80.6%)	12 (12.9%)	2 (2.2%)	43 (71.7%)	14 (23.3%)	6 (10%)
	Drops	18 (19.4%)	33 (35.5%)	6 (6.4%)	17 (28.3%)	31 (51.7%)	13 (21.7%)
	P	0.197	0.0043	0.0012			
	P1		<0.001	<0.001		<0.001	<0.001
	P2			<0.001			<0.001

Relation of activity & leak	Yes	93 (100%)	59 (63.4%)	42 (45.2%)	60 (100%)	41 (63.4%)	29 (48.3%)
	No	0	34 (36.6%)	51 (54.8%)	0	19 (36.6%)	31 (51.7%)
	P	-	0.535	0.701			
	P1		<0.001	<0.001		<0.001	<0.001
	P2			0.012			0.026
Type of Activity	Posture change	54 (58%)	31 (33.3%)	17 (18.3%)	44 (73.3%)	26 (43.3%)	12 (20%)
	Coughing	37 (39.8%)	19 (20.4%)	10 (10.8%)	41 (68.3%)	21 (35%)	10 (16.7%)
	Laughing	41 (44.1%)	17 (18.3%)	8 (8.6%)	52 (86.7%)	16 (26.7%)	8 (13.3%)
	Lifting heavy objects	19 (20.4%)	9 (9.7%)	3 (3.2%)	50 (83.3%)	21 (35%)	11 (18.3%)
	Walking	23 (24.7%)	10 (10.8%)	6 (6.5%)	36 (60%)	19 (31.7%)	6 (10%)
	Exercise	12 (12.9%)	5 (5.4%)	2 (2.2%)	5 (8.3%)	3 (5%)	3 (5%)
	Activities/ patient	2	1.5	1.1	3.8	2.6	1.7
	P	0.0028	0.182	0.361			
	P1		0.958	0.848		0.599	0.567
	P2			0.982			0.885

P indicates significant between both groups; P1: indicates significance of difference versus Ass 1; P2: indicates significance of difference versus Ass 2

The calculated ICIQ-SF score at Ass 1 was significantly (P=0.0082) lower in Group D than in Group R women. All women showed progressive decreases in their ICIQ-SF scores at Ass 2 and Ass 3 in comparison to Ass 1 scores with significantly lower scores determined at Ass 3 than Ass 2 scores. Further, Ass 2 and Ass 3 ICIQ-SF were significantly lower in Group D than in Group R women as shown in Table 4 and Figure 2. The determined ICIQ-SF score at Ass-3 had decreased by 61.2 (±12%) and 72 women (77.4%) had decreased their score by >50% in Group-D women. At Ass 3 of Group R women, the mean percentage of decrease in ICIQ0SF was 48.2 (±10.8%), and 22 women (36.7%) had decreased score by >50. ICIQ-SF score of Group D women showed a significantly (P<0.001) higher percentage of decrease with a significantly (P<0.001) higher number of women decrease by >50% than scores of Group R women.

According to the PUQ, women using <5 pads/day were significantly higher among Group D than Group R at Ass 1, while at Ass 2 and Ass 3, the number of women using no pads was significantly higher among Group D than Group R. In both groups, the frequency of women using no pads at Ass 3 was significantly higher than at Ass 2. Similarly, the mean number of daily used pads was significantly decreased with time-course assessments in both groups and was significantly lower in Group D than Group R. About 63 women (41.2%) stopped using pads at the time of Ass 2 and 130 women (85%) at the time of Ass 3 with a significantly higher number of women stopping pads usage among Group D women. The mean number

of pads used decreased progressively with assessments with a significant difference between the number defined at each assessment and a significantly lower mean number for Group D women than Group R women. The mean percentage of decrease in the number of used pads was significantly (P=0.014) higher among Group D than Group R women, and only one woman (0.65%) showed a decrease in number of the used pads by ≤50% (Table 4, Fig. 3).

