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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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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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Contents :

Letter from the Editor:

Dear colleagues,

very interesting subjects are included in this edition. MRI is superior to clinical examinations. When used as the first staging technique, it enables accurate evaluation of the tumor's volume and extension, which improves field planning for external pelvic radiation and brachytherapy.There was an indirect correlation between maternal anemia and neonatal birth weight in women with mild preeclampsia. B-Lynch suture is more effective than Nausicca suture in controlling excessive uterine bleeding and preventing emergency hysterectomy during caesarean section. There was a significant increase in sleeping issues, irritability, depressed mood, anxiety, and problems voiding mental and physical exhaustion in cases with metabolic syndrome. Metformin use in obese diabetic pregnant women improves maternal and neonatal outcomes. sublingual dose of Misoprostol (400 mcg) one hour before surgery significantly reduces the intraoperative blood loss and the operation time during myomectomy. Caesarean section scar in women after 6 weeks from primary CS assessed by using 2D-TVUS was not affected by the site of CS incision, surgeon's experience, visceral or parietal peritoneum closure and labor stage at the time of CS. Endometriosis is a common diagnosis in women with unexplained infertility and chronic pelvic pain. Laparoscopy should be indicated when diagnosis is suspected, together with tissue sampling and histopathologic examination. the first step in providing patients with scientifically based counselling is the creation of a nomogram of AFC values for assisted reproductive technologies and also for the natural conception chance and pregnancy outcome.

Best regards.

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Diagnostic Accuracy of MRI for Cervical Malignancy with Histopathologic Correlation

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Running title: MRI cervical malignancy

Abstract

Background and Aim: The determination of lymph node metastases, parametrial invasion, and pelvic side wall invasion—all known to be significant prognostic factors—as well as the precise measurement of tumor size present the greatest challenges in cervical cancer. The only gynaecological cancer that is currently primarily staged clinically, according to the FIGO classification, is cervical cancer. The aim of this work is to evaluate the role of MRI in the accurate staging of cancer cervix compared to clinical FIGO staging.

Methods: This prospective study included 21 patients (19 with primarily untreated pathologically proven cervical cancer who underwent pretreatment MRI and 2 post chemo-radiotherapy cases who underwent post-treatment MRI).

Results: This study found that 100% sensitivity and 100% specificity in detecting parametrial invasion contrasts with clinical staging's 20% sensitivity. Vaginal invasion may be detected with 100% sensitivity in both stage IIA and IIIA using MRI, which is very sensitive. A hyperintense vaginal thickening (tumor) or the mass itself next to the vaginal wall are the two most clear indicators of vaginal involvement on high-resolution T2-weighted sequences. These sequences also indicate the segmental discontinuity of the typical hypointense signal of the vaginal wall. Stage IIa is represented by vaginal invasion, and stage IIIa is represented when this invasion reaches the lower vaginal third.

Conclusions: Research has demonstrated that MRI is superior to clinical examinations. When used as the first staging technique, it enables accurate evaluation of the tumor's volume and extension, which improves field planning for external pelvic radiation and brachytherapy.

Key words: MRI; cervical cancer; histopathology.

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Introduction

Following ovarian and endometrial cancers in frequency, uterine cervical cancer is the third most frequent gynaecological malignancy. The majority of individuals with cervical cancer are discovered at an advanced stage and are therefore not candidates for surgical staging because nearly 80% of cases occur in developing nations (1).

Squamous cell carcinoma is the most prevalent kind histologically. Small cell carcinoma, adenoid-cystic carcinoma, and adenoid-basal carcinoma are some more forms that are mentioned (2)

The determination of lymph node metastases, parametrial invasion, and pelvic side wall invasion—all known to be significant prognostic factors—as well as the precise measurement of tumor size present the most difficult clinical examinations of individuals with cervical cancer. Cervical carcinoma is the only gynecological cancer that is now largely staged clinically, despite the inherent limitations of the clinical examination (3).

While preoperative MR imaging criteria are not formally included in the revised FIGO staging system, it is acknowledged that staging based on MR imaging findings has advantages and is encouraged when available. This is because cervical carcinoma is more common in developing countries where imaging resources are limited (4).

The local extent of the disease and the spread of extrauterine tumours can be precisely defined and depicted by MR imaging, it has been demonstrated. MR imaging can show metastatic dissemination, including peritoneal deposits, and can accurately depict the depth of myometrial and cervical stromal invasion. The most frequent way for extrauterine diseases to spread is through lymph nodes, and it is also the best indicator of a disease's propensity to return. (5) .

The purpose of MRI sequences is to identify changes in the thermally induced random (Brownian) mobility of water molecules within tissues. The amount of this motion, also known as diffusion, as determined by diffusion-weighted imaging is related to the average distance covered by water molecules during a given period of time. The amount of signal loss is inversely correlated with the water velocity (mean diffusional route length), with bulk water exhibiting the highest levels of signal loss. (6).

Aim of the work : Comparing clinical FIGO staging with MRI for the purpose of accurately staging cervical cancer

Materials and Methods

Patients' selection:

This prospective study included 21 patients (19 cases with primarily untreated pathologically proven cervical cancer who underwent pretreatment MRI and 2 post chemo-radiotherapy cases who underwent post-treatment MRI).

History and investigation:

All the patients were undergoing:

I. Careful history taking and examination:

II.Investigation:

*Chest x ray.

*US abdomen and pelvis

*CT abdomen and pelvis.

*Cystoscope.

*Biopsy.

*Radiographic evaluation of skeleton was used wherever needed.

Imaging: Using the typical pelvic surface array multichannel coil, an MRI examination was performed on the patients while they were lying flat.

Clinical staging :

Clinical staging was carried out on each patient by gynaecologists with at least five years of expertise using the prior FIGO

staging system, The MRI results were hidden from view by the gynaecologists

Histopathology assessment:

Radical hysterectomy was performed on nine individuals. The remaining patients had pelvic lymph node sampling with CT guidance, colposcopic vaginal biopsy, and laparoscopic staging. A pathologist examined each specimen they collected without consulting the MR pictures.

The histopathological stage was applied to individuals who

had surgical treatment (stage IIA). After connecting with MRI data and other investigations, the two gynecologists reached a consensus evaluation that became the gold standard for patients who did not have surgery. In this patient population, hydronephrosis was seen as conclusive evidence for stage III disease (ureteral involvement/pelvic sidewall invasion). Positive urine cytology test findings and cystoscopy results were accepted as evidence of stage IVA disease.

A team of radiation oncologists and gynecologic oncologists performed the staging workup of the post-radiotherapy cases and evaluated them with rectovaginal inspections while under general anaesthesia.

Each patient's FIGO stage and MRI-based stage were compared to the gold standard stage. patients whose MRI staging was performed correctly and incorrectly was counted, and the causes of incorrect staging were documented.

Statistical analysis: Data were checked, entered and analyzed by using SPSS version 20.

Results

The patient's age ranged from 23 to 80 years with the mean age 58.9±17.9. The most common presenting symptom of the studied group was offensive watery discharge. The final histopathological type of cervical cancer with squamous cell carcinoma (15 cases 78.4 % of the studied group) (table2).

The current study announcing 100% specificity and 100% sensitivity in the identification of parametric invasion in contrast to clinical staging, which only achieved 20% sensitivity.

MRI has 100% sensitivity in identifying vaginal invasion in both stage IIA and IIIA, making it a highly sensitive method. The characteristic hypointense signal of the vaginal wall is segmentally interrupted in high-resolution T2-weighted sequences, exhibiting a hyperintense thickening of the vagina (tumor) or the mass itself in close proximity to the vaginal wall, which helps to better understand the symptoms of vaginal involvement. When it reaches the bottom part of the vagina, it is in stage IIIa, and stage IIa for vaginal invasion, (table 4).

Table (1) shows the age, main presenting symptoms of the studied group.

Item	Average	Mean±SD
Age	25-78	17.9 ±58.9
Symptoms	**Number**	**%**
Post-menopausal bleeding	5	29.7
Offensive watery discharge	7	37.8
Abnormal vaginal bleeding	5	24.3
Pelvic pain and loin pain	2	2.7
Total	19	100

Table (2) shows the pathological types among the studied group.

Pathology	Number	%
Squamous cell carcinoma	15	78.4
Adenocarcinoma	4	21.6
Other rare types		0
Total	19	100

Table (3) shows the number of cases in each stage as detected by golden standard , MRI and clinical FIGO stage.

Stage	Number of cases in each stage by pathology	Number of cases in each stage by MRI	Number of cases in each stage on clinical
IB1	1	1	1
IB2	2	3	2
IIA	1	1	9
IIB	10	10	2
IIIA	1	1	1
IIIB	1	1	2
IVA	1	1	1
IVB	2	1	1
Total	19	19	19

Table (4) shows the validity of MRI in detection of cervical tumor extension.

Stage	Sensitivity	Specificity	PPV	NPV
IB1(limited to the cervix)	100 %	100 %	100 %	100 %
IB2(limited to the cervix)	100 %	96.1%	83.11%	100 %
IIA(upper 2/3 of vagina)	100 %	100 %	100 %	100 %
IIB (parametrium)	100 %	100 %	100 %	100 %
IIIA(lower 1/3 vagina)	100 %	97.13%	50.22%	100 %
IIIB (pelvic side wall)	100 %	100 %	100 %	100 %
IVA (UB invasion)	66.12%	100 %	100 %	94.01%
IVB (Distant metastsis)	50.13%	100 %	100 %	97.01%

Discussion

According to Corinne et al., (1) similar findings were seen in our most recent analysis, where most of our patients (76%) were past stage IIA, the critical threshold for surgical interference.)

According to a study by Nilu et eighty percent of instances of cervical cancer are found in underdeveloped countries, and most individuals are diagnosed at an advanced stage, which precludes them from being surgically staged. al., the researched group had a mean age of 46 years and 51 years, respectively, with typical ages ranging from 28 to 65 years and 21 to 80 years. Comparable information was discovered in the current investigation; the group under analysis had an average age of 58 years, with a range of 23 to 80 years. (3)

Mohammed et al. found that irregular bleeding was the most presenting symptom, accounting for a total percentage of 86.6 percent, but in the current investigation, the

foul watery discharge, accounting for 14.9% of cases among 14 patients. With 29 instances (78.4%) of cervical cancer being squamous cell carcinoma, adenocarcinoma accounted for 8 cases (21.6%) of cervical carcinoma, making it the most common histological type. (7) The incidence was almost in line with the findings of the Nilu et al (2020) research, which showed that 68/75 patients, or 90.7% of the patients, had squamous cell carcinoma and 9.3% had adenocarcinoma. (3)

According to Harpreet et al. (2019), 80–90% of cervical carcinomas originate from squamous cells. (8)

Our study's findings show that the staging abilities of clinical FIGO staging, and MRI differ significantly. This implies that the addition of MR may improve the staging's accuracy and alter the course of treatment.

In a study of 37 patients, we examined the validity of MRI as a tool, comprehensive method for assigning patients with cervical carcinoma to the proper course of management. accuracy of MRI 94.5 %, was while clinical FIGO staging had an accuracy rate of 51.3% (19/37), meaning that it was inaccurate in 5.4% of cases.

According to Nilu et al. (2020), 1.5T MRI data were used in 67 instances. 89.3% (67/75) of cervical cancer cases were successfully staged by MRI, compared to 61.3% (46/75) of cases by clinical FIGO staging, according to Nilu et al. (2020). The overall staging accuracy of MRI, according to Evis et al. (2018), staging accuracy in MRI varies from 75% to 96%. (3,9)

In line with Yoshikazu et al. (2017) findings that cervical malignancies, regardless of histopathologic type, show as hyperintense masses on T2-weighted images, cervical cancer was diagnosed in our study as a mass of intermediate to hyperintense on T2W(10).

According to a study by Tejinder et al. (2015), when compared to the results of the FIGO clinical stage, MRI can more accurately define the size, location, and extension of cervical tumors into neighboring structures due to its superior soft tissue characterization and multiplanar scanning capabilities. (11) According to Evis et al. (2018). The most difficult clinical evaluations of individuals with cervical cancer involve assessing the invasion of the pelvic sidewall and parametrium. In 48% of the instances (18 out of 37), the present study's FIGO clinical criteria were found to be inaccurate; most of these cases missed the parametrial invasion and underestimated the patient's risk (9)

Comparing the current study's 100% sensitivity and 100% specificity in detecting parametric invasion to clinical staging's 20% sensitivity

The identification of vaginal invasion by MRI is quite sensitive, demonstrating 100% sensitivity in both stage IIA and IIIA. the segmental interruption of the vaginal wall's typical hypointense signal, as well as a hyperintense thickening of the vagina (tumor), or proximity to the vaginal wall. Stage IIa of a vaginal invasion is stage IIa, while stage IIIa of a vaginal invasion is stage IIIa. According to Claudia et al. (2019), MRI has a 93% percentage sensitivity in vaginal invasion diagnosis. (12)

The research conducted by Mohamed et al. (2020) found 100% sensitivity and 100% specificity of UB invasion, while Claudia et al. indicated that MRI has proven to be a reliable approach for detecting bladder invasion with 83% sensitivity and specificity close to 100%. With 100% specificity, our study only had 66% sensitivity (7))

Nodal disease, which is not part of the FIGO staging system, has a significant impact on survival, and the presence of metastatic nodes suggests a worse prognosis within each stage.

According to Choi et al (2013), surgical experience from pelvic lymphadenectomy has verified an error rate due to hidden pelvic lymph nodes, and further metastases

may be discovered in the para-aortic nodes. Unfortunately, FIGO's clinical staging and pelvic investigations cannot identify such conditions. (13)

With 10 mm being the generally Accuracy of MRI in diagnosing pelvic node metastases from uterine cervical cancer was quite high in the current investigation, with an agreed upper limit for the short axis of normal pelvic nodes. Based on our research, 12/12, or 100%, of LN with metastatic evidence that was pathologically verified had a short axis diameter of greater than 10 mm. Not all scientists disagree with our findings Choi et al(2013), Mohammed et al,(2020) Claudia et al (2012) and Nilu et al(2020) .(3,7,12,13)

The current investigation found that the FIGO staging criteria had low sensitivity for assessing lymph node metastases as well as parametrial and pelvic sidewall invasion.

Lastly, we concur that FIGO staging could not accurately reflect the appropriate degree of sickness and, hence, cannot provide prognostic information about the disease's prognosis. This is in line with Tejinder et al. (2015), Evis et al. (2018), and Nilu et al. (2020) (3,9,11).

Conclusion

Although MRI is not commonly used by oncology services for staging cervical malignancies and has not yet received official FIGO approval, it is crucial to the therapy planning process and follow-up.

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Effect of maternal anemia on perinatal outcomes in mothers with mild preeclampsia. A cross-sectional study

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Abstract

Background: One of the most common nutritional deficiencies that pregnant women have is anemia. Both the mother and the fetus' lives are in danger from anemia. There is ongoing debate over how much maternal anemia affects both maternal and newborn health. Preeclampsia is also linked to a constriction of the plasma volume, with evidence of diminished plasma volumes both throughout pregnancy and after delivery.

Objectives: Studying the impact of maternal anemia during the third trimester on birth weight at delivery in a sample of infants whose mothers had mild preeclampsia is the goal of the study.

Methodology: All patients were subjected to careful history-taking through clinical examination and laboratory investigations, including CBC, liver functions, and renal functions. Apgar score and birth weight were recorded for the studied neonates.

Results: A comparison between patients with normal and low Hb levels showed that neonates of mothers with normal Hb levels had significantly higher birth weight when compared with those with low Hb levels.

Conclusion: There was an indirect correlation between maternal anemia and neonatal birth weight in women with mild preeclampsia.

Key words: Maternal anemia, neonatal birth weight, preeclampsia.

Introduction

In both developed and developing countries, preeclampsia is common. According to the World Health Organization, high blood pressure during pregnancy accounts for 16% of maternal deaths in developed nations and up to 25% in underdeveloped nations [1].

Preeclampsia is a placental syndrome that manifests clinically late in pregnancy and causes maternal hypertension, proteinuria, and occasionally malfunction of the liver and central nervous system [2].

Preeclampsia is the main factor in intrauterine growth

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restriction, miscarriages, and stillbirths, as well as maternal and neonatal morbidity and mortality [3].

Moderate-to-severe maternal anemia has been identified as a factor in poor maternal and perinatal outcomes. Given that there was a substantial chance of low birth weight [4],.

Accordingly, the inverse relationship between maternal hemoglobin concentration and newborn size is most likely caused by a reduction in plasma volume. Preeclampsia is associated with maternal hemoconcentration, which is often attributed to decreased plasma volume expansion and is also an identified risk factor for poor perinatal outcomes due to plasma volume constriction [5].

So an evaluation of the relationship between maternal anemia and fetal birth weight in cases of preeclampsia may be needed.

Patients and methods

The present study is a cross-sectional case-control study. It was conducted at the Obstetrics and Gynecology Department, Faculty of Medicine, Suez University, on 200 patients with mild preeclampsia. The presence of proteinuria > 300 mg during 24 hours of collection without end-organ damage, as well as hypertension (blood pressures of > 140/90 mm Hg and less than 160/110 mm Hg) on 2 different occasions at least 6 hours apart, were both considered to be indicators of mild preeclampsia [6].

Before involving the patients in the trial, their signed informed consent was obtained. The study's participants were split into two groups according to their hemoglobin level prior to delivery within 48 hours; group A included 100 patients whose hemoglobin level was within normal. WHO defines a normal hemoglobin level as a level above 11.0 g/dl [7]. Group B included 100 patients whose hemoglobin level was lower than normal.

Exclusion criteria included patients with HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), gestational diabetes, cyanotic heart disease, chronic hypertension, chronic renal disease, asthmatic patients, severe malnutrition cases, low maternal age patients, patients with blood diseases, cases with severe preeclampsia, smoker patients, twin pregnancies, and cases that needed blood transfusion.

Methods

A detailed history was taken from the patients, including personal information such as name, age, special habits, occupation, and address. Menstrual history was taken, including the first day of the last menstrual period and the estimated gestational age by date. Obstetric history included parity, gravidity, and symptoms of preeclampsia. Her medical history included diabetes mellitus, hypertension, blood diseases, drug intake, and whether she used iron supplements or not. Family history included diabetes mellitus, hypertension, and congenital anomalies. A general examination included measurements of blood pressure, pulse, and temperature; the presence of pallor or jaundice; and the presence of petichae or ecchymosis of the skin to exclude the presence of coagulation defects or blood diseases. Abdominal examination to detect the size of the uterus, scars from previous operations, and edema. Investigations done on mothers included a complete blood picture within 48 hours prior to delivery, prothrombin time, partial thromboplastin time, random blood glucose, urine analysis, and liver and renal function tests. Doppler ultrasound was performed to exclude placental insufficiency as a cause of LBW. The following was done to the newborn as an assessment of gestational age at delivery, birth weight at delivery, and Apgar score.

Ethical considerations

The investigator kept a list of sub-

investigators and other suitably competent individuals to whom substantial trial-related activities were assigned and made sure that everyone helping with the trial was properly informed about the protocol and the trial-related duties.

Patient information and informed consent

Before being admitted to the clinical trial, the patients were informed about the nature, scope, and possible consequences of the clinical trial in a way that was understandable to them.

Confidentiality

In the case report form, the patients' numbers and initials were the only information entered. The investigators maintained patient privacy whenever the patient's name appeared on any other document (such as a pathology report or reservation note). In order to identify records and facilitate communication with patients, the investigator initially retained the patients' identifying information, including their numbers, names, and contact details.

Protocol approval

The protocol and all related documents were declared for ethical and research approval by the ethical committee, Faculty of Medicine, Suez University.

Statistical analysis

Using the Statistical Package for Social Science (BM Corp., 2011), the gathered data was updated, coded, tabulated, and brought onto a PC. Armonk, NY: BM Corp., BM SPSS Statistics for Windows, Version 20.0. Data were shown, and appropriate analysis was carried out based on the kind of data found for each parameter.

Results

In the present study, comparisons between mothers with normal and low hemoglobin levels regarding maternal characteristics showed no significant differences between women with normal and low Hb regarding maternal age and BMI (Table I).

Also, there were no statistically significant differences between patients with normal and low Hb regarding preeclampsia features, including systolic and diastolic blood pressure (Table II).

In addition, there were no significant differences between patients with normal and low Hb regarding WBCs, platelets, glucose, bilirubin, PT, and creatinine levels (Table III).

In the present study, comparisons between patients with normal and low Hb levels showed that neonates of mothers with normal Hb levels had significantly higher birth weight when compared with those with low Hb levels (Table IV).

However, no statistically significant differences were found between both groups regarding gestational age and Apgar score. Importantly, there was a direct correlation between maternal hemoglobin and neonatal weight in women with mild preeclampsia (Table V).

Discussion

Anaemia during pregnancy affects over half of all pregnant women worldwide, and this is a severe global health concern. Iron deficiency is the most common cause of anemia during pregnancy; deficits in other micronutrients are less common [8].

Anaemia is one of the most prevalent dietary deficiencies affecting expecting moms. The two criteria used to determine anemia are hemoglobin levels falling below 11 gm% and hematocrit levels falling below what is thought to be typical for a certain individual [9].

There is an antagonistic link between anemia and unfavorable birth outcomes. Low birth weight and premature delivery are significantly increased by anemia; nevertheless, other contentious research could not find any correlations [10].

Other research indicates that there isn't a link between low pregnancy outcomes and maternal anemia [11].

A number of investigations that shown a higher frequency of low birth weight in conjunction with a high level of hemoglobin in the mother attest to the importance of suitable expansion of the plasma volume in enabling the best possible growth of the fetus [12].