Table 4: The calculated mean value of the total ICIQ-SF score and Pads Usage Questionnaire determined at the three assessments

Score			Group-D			Group-R		
			Ass-1	**Ass-2**	**Ass-3**	**Ass-1**	**Ass-2**	**Ass-3**
ICIQ-SF	Mean		13±4.2	7.7±2.9	4.9±2.2	14.6±2.6	10.4±1.7	7.6±1.9
	P		0.0082	<0.001	<0.001			
	P1			<0.001	<0.001		<0.001	<0.001
	P2				<0.001			<0.001
	Mean % of ↓			61.5±12			48.2±10.8	
	P		<0.001					
	↓ by <50%			21 (22.6%)			38 (63.3%)	
	↓ by >50%			72 (77.4%)			22 (36.7%)	
	P		<0.001					
PUQ	The number of pads used	0	0	48 (51.6%)	84 (90.3%)	0	15 (25%)	46 (76.7%)
		<5	48 (51.6%)	34 (36.6%)	8 (8.6%)	13 (21.7%)	29 (48.3%)	14 (23.3%)
		6-10	42 (45.2%)	11 (11.8%)	1 (1.1%)	37 (61.7%)	16 (26.7%)	0
		>10	3 (3.2%)	0	0	10 (16.6%)	0	0
		P	0.0001	0.0024	0.031			
		P1		<0.001	<0.001		<0.001	<0.001
		P2			<0.001			<0.001
	The mean number of pads used		6±2.5	2.3±2.6	0.3±1	8.05±2.3	3.9±2.4	0.85±1.6
			<0.001	0.0002	0.01			
				<0.001	<0.001		<0.001	<0.001
					<0.001			<0.001
	Mean% of ↓			96.9±10.5			91.7±15.5	
	P		0.014					
	↓ by <50%			1 (1.1%)			0	
	↓ by >50%			92 (98.9%)			60 (100%)	
	P		0.421					

Ass: Assessment; ICIQ-SF: The International Consultation on Incontinence Questionnaire-Short Form; PUQ: Pads Usage Questionnaire; P indicates significant between both groups; P1: indicates significance of difference versus Ass-1; P2: indicates significance of difference versus Ass-2