A U-shaped curve connection between maternal haemoglobin concentrations and pregnant trimesters was seen in most studies. Therefore, pregnant women with moderate-to-severe anemia had an approximately twofold risk of low birth weight babies during the first and second trimesters; the association was the opposite during the third trimester [13].

When comparing the maternal characteristics of mothers with normal and low hemoglobin levels, the current study did not find any statistically significant differences in either maternal age or BMI.

This is in line with the findings of Bencaiova et al. (2012), who support the prevalence of anemia and low iron stores in expectant mothers as well as their analysis of the relationships between risk factors such as age, parity, body mass index (BMI), sociodemographic background, and abnormal iron status or hemoglobin levels. This study [14] demonstrated that moms over the age of thirty were the only ones who were at risk for developing anemia.

Neonatals of mothers with normal hemoglobin levels had significantly larger birth weights than those of mothers with low hemoglobin levels, according to the current study's comparison of patients with normal and low hemoglobin levels. The correlation study, which demonstrated a direct relationship between mother hemoglobin and newborn birth weight, further supported these findings. This is consistent with a research by Bodeau-Livinec et al. (2011), which discovered a link between lower birth weight and maternal anemia [15].

However, Amburgey et al. (2009) sought to determine whether birth weight would show an inverse relationship to hemoglobin concentration in a group of infants whose mothers had preeclampsia, a condition in which plasma volume constriction is common. After reviewing both paper and computerized charts, 142 nulliparous women with preeclampsia were found (low platelets syndrome, increased liver enzymes, and hemolysis were excluded). To determine the birth weight percentile, cross-sectional hybrid growth curves were utilized. Measurements were made of the mother's hemoglobin level during the third trimester. The average gestational age at delivery was 35.9 +/- 1.9 weeks. The mean hemoglobin z-scores of mothers with preeclampsia were significantly greater than those of the control group. Maternal hemoglobin levels and birth weight had a negative correlation. The scientists came to the conclusion that there is a statistically significant inverse relationship between the percentile of birth weight and the mother's hemoglobin concentration [16].

The discrepancy between the results of our investigation and the prior study could be attributed to the diverse characteristics of the individuals analyzed; in contrast to the anemia observed in our study, the majority of patients in the previous study showed hemoconcentration. This is explained by the fact that the patients in our study had moderate preeclampsia.

Conclusion

Mothers with mild preeclampsia and normal Hb levels had significantly higher birth weight when compared with those with mild preeclampsia and low Hb levels.

Conflict of interest

None

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Table I: Comparison between mothers with normal and low hemoglobin levels regarding the demographic characteristics

	Normal Hb (n=100)	Low Hb (n=100)	Student T test	
			t	p
Age (years)	23.3 ± 2.4	23.9 ± 2.9	-1.18	0.24
BMI (Kg/m²)	28.3 ± 1.8	27.9 ± 1.5	1.32	0.18

Table II: Comparison between mothers with normal and low hemoglobin levels regarding preeclampsia features

	Normal Hb (n=100)	Low Hb (n=100)	Student T test	
			t	p
SBP (mm Hg)	149.4 ± 6.0	150.5 ± 6.7	-0.87	0.38
DBP(mm Hg)	95.3 ± 3.2	95.0 ± 2.9	0.61	0.53

Table III: Comparison between mothers with normal and low hemoglobin levels regarding the other laboratory findings

	Normal Hb (n=100)	Low Hb (n=100)	Student T test	
			t	p
WBCs (×103/ml)	8.35 ± 1.7	8.53 ± 1.68	-0.52	0.6
Platelets (×103/ml)	304.8 ± 66.4	318.3 ± 59.7	-1.07	0.28
Random bl. Glucose (mg/dl)	154.8 ± 9.0	153.0 ± 10.1	0.94	0.34
Total Bilirubin (mg/dl)	0.8 ± 0.17	0.81 ± 0.23	-0.28	0.77
PT (sec.)	13.1 ± 0.9	13.0 ± 0.8	0.7	0.48
Creatinine (mg/dl)	0.86 ± 0.18	0.82 ± 0.17	1.22	0.22

Table IV: Comparison between mothers with normal and low hemoglobin levels regarding the neonatal parameters

	Normal Hb (n=100)	Low Hb (n=100)	Student T test	
			t	p
Gestational age (wks)	37.9 ± 1.43	38.2 ± 1.34	-1.07	0.28
Neonatal weight (gm)	3100 ± 220	2900 ± 220	-4.48	0.04*
Apgar score	8.1 ± 1.5	8.0 ± 1.5	0.26	0.79

Table V: Correlation between maternal hemoglobin level and the neonatal parameters

	Hb	
	R	P
Gestational age	-0.11	0.26
Neonatal weight	0.86	*0.04
Apgar score	0.048	0.63

Efficacy of Different Uterine Compression Sutures in Controlling Excessive Uterine Bleeding during Caesarean Section

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Abstract

Introduction : Obstetric hemorrhage remains the leading cause of maternal mortality in both developed and developing countries. Postpartum hemorrhage is blood loss more than 500 ml in vaginal delivery and more than 1000 ml within 24 h in cesarean section. The objective of this study is to compare the safety and efficacy of Nausicaa and B-Lynch compressive sutures to control excessive uterine bleeding during cesarean section.

Methods: The study included 60 women suffering from excessive uterine bleeding during cesarean section in Ain Shams University Maternity Hospital, a tertiary referral center in Cairo, Egypt with annual rate of seven thousand cesarean sections per year Participants were randomly assigned to Nausicaa suture and B-Lynch suture done. The primary outcome was emergency hysterectomy.

Results : Nausicaa suture achieved hemostasis and prevented hysterectomy in 80% of allocated patients compared to 96.7% in B-Lynch suture. B-Lynch suture required shorter procedure time (7.2 ±3.3 vs16.1 ±4.9, 95% CI 6.8-11.2, p<0.001) compared to Nausicaa suture, with less blood loss in B Lynch suture (1473.3±429.9 ml vs1886.7±620.2 ml, 95% CI (6.8–11.1, p<0.001) compared to Nausicaa suture.

Conclusion: B-Lynch suture is more effective than Nausicca suture in controlling excessive uterine bleeding and preventing emergency hysterectomy during cesarean section.

Keywords: B-Lynch –Nausicaa suture –excessive uterine bleeding.

Introduction

Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality in both developed and developing countries 1. Postpartum hemorrhage is blood loss more than 500 ml in vaginal delivery and more than 1000 ml within 24 h cesarean section 2. First-line treatment for PPH consists of conservative management with the use of uterotonic agents, bimanual uterine massage and early

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replacement of blood 3. If conservative management fails, second-line therapy is available including intrauterine balloon tamponades, uterine compression sutures and ligation of the uterine artery/internal iliac artery, If all of the previous mentioned uterine preserving managements fail, then a hysterectomy should be done 4.

Many attempts are tried to introduce surgical conservative compressive sutures to avoid hysterectomy 5. Many compressive suture techniques were introduced as B-Lynch, Hayman, multiple square sutures and Nausicaa 6,7. Further studies are needed to compare efficacy of different compressive sutures 8.

The study objective is to compare the efficacy of Nausicaa versus B-Lynch compressive sutures to control excessive uterine bleeding during cesarean section, and avoiding life -saving hysterectomy.

Materials and Methods

The study included sixty women suffering from excessive bleeding during cesarean section after failed medical management and uterine massage and according to eligibility criteria.

The study was conducted between March 2022 through October 2022 Ain Shams University Maternity Hospitals, Cairo, Egypt.

The study was approved by Medical Ethics Committee of Obstetrics and Gynecology Department at Ain Shams University (FMASU MD 250 on 25 /8/ 2019) to ensure following the standard ethical principles governing research involving human subjects.

Eligibility Criteria

Patients thought to be at potential risk of excessive bleeding during cesarean section, as mentioned above, were approached preoperatively. The study was explained to patients for possible inclusion if excessive bleeding occurs and female patients willing to participate were asked to sign a written informed consent. Trans test and well training of the surgeons to master the technique of Nausicaa suture was done.

Inclusion criteria

Women suffering from excessive uterine bleeding during cesarean section despite uterine massage and medical interventions.

Exclusion criteria

Cases of severe hemodynamic instability needing immediate hysterectomy, Placenta accreta spectrum, patients with coagulopathy, receiving anticoagulant therapy, cases with thrombocytopenia or thrombasthenia, distorted uterus as unicornuate, bicornuate, fibroid uterus and adenomyosis uteri.

According to RCOG green top guidelines in prevention and management of postpartum hemorrhage 5 baseline full blood count, blood group, ultrasound and cross matching four units of packed red blood cells, fresh frozen plasma and platelets were prepared for potentially eligible patients. Patients were transferred to operative room, put in flat position, anesthetized and foley catheter to monitor urine output was inserted. Standard protocol of cesarean section was performed with transverse lower uterine segment incision.

Once excessive uterine bleeding was encountered during cesarean, continuous monitoring of vital data, intravenous fluid infusion of 500 cc saline, uterine massage, administration of uterotonics (5 iu oxytocin slowly intravenous, 40 IU oxytocin (syntocinon® Novartis, Egypt) on 500 cc saline at 125ml/hr, 0.5 mg Ergometrine (Methergin® Novartis, Egypt) intramuscular injection were administered unless contraindicated, until bleeding was controlled and misoprotol (Misotac® Sigma, Egypt) 800 µgm rectally.

Those cases, in whom the above mentioned

measures failed to control the bleeding, were included into either intervention groups.

Randomization & Allocation concealment

Randomization was done using computer generated random sequence. Allocation concealment was performed using sixty opaque envelopes that were numbered serially, each denoted the allocated group, according to randomization table. When the first patient was included, the first envelope was opened and the patient was allocated according to the letter inside and so on for the rest of the study population.

Blinding

Patients, outcome assessors, data analysts were blinded to group allocation. The surgeon was not due to the nature of the procedure.

Intervention Groups

Group (A) women allocated to this group had Nausicaa uterine compression suture done.

Group (B) women allocated to this group had B-Lynch uterine compression suture done.

Nausicaa suture was applied by using round bodied, 3/8 circle curved needle, 70mm with 2-metric polyglactan suture (Vicryl®,Ethicon, USA). The needle was inserted as lateral as possible from the uterine serosa to inside the uterine cavity. The needle was then threaded along horizontally inside the uterine cavity and emerged at the other side of the uterine serosa. The sutures penetrated the full thickness of the myometrium without suturing the anterior and posterior walls together. A flat surgical knot was then tied well. To achieve a better hemostatic effect, the assistant often needed to clench the sutured myometrium while the surgeon tied off the knots. Additional sutures were made 1.5-2 cm parallel to the previous sutures until bleeding stopped 7. (Figure1).

The technique of this type uterine compressive suture was first described by Shih et al., 7.

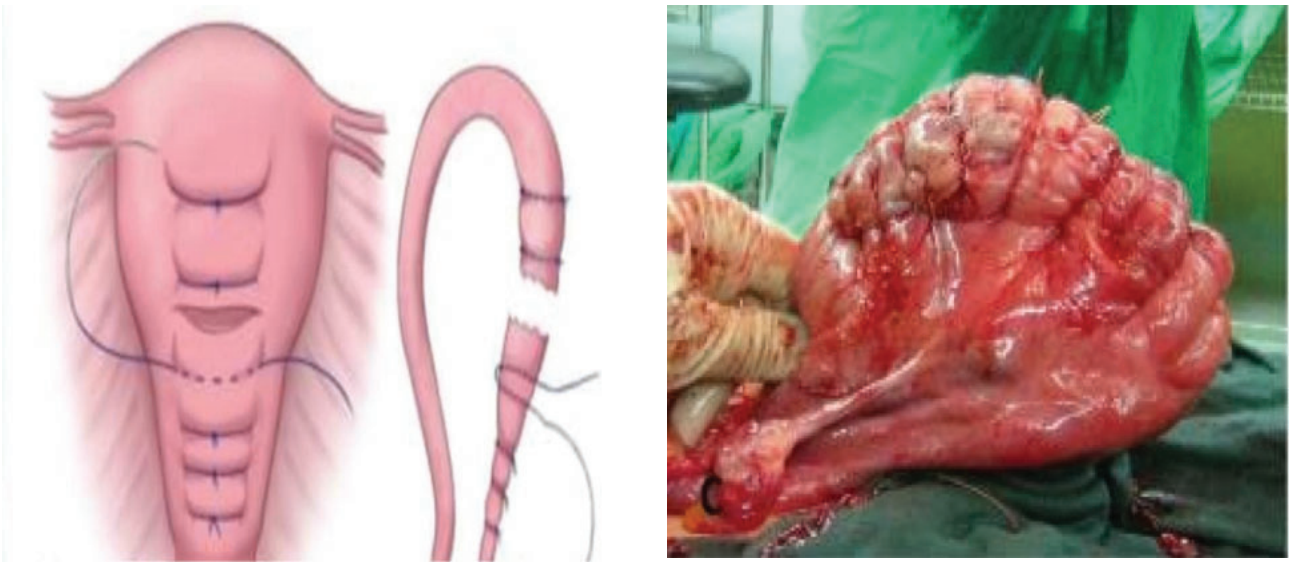

Fig.1 Nausicaa suture figure by Shih et al., [7].

B-Lynch suture was applied by using round bodied, 3/8 circle curved needle, 70mm with 2-metric polyglactan suture (Vicryl®, Ethicon, USA) by starting in the uterus 3 cm from the right lower edge of the uterine incision and 3 cm from the right lateral border, then passing through the uterine cavity to emerge at the upper incision margin, 3 cm above and approximately 4 cm from the lateral border. It was passed over to compress the uterine fundus, then the suture was passed posteriorly and vertically to enter the posterior wall of the uterine cavity at the same level as the upper anterior entry

point. It was pulled under moderate tension assisted by manual compression exerted by the first assistant. The surgeon passed the suture through posteriorly and vertically over the fundus to lie anteriorly and vertically compressing the fundus on the left side as occurred on the right. The needle passed in the same manner on the left side through the uterine cavity and out approximately 3 cm anteriorly and below the lower incision margin on the left side. The suture was tight, assisted by bi-manual compression to minimize trauma and to achieve hemostasis, and then, surgical knot was made 9. (Figure 2).

This procedure followed the steps described by Matsubara et al., 6

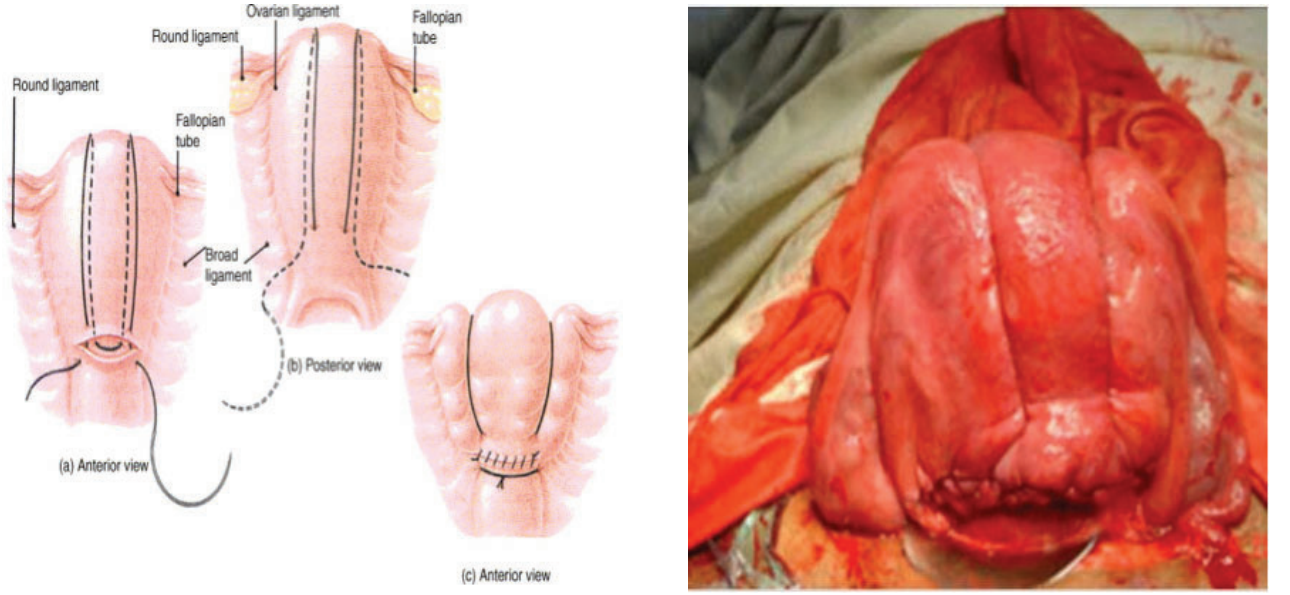

Fig. 2 B-Lynch suture figure by Matsubara et al., [6].

If either uterine compressive sutures techniques failed to control bleeding, 3rd line procedures were then attempted (systemic pelvic devascularization), then emergency life- saving hysterectomy was done.

All surgical procedures were done by the same team led by a senior obstetrician, with a wide expertise in performing complicated cesarean sections and surgical management of excessive bleeding during cesarean section and emergency hysterectomy.

In postoperative care, the patients were transferred to ICU or postpartum observation room with assessment of vital data every 15 minutes, postoperative hemoglobin, hematocrit level at 6 hours, day 1 and day 3 samples withdrawn 10, uterine contractility, urine output, vaginal bleeding were monitored.

The primary outcome was the need for emergency hysterectomy. The secondary outcomes were the amount of blood loss assessed by number of soaked towels and suction titration), peripartum hemoglobin level drop (%) 6 hours post delivery and hematocrit value change (%), total blood loss (amount of blood loss included in soaked towels 'fill soacked 150 ml, half soacked 100ml' and suction titration number of received blood components (packed RBCs-fresh frozen plasma and platelets), procedure time (minutes),need for devascularisation, ICU admission, venous thromboembolism (6weeks after delivery), postoperative fever (1week after delivery), hospital stay, number and cost of suture material used.

Statistical methods

Sample size justification

This is a pilot study, no previous published trials were retrieved from which power

calculation could be performed.

Arbitrary number of 60 cases will be included (30 cases in each group).

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Quantitative normally distributed data described as mean±SD (standard deviation) after testing for normality using Shapiro-Wilk test, then compared using independent t-test if normally distributed and Mann Whitney test if not normally distributed. Qualitative data described as number and percentage and compared using Chi square test and Fisher's Exact test for variables with small expected numbers. Logistic regression was used to find out factors affecting stress, depression and anxiety. The level of significance was taken at P value < 0.050 was significant, otherwise was non-significant

Results

The clinical characteristics of the patients

A total of 60 women were recruited in the current study, over the designated study

period, according to the shown participant flowchart (Figure3).

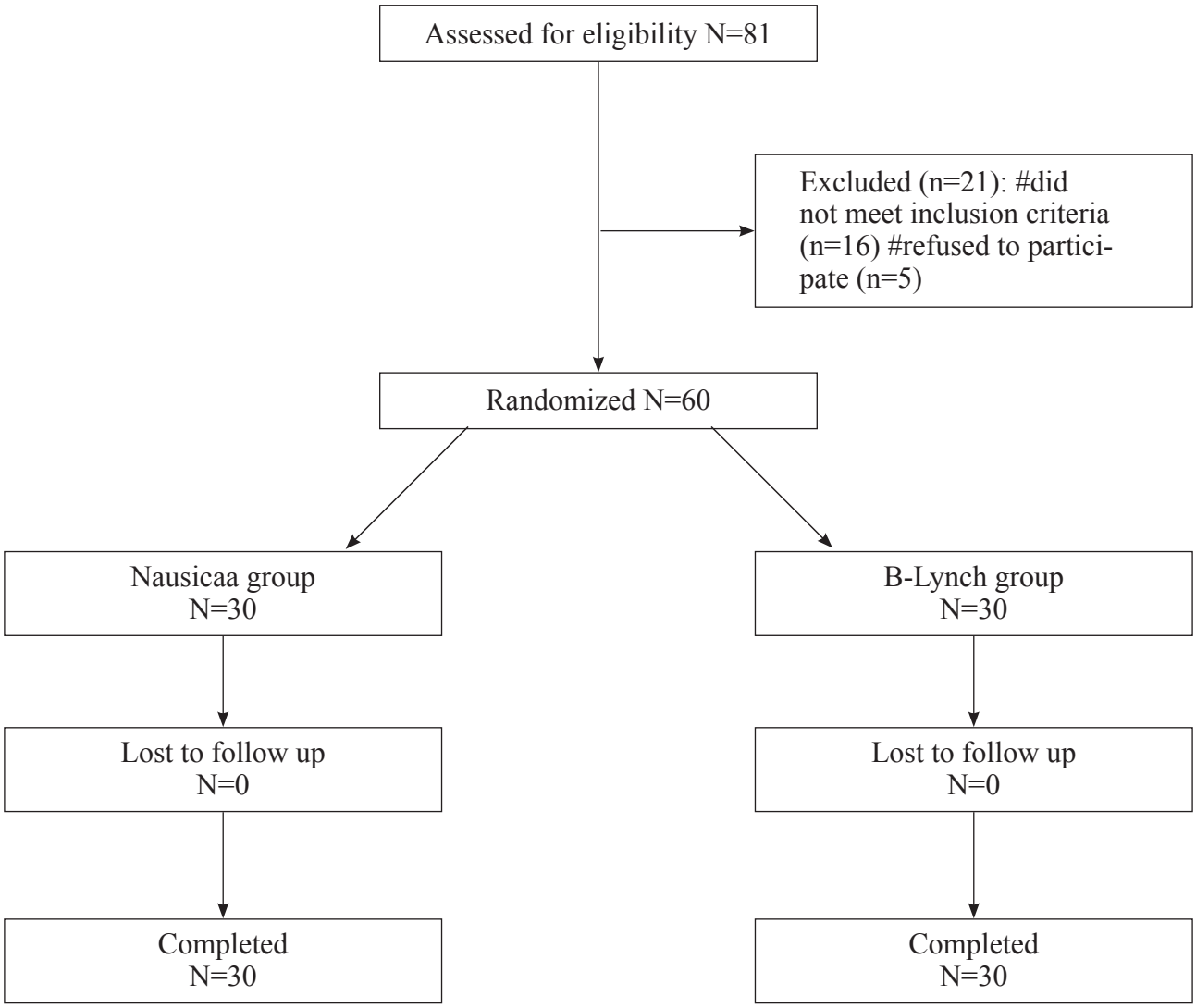

Fig.3 Participant flowchart

Women in both groups were not different regarding their demographic and baseline characteristics as shown in Table (1).