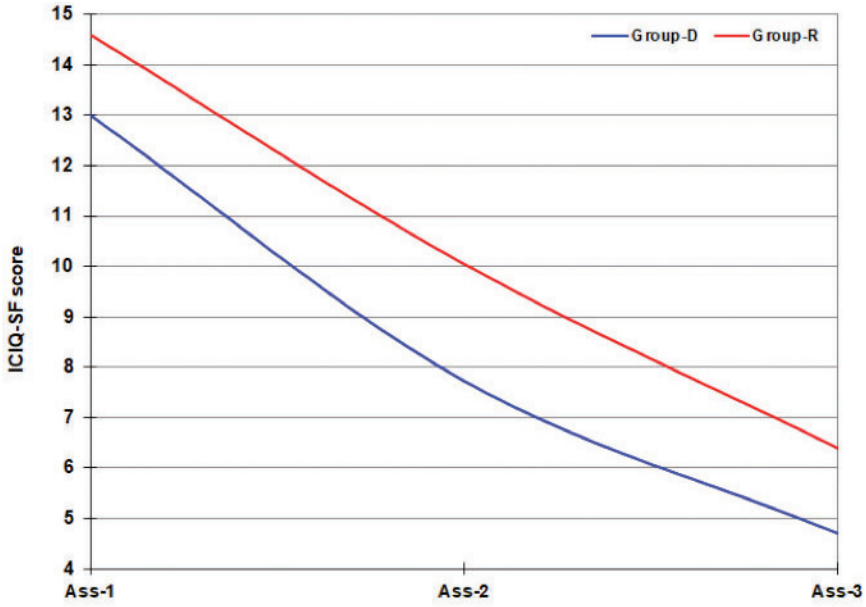

Fig. (2): Mean ICIQ-SF of women of both groups

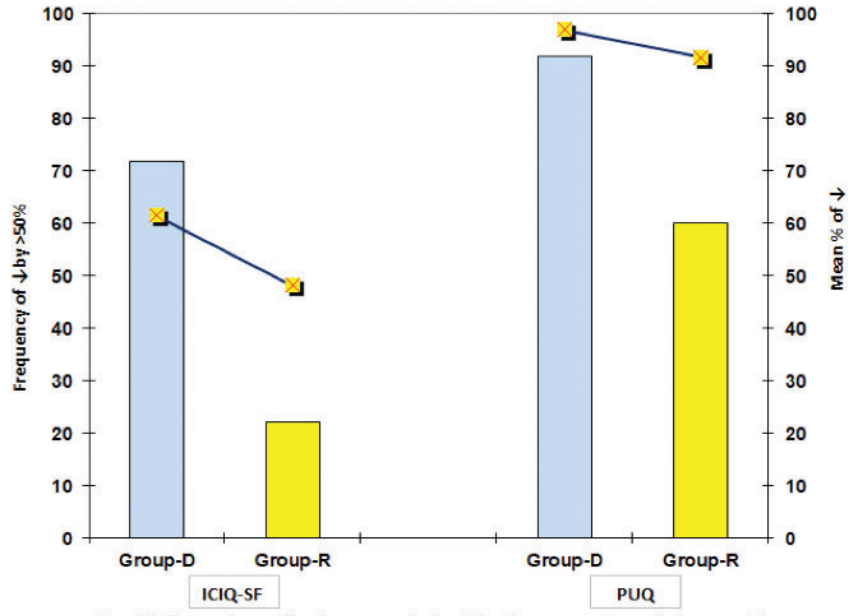

Fig. (3): Procedure effectivness as judged by the percentage of change at Ass-3 in relation to at Ass-1 for ICIQ-SF and PUQ

The mean scores of five domains of FSFI score determined at Ass 2 and Ass 3 of women of both groups were comparable to scores determined at Ass 1 with insignificant differences between Ass 2 and 3. However, desire was the only domain that significantly changed at both Ass 2 (P=0.011) and Ass 3 (P<0.001) for Group D patients concerning Ass 1 scores with significantly (P=0.0001) higher desire score at Ass 3 than at Ass 2. Moreover, Ass 3 desire scorings of Group R women were significantly (P=0.030) higher than Ass 1 scores and were non-significantly (P=0.113) higher than Ass 2 scores which were non-significantly (P=0.518) higher than Ass 1 scores. The differences between the three assessments of women of both groups were non-significant (Table 5, Fig. 4).