Table (1): Baseline characteristics of the studied groups.

Variables		Nausicaa (N=30)	B-Lynch (N=30)	P-value
Age (years)	**Mean±SD**	26.3±3.7	27.0±3.6	0.500
	Range	21.0–34.0	21.0–34.0	
BMI (kg/m^2)	**Mean±SD**	26.8±1.7	27.9±2.9	0.467
	Range	23.7–38.2	24.5–35.8	
Parity	**Median**	2.0 (1.0–2.0)	2.0 (1.0–3.0)	0.735
	Range	0.0–5.0	0.0–4.0	
Previous CS	**Median**	1.0 (1.0-2.0)	1.0 (0.0-2.0)	0.836
	Rauge	0.0-5.0	0.0-3.0	
GA (weeks)	**Mean±SD**	38.6±1.1	38.2±1.4	0.266
	Range	35.0–40.0	35.0–40.0	
Comorbidities	**DM**	4 (13.3%)	3 (10.0%)	0.999
	GDM	3 (10.05)	2 (6.7%)	0.999
	HTN	4 (13.3%)	4 (13.3%)	0.999
	PIHTN	4 (13.3%)	4 (13.3%)	0.999
Blood group	**A**	23 (76.7%)	23 (76.7%)	0.999
	B	6 (20.0%)	5 (16.7%)	
	AB	1 (3.3%)	2 (6.7%)	
RH	**Positive**	24 (80.0%)	7 (23.3%)	0.999
	Negative	6 (20.0%)	23 (76.7%)	

*DM:Diabetes mellitus *GA:Gestational age. *HTN:Hypertension. PIHTN: Pregnancy induced hypertension.

Study Outcomes

Procedure time and Number of suture material

Both groups used one suture ampoule of suture material. The procedure time for Nausicaa suture ranged from 5 to 22 minutes (mean16.1±4.9), while the procedure time in B-Lynch suture ranged from 4-20minutes(mean7.2±3.3) (95%CI 6.8-11, p-value <0.001).This was statistically significant. It is noteworthy that prior to the formal recruitment of the study cases, the team conducting the study trained on the Nausicaa suture being a relatively new procedure. The formal enrollment of cases in the study was started after the team felt confident they mastered the maneuver and were capable of performing it within reasonable time.

Efficacy of interventions in controlling bleeding

As the primary outcome of the study, the success rate Nausicaa suture to achieve hemostasis and prevent hysterectomy was 80%, compared to 96.7% in B-Lynch suture (RR 5.99, 95%CI -27.4%−99.2%, p- value 0.103).This was statistically non -significant.

Although, there is an obvious difference in number, statistical significance was not reached. This is due to the fact this is a pilot study, where no previous data were available to adequately calculate the sample size to achieve power regarding this outcome.

However, there was a significant difference between both groups regarding the need for devascularisation, in the form of uterine

and internal illiac artery ligation, which was done in 11 cases in Nausicca group(36.7%) compared to 4 cases in B-Lynch group (13.5%) (RR 2.75, 95%; CI -7.9%-89.6%. p-value 0.037).

Intraoperative Blood loss and the need for transfusion

The baseline hemoglobin was not different between both groups (11.3 ±0,4 gm/dl for both group A and B). However, there was a statistically significant difference in the postoperative hemoglobin measured 6 hours postoperatively (8.9 gm/dl ±1.0 for group A versus 0.4 g/dl ± 0.7 for group B, p=0.034).

Furthermore, the hemoglobin drop was more pronounced for group A (2.5 gm/dl ± 0.8) compared to group B (1.9 gm/dl ±0.6). This difference reached statistical significance (p=0.004).Similar findings were also observed for the hematocrit values. Intraoperative blood loss was significantly higher among Nausicaa group than among B-Lynch group.

Blood loss ranged from 1000-3800ml in Nausicaa suture and ranged from 800-2500 ml in B-Lynch suture (95% CI 137.6-689.1, p-value<0.001).

This was reflected on the need for blood transfusion. Fourteen cases (46.7%) of group A needed transfusion of blood products while six cases (6%) needed such transfusion in group B. This was statistically different (RR 2.33, 95%CI -1.6-83.7, p-value 0.028).

Regarding ICU admission, four cases (13.3%) required ICU admission in Nausicca suture group, while one case (3.3%) required ICU admission in B-Lynch group (RR 4, 95%; CI-122.9-98.9%). No cases of venous thromboembolism in both groups were encountered over a six week postpartum follow up period.Longer days of hospital stay was needed for Nausicaa group compared to B-Lynch group (Mean3.2 versus 2.2,95%; CI 0.4-1.5, p-value 0.001). However, there was no significant difference in both groups regarding postoperative fever (3 patients 10% in group A, versus 2 patients 6.7% in group B) (RR 1.5, 95%CI -370.7-92%, p-value 0.999) (Table2).

Table (1): Study Outcomes

Outcome	Nausicaa group	B-Lynch group	95% CI	P-value
Procedure time	mean16.1±4.9	mean7.2±3.3	6.8–11.1	<0.001
Hysterectomy	6 (20.0%)	1 (3.3%)	-27.4%−99.2(RR5.99)	0.103
Devascularisation	11(36.7%)	4 (13.5%)	-7.9%-89.6(RR2.75)	0.037
Blood loss	1000-3800	800-2500	137.6-689.1	<0.001
Hemoglobin drop	1.3–5.2	1.0–3.4	0.2–0.9	0.004
Hematocrit drop	3.8–15.2	2.9–10.0	0.5–2.7	0.005*
Blood transfusion	14 (46.7%)	6(6%)	-1.6-83.7(RR2.33)	0.028
ICU admission	4(13.3%)	1(3.3%)	-122.9-98.9(RR4)	0.353
Hospital Stay	Mean3.2	Mean2.2	0.4-1.5	0.001
Postoperative fever	3(10%)	2(6.7%)	-370.7-92	0.999

Discussion

Obstetric hemorrhage remains the leading cause of maternal mortality worldwide 11. Most cases of excessive bleeding during cesarean section are controlled by conservative measures as uterotonics and uterine massage 12.

If excessive bleeding during cesarean section is still encountered, uterine compressive sutures with or without devascularization are done. However, if there is still ongoing bleeding the last resort will be life-saving cesarean hysterectomy 13.

The B-Lynch uterine compressive suture to control excessive uterine bleeding was first described by Christopher B-Lynch in 1997 and after that B-Lynch compressive suture became a popular surgical technique to control excessive uterine bleeding 14. A new compressive suture termed Nausicaa suture was first described by Shih et al. 7. who reported its efficacy in controlling postpartum hemorrhage. Few studies compared this type of uterine compressive suture to the other types. The current study was performed to compare Nausicaa suture and B-Lynch suture in their efficacy in controlling excessive bleeding during cesarean section.

Those women were randomized into one of 2 groups: Group (A) had Nausicaa suture applied while group (B) had B-Lynch suture applied.

To the best of our knowledge, there are no published studies comparing Nausicaa vs B-Lynch in controlling excessive bleeding during cesarean section. The available publishes studies mainly address B-Lynch suture and there is relative paucity of trials involving Nausicaa suture.

The study was performed in Ain Shams University Maternity Hospital during the period from March 2022 to October 2022.The study included sixty women who suffered from excessive uterine bleeding during cesarean section, not responding to uterine massage or maximum dose of ecbolics.

In the current study there was no significant difference regarding age, BMI, gestational age number of previous caesarean sections or associated comorbidities between the 2 groups.

Our results showed that Nausicaa suture group achieved hemostasis and prevented hysterectomy in 80% of women compared to in 96.7% in B-Lynch suture group contrary to our results, Nausicaa suture prevented hysterectomy in 97% of participating women by Shih et al. 7 who first described this procedure may be due to difference in eligibility criteria as the cases of placenta accreta spectrum were not included in the current study. Similar to our results, B-Lynch suture achieved hemostasis and prevented hysterectomy in 100% and 96.8% of participating women in the study by Kalkal et al. 15 and Harma et al. 16 respectively.

In the current study, 36.7% of women in Nausicaa suture group required devascularization,while 4% of women in B-Lynch group required devascularization. No published studied was found mentioning the need for devascularization with Nausicaa suture. Conversely, 20% of women participating in B-Lynch group suture in the study by Sentilhes et al. 17 needed devascularization. This could be attributed to the difference in skills or indications of devascularization procedure.

We found that procedure duration was significantly longer among Nausicaa group than among B-Lynch group. Duration to perform B-Lynch suture in this study ranged from 4 to 20 minutes compared to procedure time of 5 to 22 minutes to perform Nausicaa suture. On the other hand, procedure time to perform B-Lynch suture was about 35 minutes by Abdelfatah et al. 18 and 4.7 minutes to 7.9 minutes by Karena et al. 19 this may be explained by the difference in training and skills for suture application. Procedure time to perform Nausicaa suture was about 20 minutes by Shih et al.7 which is close to our study.

The Blood loss in women who had Nausicaa suture in this study ranged from 1000-3800 ml compared to 800-2500 ml in women participating in B-Lynch suture group. On the other side, the blood loss in women who had Nausicaa suture done was 500-4100 in Shih et al. 7 Women had B-Lynch suture done in the studies of Gadappa et al. 20 and Tariq et al. 21 had blood loss of 1000-1500 ml. The difference in amount of blood loss may be attributed to the time of the decision of compression suture application. The time taken till decision for suture application plays a major role in the amount of blood loss consequently, the amount of blood transfused to the patients.

In the current study, hemoglobin drop was more significant in Nausicaa suture group compared to B-Lynch suture group. (2.5 gm%) which was in compared to (1.9 gm%) for women in B-Lynch group. This results go in agreement with Shih et al. 7 (hemoglobin drop for Nausicaa suture was 2.5 gm%) and Kalkal et al. 15 (hemoglobin drop for B-Lynch suture group was 2 gm%).

In our study, 14% of participating women in Nausicaa suture group required blood transfusion compared 20% of participating women in B-Lynch suture group. Contrary to our findings, 38% of women who had in Nausicaa suture in the study of Shih et al. 7 and 29% of women who had B-Lynch sutures in the study by Koh et al.22. Received blood transfusion. This may be due to difference in protocol of initiation of blood transfusion in different centres.

In the current study, four women (13%) in Nausicaa suture group required ICU admission compared to one woman (3.3%) in B-Lynch group. On the other hand, eight women (11%) required ICU admission in Shih et al. 7 and three women required ICU admission in B-Lynch group (17%) in Harma et al, 16 study. This may be due to difference in protocol of ICU admission among different hospitals.

Based on the results of this study, B-Lynch suture seems more effective than Nausicca suture in controlling excessive uterine bleeding during cesarean section and avoiding the need of hysterectomy. Also, B-Lynch suture requires shorter procedure time with less blood loss compared to Nausicca suture, which is of critical value during these life threatening situations.

Among the points of strength of the current study is its randomized controlled design that it was strictly adherent to during its performance.

Additionally, it was conducted at a tertiary center, well equipped to deal with such complex and emergent cases.

Furthermore, it is the only published trial. According to our latest literature search comparing Nausicaa compressive suture to the widely spread B-Lynch suture.

Points of limitations include its single center performance, for which we hope to recruit other centers in a multicenter trial. Also, the study was powered to detect the primary outcome of achieving hemostasis and avoidance of hysterectomy, but not to detect other rare outcomes as maternal mortality. Lastly, Long term impact of other morbidities and effect of such compressive sutures on fertility needs longer follow up. Also it is a pilot study and there were no available published results to calculate the needed sample size upon. So, an arbitrary number of 30 cases per group was adopted. Based on the findings of our study, we suggest that adequately powered studies be conducted based on sufficient sample size calculation. These points should be considered before generalizability of our findings to be implemented.

Conclusion

B-Lynch suture is more effective than Nausicca suture in controlling excessive uterine bleeding during cesarean section and avoiding the need of hysterectomy. Also,

B-Lynch suture needs shorter procedure time with less blood loss compared to Nausicca suture, which is of critical value during these life threatening situations.

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Author Contributions

Conception of ideas and study design & study design by Mohamed Hamed Salama,(Orcid ID : 0000-0002-3951-6499) performance of surgical interventions by Ahmed Mohamed Zeinhom (Orcid ID : 0009-0006-3195-3885), Ahmed Mohammed Selim (Orcid :0009-0009-9494-2456) and Amany Salah eldin Abdelhafeez abdelhady, Manuscript preparation Mohamed Hamed Salama & Amany Salah eldin Abdelhafeez abdelhady (Orcid ID : 0009-0008-7422-5954)under supervision of Amr El Helaly (Orcid ID: 0000-000304134-1146)and Noha Rabie(Orcid ID :0000-00030202-2679).

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Protocol Registration

The study protocol was registered at clinicaltrials.gov (NCT 05270473).

Availability of Data and Materials

All data generated or analyzed during this study are included in this article and supplementary information file. Data sets are available on Harvard Dataverse https://doi.org/10.7910/DVN/KVMW95.

Declarations

Ethical Approval and consent to participate

The study was approved by Medical Ethics Committee of Obstetrics and Gynecology Department at Ain Shams University (ID: MD250/2019) to ensure following the standard ethical principles governing research involving human subjects. Written and oral informed consent was obtained from all individual participants included in the study.

Consent for publication

The manuscript is approved by all authors for publication.

Competing interests

No conflict of interest for all authors.

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Impact of Metabolic Syndrome on Menopausal Symptoms among Postmenopausal Women

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Abstract

Background: Menopause, defined as the full cessation of the menstrual cycle for more than twelve months, is a natural physiological phase that is directly induced by the decrease of estrogen levels. A group of conditions that consists of insulin resistance, central obesity, hypertension, and dyslipidemia is called metabolic syndrome. In older women, the menopause itself raises the risk of metabolic syndrome.

Aim: This study aimed to investigate the relationship between menopausal symptoms and metabolic syndrome in postmenopausal women.

Methods: A cross-sectional study that split menopausal women into two groups based on whether or not they had metabolic syndrome. The research was conducted at Suez Canal University Hospital's obstetrics and gynecology department. We used menopausal rating scale to assess menopausal symptoms in two women groups, one group consists of women with metabolic syndrome according to WHO definition while the other group was free.

Results: The median age was 57 years and 55 years among postmenopausal women without metabolic syndrome and those without respectively. BMI, systolic and diastolic blood pressure, fasting blood sugar, serum triglycerides and waist circumference were significantly higher among women with metabolic syndrome. While serum HDL had a significant lower level in women with metabolic syndrome. All somatic and psychological domains were significantly higher among women with metabolic syndrome compared to women without metabolic syndrome. Bladder symptoms were significantly higher among women with metabolic syndrome. There were 6.2% and 5.6% had asymptomatic, 91.9% and 94.4% had mild to moderate and 1.9% and 0 had severe to very severe menopausal symptoms among menopausal women with and without metabolic syndrome respectively. Psychological domain was significantly correlated with fasting blood sugar serum triglycerides and waist circumference. Total Menopause Rating Scale had significant positive correlation with systolic and diastolic blood pressure, waist circumference, fasting blood sugar

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and serum triglycerides. Using univariate binary logistic regression, only serum triglycerides had a significant association with severity of Menopause Rating Scale.

Conclusion: There was a significant increase in sleeping issues, irritability, depressed mood, anxiety, and problems voiding mental and physical exhaustion in cases with metabolic syndrome.

Keywords: Metabolic Syndrome, Menopausal Symptoms, Postmenopausal, Menopause Rating Scale.

Introduction

Menopause, defined as the full cessation of the menstrual cycle for more than twelve months, is a natural physiological phase that is directly induced by the decrease of estrogen levels. It produces a range of symptoms that fall into the categories of somatic, psychological, sexual, and vasomotor symptoms. Menopausal women may experience symptoms that are severe enough to interfere with their regular day-to-day activities. Menopausal symptoms' impact on the quality of life of has been extensively established (1).

Menopause typically occurs after the age of 45, however symptoms commonly begin to show up several years before. Middle-aged women's general health and well-being, as well as health issues associated to the menopause, are now serious health concerns. Menopausal women's health is gaining attention because, as life expectancy generally rises, more women are predicted to experience menopause for between 25% and 33% of their lives. In comparison to other nations, the age of menopause among Egyptian women was documented as 46.7 years (2,3).

Egyptian women respond and view menopause very differently than women in western nations, largely because of cultural and educational disparities. To estimate menopausal symptoms, numerous techniques have been developed for epidemiological and research objectives. The Menopause Rating Scale (MRS), one of these instruments, is suggested for use in clinical practise because it is made to rate a profile of symptoms in order to determine the severity of complaints connected to age and menopause. It has Arabic language validation (4).

The Quality-of-Life group defined as an individual's assessment of their place in life within the framework of their culture and values, as well as in connection to their aspirations, concerns, and standards (2).

Quality of life research after menopause has grown to be a crucial aspect of clinical treatment. In contrast to industrialized nations, limited information about menopausal symptoms and how they affect postmenopausal women's quality of life is accessible in developing nations (5).

A group of conditions that consists of insulin resistance, central obesity, hypertension, and dyslipidemia is called metabolic syndrome. It is linked to an elevated risk of having cardiovascular disease (CVD) and diabetes mellitus type 2 (T2DM) and in older women, the menopause itself raises the risk of MetS (6). This study aimed to investigate the relationship between menopausal symptoms and metabolic syndrome in postmenopausal women.

Methodology

This was a cross-sectional study that split menopausal women into two groups based on whether or not they had metabolic syndrome. We compared the two groups' menopausal symptom severity using a menopausal rating scale. The research was conducted at Suez Canal University Hospital's obstetrics and gynecology department.

Women who visited the Suez Canal University Hospital's obstetrics and gynecology clinic. The included were women over 45 going through menopause

as well as simple instances of hypertension and diabetes mellitus. Menopausal women with long-term medical or surgical problems, surgical menopause, early ovarian failure, menopausal women receiving ongoing psychiatric therapy, or both were excluded.

Sample Size justification

According to the following equation.

$n = (Z\alpha/2+Z\beta)2 *2*\sigma2 / (\mu1-\mu2)2$ (7)

, the estimated sample size was 322 participants (161 participants in each group) after adding of 20% for non-responders at 95% confidence ($Z\alpha/2 = 1.96$) and power 80% ($Z\beta = 0.84$). From Cengiz et al study, σ was 8.8, $\mu1$ was 19 and $\mu2$ was 16 in metabolic syndrome and control groups respectively (8).

Data collection tool:

We used menopausal rating scale to assess menopausal symptoms in two women groups, one group consists of women with metabolic syndrome according to World Health Organization (WHO) definition while the other group was free.

According to WHO criteria, metabolic syndrome is defined as abdominal obesity with a waist circumference of 88 cm for women, serum triglycerides of 150 mg/dL (1.7 mmol/L) or a medication treatment for elevated triglycerides, a serum high-density lipoprotein (HDL) cholesterol of <50 mg/dL (1.3 mmol/L) for women or a medication treatment for low HDL cholesterol, a fasting plasma glucose (FPG) of 100 mg/dL (5.6 mmol/L) or a medication treatment for elevated blood glucose, a blood pressure of 130/85 mmHg or a medication treatment for elevated blood pressure, and a metabolic syndrome definition for women.

Data from cases was collected according to MRS. MRS Arabic validated version will be used (9) women who are attending outpatient clinics at Suez Canal University (SCU) hospital from 9 pm to 12 pm will be offered to fill in data after explaining the items for them. Total MRS score ≤ 11, 12-35 and ≥ 36 are considered as asymptomatic, mild to moderate and severe to very severe, respectively (10,11).Then those eleven symptoms were arranged into subgroups as urogenital, psychological and physical. The researcher will help women who can't read by asking them direct questions.

The score of MSR was recorded and compared between the two groups.

Statistical analysis:

Version 26 of the SPSS program was used to statistically analyze and computerize the data that had been gathered. The Kolmogorov Smirnov test evaluated the normality of data. Tables and graphs were used to display the data when suitable. Frequencies and relative percentages were used to depict qualitative data. As said, the chi square test ($\chi2$) and Fisher Exact tests were employed to look into any associations between the qualitative variables. The mean and standard deviation in addition to median (minimum and maximum values) were used to express quantitative data. The difference between the two groups' quantitative non-parametric variables was computed using the Mann Whitney test. P-value < 0.05 denotes a significant difference, whereas P≥ 0.05 denotes a non-significant difference. Spearman correlation was used to assess the relation between two non-parametric variables while univariate logistic regression was used to find the relation between variables and severity of MRS.