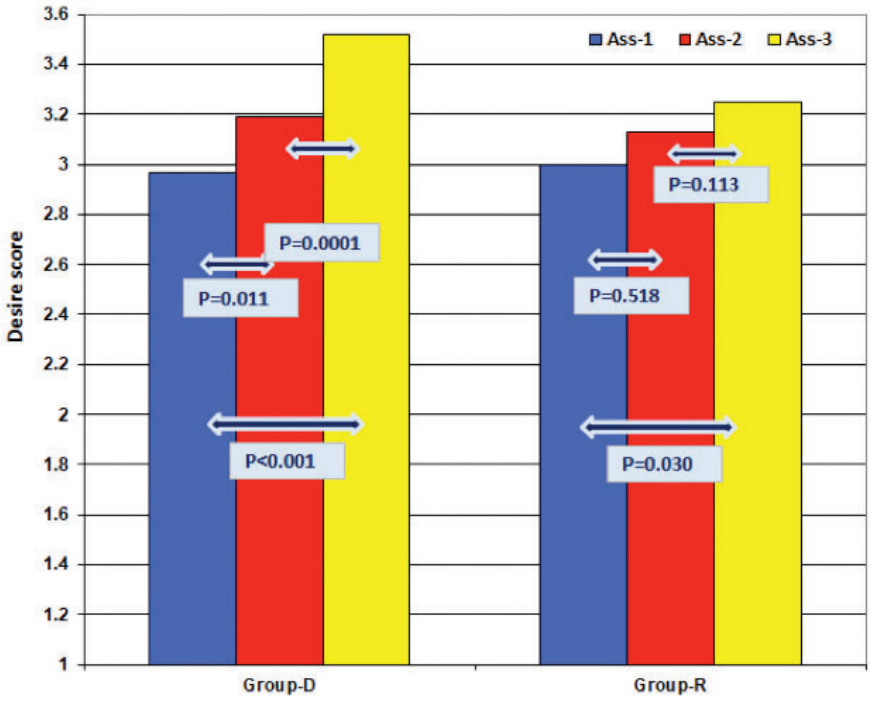

Fig. (4): Desire score of women of both groups

The calculated total FSFI scores at the three assessments showed non-significant differences between patients of both groups. Among Group D women, the total Ass-2 FSFI score was non-significantly higher than the Ass 1 score, while was significantly (P=0.027) higher than the Ass 3 score, which also was significantly (P=0.071) higher than the Ass 1 score. Regarding Group R, Ass 2 total FSFI score showed insignificant differences between Ass 1 and Ass 3 scores, while Ass 3 score was significantly (P=0.013) higher than Ass 1 score, (Table 5, Fig. 5).

Table 5: Scores of individual domains and total FSFI score determined at the three assessments

		Group-D			Group-R		
Domain Time		Ass-1	Ass-2	Ass-3	Ass-1	Ass-2	Ass-3
Desire	Mean	2.99±0.71	3.25±0.65	3.66±0.74	3.07±0.84	3.17±0.85	3.44±0.99
	P	0.541	0.527	0.129			
	P1		0.011	<0.001		0.518	0.030
	P2			0.0001			0.113
Arousal	Mean	2.82±1	2.89±0.95	2.9±0.9	2.81±0.95	2.86±0.97	2.93±0.89
	P	0.906	0.882	0.721			
	P1		0.871	0.786		0.965	0.976
	P2			0.986			0.982
Lubri-cation	Mean	2.57±0.9	2.59±0.91	2.69±0.75	2.6±0.85	2.56±0.8	2.69±0.85
	P	0.402	0.353	0.845			
	P1		0.898	0.545		0.818	0.907
	P2			0.815			0.981

Orgasm	Mean	2.78±0.53	2.81±0.89	2.92±0.92	2.9±1	3.1±0.94	2.98±1.1
	P	0.355	0.053	0.729			
	P1		0.835	0.430		0.527	0.894
	P2			0.667			0.804
Satis-faction	Mean	2.65±1.04	2.5±1.02	2.61±1.22	2.37±1	2.51±0.6	2.53±0.86
	P	0.112	0.938	0.631			
	P1	-	0.355	0.846		0.652	0.583
	P2			0.514			0.993
Pain	Mean	2.17±0.58	2.06±0.79	2.11±0.77	2.1±0.9	2.2±0.55	2.25±0.44
	P	0.561	0.242	0.186			
	P1		0.568	0.913		0.682	0.424
	P2			0.815			0.909
Total score	Mean	13.41±1.88	13.52±2.12	14.2±2.1	13.25±2.1	13.85±1.54	14.1±1.7
	P	0.638	0.301	0.833			
	P1		0.715	0.0071		0.082	0.013
	P2			0.027			0.336