Results

Upon comparing basic characteristics between the two studied groups, median of age was 57 years and 55 years among postmenopausal women without metabolic syndrome and those without respectively. More than half of both groups were married (53.4% and 51.9%). Twenty-nine percent and twenty-eight percent were illiterate among women with MetS and women

without. BMI, systolic and diastolic blood pressure, fasting blood sugar, serum triglycerides and serum triglycerides were significantly higher among women with metabolic syndrome. While serum HDL was significantly lower among women with metabolic syndrome (Table 1). All somatic and psychological domains were significantly higher among women with metabolic syndrome compared to women without metabolic syndrome. Bladder symptoms were significantly higher among women with metabolic syndrome while sexual problems and vaginal dryness showed no difference between both groups (Table 2). There were 6.2% and 5.6% had asymptomatic, 91.9% and 94.4% had mild to moderate and 1.9% and 0 had severe to very severe menopausal symptoms according to MRS among menopausal women with and without metabolic syndrome respectively (Figure 1). Somatic domain was positively correlated with systolic and diastolic blood pressure, waist circumference and serum triglycerides. While it was negatively correlated with HDL. Psychological domain was significantly correlated with fasting blood sugar serum triglycerides and waist circumference. While it was negatively significantly correlated with serum HDL. Urogenital domain was significantly positively correlated with systolic blood pressure and waist circumference. Total MRS had significant positive correlation with systolic and diastolic blood pressure, waist circumference, fasting blood sugar and serum triglycerides. In addition it had negative correlation with serum HDL (Table 3). Using univariate binary logistic regression, only serum triglycerides had a significant association with severity of MRS (Table 4).

Table 1. Comparing basic characteristics among the two studied groups.

Variable		**Postmenopausal without MetS (n= 161)**	**Postmenopausal with MetS (n= 161)**	**P value**
Age (years)	Median (min, max)	57 (46, 67)	55 (46, 67)	0.106[a]
Marital status	Married	86 (53.4%)	83 (51.9%)	0.962 [b]
	Widow	37 (23%)	40 (25%)	
	Divorced	26 (16.1%)	24 (15%)	
	Single	12 (7.5%)	13 (8.1%)	
Educational level	Illiterate	47 (29.2%)	46 (28.7%)	0.434 [c]
	Read and write	7 (4.3%)	2 (1.3%)	
	Primary	24 (14.9%)	24 (15%)	
	Preparatory	13 (8.1%)	16 (10%)	
	Secondary	35 (21.7%)	46 (28.7%)	
	High school	12 (7.5%)	10 (6.3%)	
	University	23 (14.3%)	16 (10)	
BMI	**Median (min, max)**	23.9 (18.2, 32.7)	24.9 (18.4, 33.5)	**0.020*** [a]
Systolic B.P (mmHg)	**Median (min, max)**	110 (90, 140)	130 (90, 160)	**<0.001*** [a]
Diastolic B.P (mmHg)	**Median (min, max)**	70 (50, 90)	85 (50, 110)	**<0.001*** [a]

Waist circumference (cm)	**Median (min, max)**	84.8 (67, 111)	91.2 (71, 113)	**<0.001*** [a]
FBS (mg/dl)	**Median (min, max)**	98 (64, 140)	114.5 (60, 166)	**<0.001*** [a]
Serum triglycerides (mg/dl)	**Median (min, max)**	134 (83, 290)	266.5 (143, 611)	**<0.001*** [a]
Serum HDL (mg/dl)	**Median (min, max)**	59 (29, 110)	35 (22, 81)	**<0.001*** [a]

a; Mann Whitney U test, b; Chi-square test, c; Fisher Exact test

*p is significant at <0.05

BMI; Body Mass Index, B.p; Blood pressure, FBS; fasting blood sugar, HDL; high density lipoprotein

Table 2. Comparing the MRS between the two studied groups.

Domain	Variable		Postmeno-pausal with-out MetS (n= 161)	Postmeno-pausal with MetS (n= 161)	P value
Somatic	Hot flushes, sweating	**Mean± SD**	1.5± 1.2	1.8± 1.2	**0.008***
		Median (Range)	1 (0, 4)	2 (0, 4)	
	Heart discomfort	**Mean± SD**	1.5± 1.2	1.7± 1.1	**0.034***
		Median (Range)	1 (0, 4)	2 (0, 4)	
	Sleeping problems	**Mean± SD**	1.9± 1.2	2.4± 1.2	**0.001***
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Muscle and joint problems	**Mean± SD**	1.9± 1.2	2.3± 1.3	**0.009***
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Total somatic score	**Mean± SD**	6.8± 2.6	8.2± 2.6	**<0.001***
		Median (Range)	7 (0, 12)	8 (1, 14)	
Psycho-logical	Depressive mood	**Mean± SD**	1.6± 1.2	2.1± 1.3	**0.002***
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Irritability	**Mean± SD**	2.1± 1.2	2.4± 1.1	**0.027***
		Median (Range)	2 (0, 4)	3 (0, 4)	
	Anxiety	**Mean± SD**	1.6± 1.3	1.9± 1.4	**0.026***
		Median (Range)	1 (0, 4)	2 (0, 4)	
	Physical and mental exhaustion	**Mean± SD**	2.0± 1.2	2.3± 1.2	**0.041***
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Total Psychological score	**Mean± SD**	7.4± 2.9	8.7± 3.5	**0.001***
		Median (Range)	7 (0, 16)	8 (1, 16)	

Urogenital	Sexual problems	**Mean± SD**	1.8± 1.2	2± 1.3	0.158
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Bladder problems	**Mean± SD**	1.4±1.3	1.7±1.3	**0.037***
		Median (Range)	1 (0, 4)	2 (0, 4)	
	Vaginal dryness	**Mean± SD**	1.8±1.3	1.8± 1.2	0.612
		Median (Range)	2 (0, 4)	2 (0, 4)	
	Total urogenital score	**Mean± SD**	5.1± 2.3	5.4± 2.6	0.099
		Median (Range)	5 (0, 11)	6 (0, 12)	
Total MRS score		**Mean± SD**	19.3± 4.9	22.3± 6.3	**<0.001***
		Median (Range)	20 (1, 29)	22 (4, 38)	

Mann Whitney U test, *p is significant at <0.05

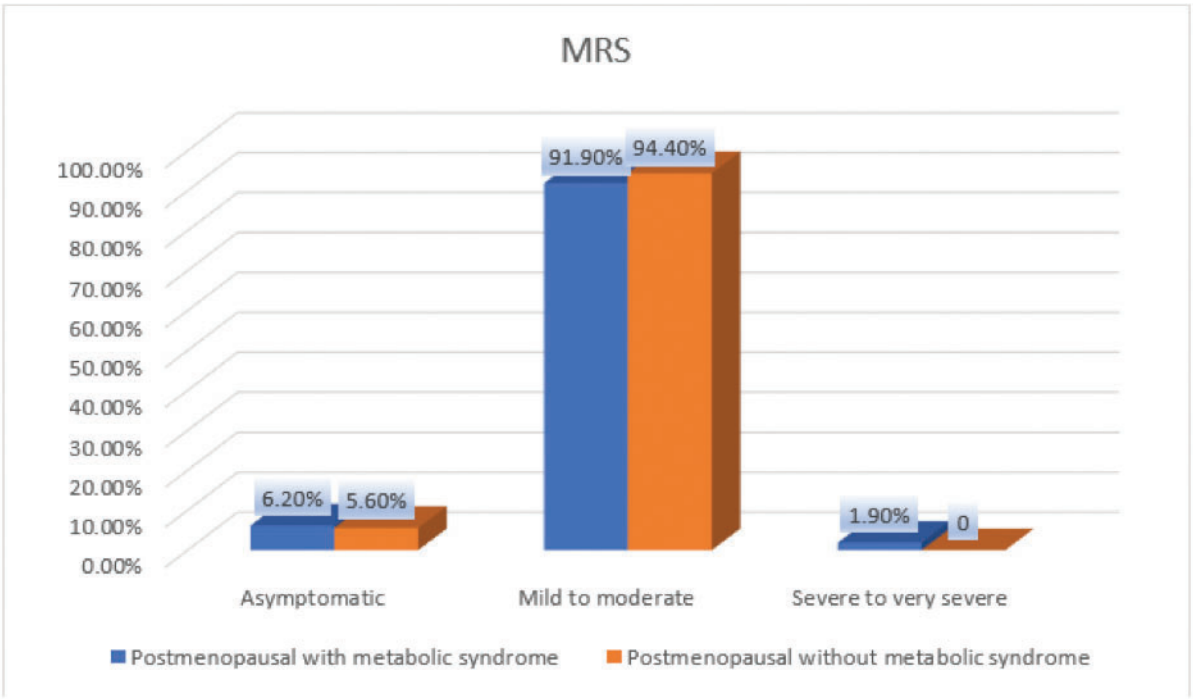

Figure 1. Menopausal rating score categories among the participants.

Table 3. Correlation between MRS domains and other variables.

		somatic subscale	**Psychological subscale**	**Urogenital subscale**	**MRS score**
Age (years)	R	-.022	-.062	-.025	-.065
	p.value	.689	.266	.649	.247
BMI	R	.105	-.049	.009	.027
	p.value	.060	.379	.868	.627
Systolic B.P mmHg	R	**.172**	.097	**.114**	**.184**
	p.value	**.002***	.083	**.040***	**.001***

Diastolic B.P $_{mmHg}$	R	**.210**	.105	.075	**.182**
	p.value	**.000***	.059	.181	**.001***
waist circumference $_{cm}$	R	**.180**	**.144**	**.138**	**.220**
	p.value	**.001***	**.009***	**.013***	**.000***
fasting blood sugar $_{mg/dl}$	R	.098	**.127**	.061	**.157**
	p.value	.078	**.023***	.278	**.005***
serum triglycerides $_{mg/dl}$	R	**.158**	**.121**	.045	**.158**
	p.value	**.005***	**.031***	.425	**.005***
serum HDL $_{mg/dl}$	R	**-.125**	**-.121**	-.013	**-.115**
	p.value	**.025***	**.030***	.809	**.040***

Spearman correlation, *p is significant at <0.05

BMI; Body Mass Index, B.p; Blood pressure, HDL; high density lipoprotein

Table 4. Univariate logistic regression for predicting Severity of MRS.

	Univariate analysis				
	EXP (B)	**Wald**	**Sig.**	**95% CI**	
				Lower	**Upper**
Serum HDL$_{mg/dl}$	0.134	2.240	0.899	0.782	1.033
Serum Triglycerides $_{mg/dl}$	1.009	6.250	**0.012***	1.002	1.017
Fasting blood sugar $_{mg/dl}$	1.053	3.166	0.075	0.995	1.114
waist circumference $_{cm}$	1.084	1.510	0.219	0.953	1.233
Systolic B.P $_{mmHg}$	1.037	1.269	0.260	0.974	1.104
Diastolic B.P $_{mmHg}$	1.062	1.326	0.250	0.959	1.177

Univariate logistic regression using severe MRS as a dependent variable.

*p is significant at <0.05

B.p; Blood pressure, HDL; high density lipoprotein

DISCUSSION

Metabolic syndrome (MetS) is a composite of factors that include hypertension, low HDL cholesterol, raised TG, elevated triglycerides, and insulin resistance. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) guidelines state that a person may be classified as having MetS if they meet at least three of those requirements (12).