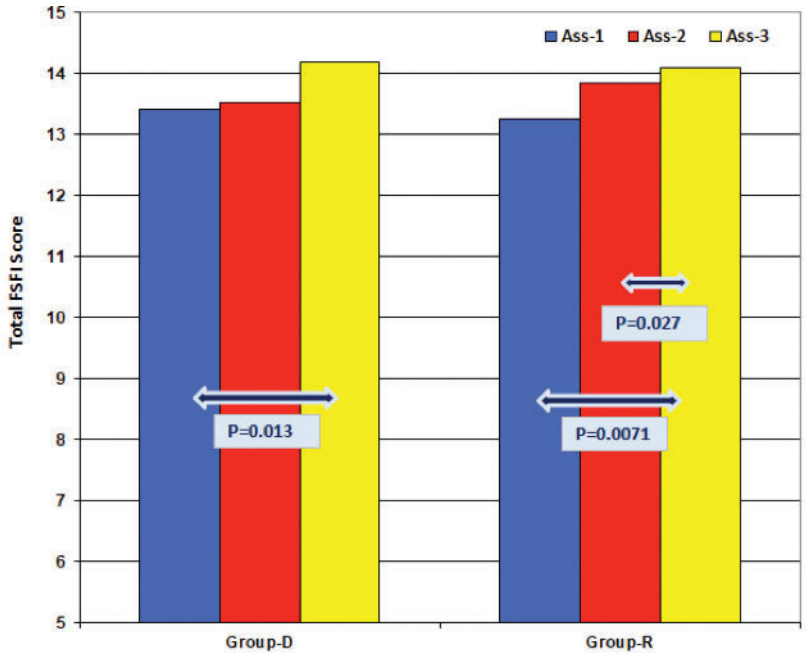

Fig. (5): Total FSFI score of women of both groups

Only 13 patients (8.5%) achieved the cutoff point for procedure effectiveness as regards sexual desire; 11 of Group D (14%) and two of Group R (3.3%) patients with non-significantly (P=0.065) higher frequency among Group D. However, the mean percentage of change of desire score among Group D patients (27.5±36.3; range: 0-150%) was significantly (P=0.024) higher than the mean percentage of change among Group R patients (13.8±22.8; range: 0-100%) as shown in figure 6. Unfortunately, no women achieved the cutoff point for procedure effectiveness as regards the total FSFI score. Moreover, 34 women (22.2%) had decreased total FSFI scores and another 35 women (22.9%) showed no change in their score, while 84 women (54.9%) had increased scores but to ≤50% with insignificant differences

between both groups as regards women's distribution according to the change in total FSFI score. On the contrary, the mean percentage of change of total FSFI score of Group-D women (6.4±12.67; range: [-25]-40) was significantly (P<0.001) higher than the mean percentage of change in scores of Group-R women (-8.26±14.9; range: [-57.14]-18.75) as shown in figure 6

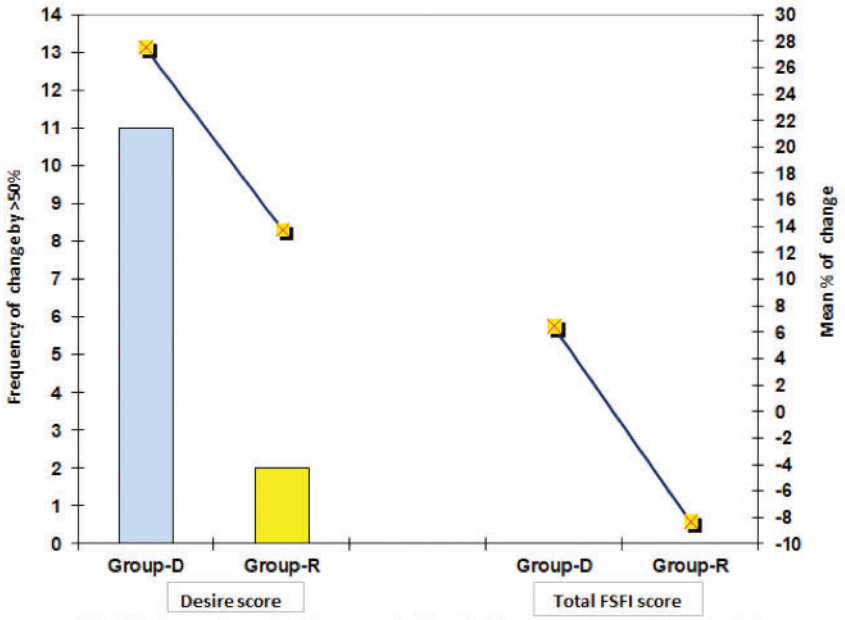

Fig. (6): Procedure effectivness as judged by the percentage of change at Ass-3 in relation to at Ass-1 for Desire and Total FSFI scores

Concerning satisfaction grading of procedural outcomes, 53 women (34.6%) were very satisfied, 39 women (25.5%) were satisfied, 35 women were neither dissatisfied nor satisfied (22.9%), 17 women (11.1%) were dissatisfied and only 9 women (5.9%). The frequency of women having very satisfactory and satisfactory outcomes was significantly (P=0.028) higher among Group-D women (Fig. 7).

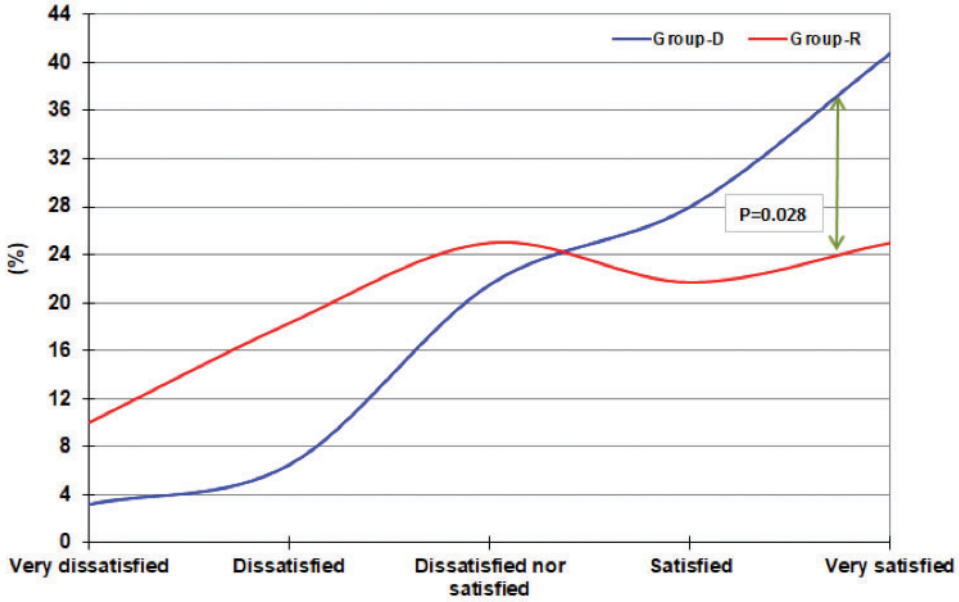

Fig. (7): Women's distribution according to satisfaction by procedure outcomes

Among the studied women, 21 women (13.7%) developed AE with non-significant (P=0.713) difference between both groups and all the reported AE were temporary and disappeared on the next day of the session. The total number of the reported AE was 31 events; 18 and 13 events affecting women of Group-D and Group-R, respectively with non-significant (P=0.874) difference between both groups. Regarding the type of AE, muscle spasm and local skin erythema were the most common AE (22.2%), respectively, and were followed by muscle pain (19.4%) and skin redness (16.1%), while pelvic and tendon pain were the least frequent and represent 9.7% each. The frequency of ported adverse events was 1.5 and 1.4 event/patient for both groups, respectively with insignificant differences between both groups (Table 6).

Table 6: Patients' distribution according to procedure-induced AE

Frequency of adverse events		
	Group D	Group R
No	81 (87.1%)	51 (85%)
Yes	12 (12.9%)	9 (15%)
P=	0.713	

Prognosis of adverse events		
	Group D	Group R
Temporary	12 (100%)	9 (100%)
Permanent	0	0
Total	12 (100%)	9 (100%)
P=	-	

Frequency of adverse events			
Events		Group D	Group R
Pain	Muscular	3 (25%)	3 (33.3%)
	Pelvic joints	2 (16.7%)	1 (11.1%)
	Tendons	2 (16.7%)	1 (11.1%)
Muscle spasm		4 (33.3%)	3 (33.3%)
Local erythema		4 (33.3%)	3 (33.3%)
Skin redness		3 (12%)	2 (22.2%)
Total		18	13
Adverse event/ Patient		1.5	1.4
P=		0.874	

Discussion

The current study depended on a tripod evaluation approach to assess the procedure effectiveness; subjectively using ICIQ-SF and pad-usage questionnaires (PUQ), objectively using the ICS-UCST and lastly the extent of patients' satisfaction. Similarly, **Barba et al.** [17] applied the same rationale and detected a statistically significant reduction in the subjective UI evaluation at the end of FMS sessions with significant objective improvement and stable subjective satisfaction scorings.

According to the FDA recommendations, the procedure effectiveness was defined as a reduction of the number of the used pads on PUQ and the ICIQ-SF score by >50% concerning pre-procedure data, the FMS therapy provided marvelous outcomes and nearly all the studied (99.4%) women achieved the cutoff point for the PUQ and 61.4% of women had reduced ICIQ-SF score by >50%. Objectively, 105 women (68.6%) had negative ICS-UCST at the end of 6-w after the last FMS session. Moreover, 92 women (60.1%) were very satisfied-to-satisfied by the procedure outcomes. In line with these results, **Samuels et al.** [18] using HIFEM technology for female UI detected its ability to safely and effectively treat a wide range of UI patients with ICIQ-SF improvement and reduction in pad usage. Thereafter, **González-Isaza et al.** [19] reported reduced scores of UI evaluation questionnaires after FMS sessions and at 14-w of follow-up and assured the favorable impacts of the procedure on clinical outcomes and QOL of women who had SUI who prefer non-surgical treatments. Also, **Filippini et al.** [20] using the "chair" device for pelvic floor muscle (PFM) stimulation detected a significant and consistent improvement in patients with UI and pelvic floor disorders

as judged by ultrasound measurements and validated questionnaires without discomfort or side effects and concluded that the used device represents valuable and effective modality for women affected by different urogenital pathologies.

In support of the efficacy of FMS as a non-invasive therapeutic modality for female UI, a systemic review concluded that FMS is an effective and non-invasive therapy for UUI treatment (21) and prospectively, **Dominguez et al.** [22] reported subjective improvement at 3-m after FMS sessions for elderly women with the debilitating condition of pelvic floor dysfunction and concluded that the noninvasiveness and safety of device allowed it to be an interesting approach for these patients. Another prospective study compared the effectiveness of FMS versus PFM training for women with SUI but ineligible for surgery and observed significantly improved urinary-related QOL scores with FMS [23].

Physiologically, the myotatic reflex, which is an inducible action, is outplayed through the Golgi tendon organs and mediated via the 1β and γ afferents to relay to the spinal cord with subsequent inhibition of the inhibitory and summations of the excitatory postsynaptic potentials resulting in shortening of the refractory period of the action potential, thus rapidly successive stimuli will affect the muscle which is in the excitatory state leading to super-threshold stimulation and development of tonic contractile status (24, 25). Similarly, exposure of PFM to a rapidly changing high-intensity electromagnetic field will induce intense muscular contractions with the regulation of the neuromuscular control and enhanced muscular blood supply resulting in muscle fiber hypertrophy and hyperplasia secondary to the more efficient stimulation. In support of this assumption, recent clinical studies using electromagnetic stimulation of upper arm muscles reported increased muscle mass and reduction of fat as judged by MRI (26) with increased muscle strength measurements, using the dynamometer that was sustained at 30 and 90 days (27).

Thus, the reported improved UI with FMS therapy could be attributed to the improved PFM contractility with subsequent improvement of urethral hypermobility and intrinsic urethral deficiency, the two pathognomonic pathological changes causing UI (28). In support of this assumption, **Frigerio et al.** [23] detected an increased volume of urethral rhabdosphincter after FMS concerning baseline assessment in women with SUI

The 2nd procedure effectiveness target was the frequency and severity of AE; only 21 of the studied women developed 31 AEs for a frequency of 1.47 AE/ affected woman and 0.2 AE/studied woman. Fortunately, these AE were transient and completely fade away before the next session, thus indicating the safety and tolerability of the procedure and go in hand with a recent study documenting that side effects of FMS procedure are minimal and transient in comparison to other active treatments and FMS could be considered as one of the safest methods for UI patient and as a suitable first step in treating UI (29). Further, one survey study detected the preference of patients with mild-to-moderate pelvic floor disorders for procedures with the greatest safety profile and quickest recovery time as FSM over procedures of the highest efficacy (30).

Unfortunately, the total FSFI score did not indicate improved sexual functions of the treated women and desire scorings were the only significantly improved scores. Similarly, a recent meta-analysis did not confirm the improved sexual function of women with UI using energy equipment as FMS (31).

The reported insignificant improvement of FSFI even with improved UI scorings and especially in women who had RUI could be attributed to the fear of UI on excitation as previously noted before treatment and to the

history of disappointed partner by history of leaks during abdominopelvic muscular contractions that occur simultaneously with excitation and orgasm. In line with this attribution, an earlier study found women with UI have poorer sexual functioning, and are more likely to restrict sexual activity for fear of incontinence (32).

Another point of view was that about 50% of the studied women were peri-menopausal, an age category that is vulnerable to PFM weakness and disorders including UI and had dry vaginas secondary to hormonal imbalance leading to sexual dysfunction (33). As long as the mechanism of action of FMS is excessive muscular stimulation, it could improve the PFM disorders but could not improve lubrication of the vagina as did hormonal therapy (34) and subsequently could not interrupt the circle of inability, fear of UI and loss of interest leading to less satisfaction and failure to approach the orgasm.

Moreover, the majority of the studied women were mostly obese or overweight, a finding pointing to a possible relation between obesity and UI. In support of this suggestion women who had recurrent UI were more obese than women who had De Novo UI and **Chen et al.** (35) detected a significant positive relationship between both BMI and percentage of trunk fat and the prevalence and severity of female UI. Further, **Nosrati et al.** (36) assured that obesity is an independent risk factor for UI and sexual dysfunction and **Infante et al.** (37) detected a high sexual dysfunction rate in obese women and considered obesity as a risk factor for female sexual dysfunctions. Considering, the applied FMS did not affect women's weight, the maintained obesity may explain the persistent sexual dysfunction.

Conclusion

The use of flat magnetic stimulation (FMS) of pelvic floor muscle using HIFEM technology could be considered a promising efficient therapeutic strategy for female UI. FMS/HIFEM strategy provided effective non-invasive control of patients' complaints with a high satisfaction rate, minimal or no adverse events and improved sexual desire. However, such effects were hampered by being costly and the frequent session may cause dropped-off sessions.

Limitation

The short duration of follow-up, small sample size, single-center study, and dependence on subjective evaluation questionnaires are the study limitations

Recommendations

Trials to reduce the costs of sessions might help to use the FMS/HIFEM strategy as frequently repeated therapy, especially for cases with incomplete symptom resolution, recurrence of manifestations after successful sessions and the application of such strategy on a wider scale patients population, especially the low-outcome strata.

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