Numerous research studies have demonstrated a higher incidence of Metabolic Syndrome in postmenopausal women, with rates ranging from 16.9% to 69.0% across various demographic groups (5,13)

This study looked at the connection between menopausal symptoms and MetS in postmenopausal women with the goal of improving the quality of life for these people.

In this cross-sectional study, 322 menopausal women were split into two groups based on whether or not they had metabolic syndrome: There were 161 women with MetS and 161 women without MetS in total.

Evaluations of menopausal symptoms have been made utilising MRS. There are three subscales that make up this 11-item scale: somatic (hot flushes, heart palpitations,

insomnia, and problems with muscles and joints); psychological (irritability, anxiety, and depressive mood, mental and physical exhaustion); and urogenital (vaginal dryness, sexual issues, and bladder issues).

Every one of the 11 symptoms has a score ranging from "0" (no complaints) to "4". (very severe symptoms). The sum of the item scores for each of the three dimensions determines the composite score for that dimension. The sum of the three subscales' sum scores determines the final score (4).

According to the results of our investigation, there were statistically significant variations in waist circumference, diastolic blood pressure (BP), and systolic B.P. across the study groups. Women with MetS showed greater mean diastolic blood pressure, systolic blood pressure and waist circumference than non-MetS women.

In their study of 574 participants, Fernandez-Alonso et al. found that obesity and severe menopausal symptoms were linked (14).

Regarding FBS, serum triglycerides, and HDL, there were statistically significant variations between research groups in the current investigation. Compared to women without MetS, those with MetS had lower HDL and higher mean fasting blood sugar (FBS) and serum triglycerides.

Various studies have employed multiple scales to assess the intensity of menopausal symptoms (15).

The study found a difference with statistical significance in the total MRS score between the MetS and control groups. The study's overall somatic score showed a statistically significant difference between both MetS and the control groups.

The psychological subscale score in this study showed a statistically significant difference between the MetS and non-MetS groups, with the MetS group scoring higher. That being said, there was no statistically significant difference in the overall scores of the urogenital subscale between the two groups.

Research indicates that menopausal symptoms are far more common and severe when combined with Metabolic Syndrome and its predominant component, abdominal obesity (16).

Numerous research has shown a correlation between MetS and psychological symptoms including depression and anxiety, although the findings are debatable. According to research by Skilton et al., among 1,598 men and women, MetS was linked to a higher incidence of depression but not anxiety, and the number of MetS components rose as depression levels rose but not anxiety levels did (17).

Furthermore, compared to women without vasomotor complaints, women who report hot flashes have an undesirable CVD risk profile, according to Gast et al (18).

Vasomotor symptoms are also linked to a higher risk of cardiovascular illnesses (12). For the previous reasons, there appears to be a connection between menopausal symptoms and MetS, but the number of papers examining the connection is few. Serum estrogen concentration is greater in obese postmenopausal individuals than in normal weight individuals (6).

When Lee et al. evaluated both groups with and without MetS, they found that while there was a difference proved statistically between the groups' somatic symptom scales and overall MRS scores, there was no significant difference between both urogenital and psychological symptom subscales (16).

In contrast to the results of the Chedraui et al. study, they said that the prevalence of depressive symptoms was lower in their MetS cases (19).

In our study, the MetS group experienced bladder issues more frequently than the non-MetS group.

The group with MetS in the Lee et al. trial

experienced more hot flashes and sweats on a higher frequency and scored higher on somatic symptoms than the group without MetS. We reasoned that the increase in vasomotor symptoms was caused by an increase in body fat, obstruction of heat dissipation, and drop in core body temperature since women with MetS have greater levels of body fat and abdominal adiposity (16).

We found that those with MetS had a higher prevalence of sleep issues. Two long-term cohort studies have demonstrated that sleep disturbances are more prevalent in the early stages of menopause (20,21).

Additionally, it is well recognized that symptoms of depression and anxiety can cause problems with sleep (22).

According to this study, the waist circumference (WC), systolic-diastolic blood pressure, serum lipids, and overall MRS score were all positively correlated.

Much like in the work of Cengiz et al., there was a positive correlation discovered between the AC, TG, total MRS score, and systolic-diastolic blood pressure. Nevertheless, no meaningful correlations between the FPG, HDL, and overall MRS scores were discovered (8).

Thurston et al. found that a higher level of total and subcutaneous abdominal adiposity were linked to a higher risk of hot flashes in the Study of Women's Health across the Nation Heart Study (SWAN) (13).

In accordance with the findings of the Cengiz et al. study, which showed a substantial positive association between the psychological subscale and serum triglycerides, we also discovered a significant link between the psychological subscale and serum triglycerides (8).

Abdominal obesity has been demonstrated by Chedraui et al. to be a substantial risk factor for joint discomfort, depression, and hot flashes (19).

According to a Gold et al. study, hot flashes are unexpectedly less common in obese people, but they also tend to occur more frequently in these circumstances (23).

Additionally, a strong association was discovered between the WC and the urogenital subscale.

Likewise, the Cengiz et al. investigation discovered a strong positive connection between the urogenital subscale and abdomen circumference (8).

The univariate logistic regression model for variables associated with severe MRS scores was ultimately discovered by this investigation. We discovered a strong correlation between the total MRS score and the triglycerides.

In a similar vein, TG levels were shown to be strongly correlated with the total psychological symptom subscale in the Cengiz et al. study's multivariate analysis (8), but Lee and colleagues found TG levels to be correlated with the total somatic symptom subscale (16).

We believe that the various results documented in the literature stem from demographic variations, including differences in socioeconomic status, ethnicity, culture, and lifestyle.

It is believed that urogenital symptoms, such as difficulties voiding and having sexual relations, worsen throughout the postmenopausal stage. Studies, however, indicate that there is little connection between MetS and urogenital symptoms (8).

MetS has been demonstrated by Ponholzer et al. to be a separate risk factor for decreased sexual desire (24).

According to a study by Esposito and Giugliano, premenopausal individuals with MetS had a significantly lower mean Female Sexual Function Index (FSFI) score (25).

Lee et al., however, have demonstrated that there is no connection between MetS and urogenital symptoms or sexual abnormalities (16).

In a multivariate linear regression analysis, Laudisio et al. found that MetS was connected with the GDS score in women (95 percent CI, 0.14–4.14; p=0.036), but not in men (95 percent CI, -3.17 to -1.49; p = 0.476) (26).

When age, gender, education level, and physical activity were taken into account in the models, Hildrum et al. found no correlation between MetS and anxiety or depression (27).

The study findings indicate that there was no significant difference in sexual issues or vaginal dryness between patients with and without MetS. However, there was a substantial rise in voiding problems among patients with MetS. We believe that our nation's cultural has a major role in this outcome.

The cross-sectional form of the research and the failure to account for the cultural differences among the research groups are the two main shortcomings of this study.

We concluded by demonstrating that, although there was no difference between the patients with and without MetS regarding the vasomotor symptoms, there was a significant increase in sleeping issues, irritability, depressed mood, anxiety, problems voiding and mental and physical exhaustion in cases with MetS. Furthermore, there may be a correlation between higher overall urogenital scores and higher WC values.

List of abbreviations

MetS: Metabolic syndrome

MRS: Menopause Rating Scale

CVD: cardiovascular disease

T2DM: diabetes mellitus type 2

WHO: World Health Organization

HDL: high-density lipoprotein

FPG: fasting plasma glucose

SCU: Suez Canal University

NCEP ATPIII: National Cholesterol Education Program Adult Treatment Panel III

BP: blood pressure

FBS: fasting blood sugar

WC: waist circumference

Ethics approval and consent to participate

All participants agreed for participation

Consent for publication

All authors agreed for publication

Availability of data and material

All data are available.

Competing interests

No

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All authors contributed in all parts of the research.

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Effect of metformin on maternal and neonatal outcomes in pregnant obese diabetic patients: New potentials for an old drug

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Abstract

Background: Pregnancy complicated by diabetes whether gestational or pregestational diabetes, could be associated with adverse maternal and neonatal outcomes; if optimum glycemic control was not achieved. Metformin is an insulin sensitizing drug that has been approved for treatment of gestational diabetes and type II pregestational diabetes. In this study, we have studied the role and effectiveness of metformin in improving glycemic control and the prevention of maternal and neonatal adverse outcomes in obese pregnant diabetic women.

Patient and Methods: This was a prospective cohort study that included 189 obese pregnant diabetic women recruited to Kasr Al Aini Obstetrics and Gynecology department over the period from September 2022 till March 2023. The study population included three groups according to the treatment modality; metformin only group, metformin and insulin group and insulin only group.

Results: The use of metformin was associated with significant reduction in the incidence of preeclampsia and neonatal lactic acidosis with a p value 0.033 and 0.002 respectively. However, use of metformin whether alone or in addition to insulin, compared to insulin alone was not shown to be superior in improving glycemic control, or reduce adverse neonatal outcomes..

Conclusion: Metformin use in obese diabetic pregnant women improves maternal and neonatal outcomes.

Keywords: Metformin, Diabetes mellitus, pregnancy, Obesity.

Introduction

Obesity is defined as a BMI > 30 kg/m, over the past decades obesity has become a growing global epidemic (1). With the increasing number of obese population, the prevalence of maternal obesity has accordingly been increasing, with rising concerns regarding obesity related health issues. Obese pregnant women are at increased risk of gestational diabetes, pregnancy induced hypertension, preterm labor and miscarriages (2).

Diabetes mellitus is an endocrine disorder characterized by hyperglycemic state, which may develop for the first time during pregnancy secondary to glucose intolerance induced by the pregnancy hormones; known as gestational diabetes (3). Diabetes mellitus type II is a state of hyperglycemia secondary to insulin resistance that may predate pregnancy known as pregestational diabetes. PGD affects 1-2 % of the pregnant population, with observed rising rates. The diabetic pregnant population are at increased risk of adverse maternal and neonatal outcomes (4).

Pharmacological therapy of diabetes during pregnancy includes metformin, glyburide and insulin (5). Metformin is a synthetic analogue of guanidine that is commonly prescribed in the treatment of type II diabetes. It can be used alone or combined with other antidiabetic drugs. Metformin exerts its effect through suppression of hepatic gluconeogenesis without inducing hypoglycemia (6). Metformin has been widely used during pregnancy both for gestational diabetic mothers and obese no diabetic mothers with established safety and successful outcomes (7).

Several studies have addressed the use of metformin during pregnancy and how it could affect maternal and neonatal outcomes. The safety of metformin use during pregnancy regarding the long term neonatal effects was established by a recent study (8). Some studies showed that metformin use was associated with lower maternal weight gain and decreased incidence of pregnancy induced hypertension (9,10) in addition it was more cost-effective and associated with lower rates of maternal and neonatal hypoglycemia and NICU admission (9,).

In this study, the effect of metformin on different maternal outcomes as glycemic control and the development of PIH; and neonatal outcomes will be assessed and compared to that of insulin either alone or combined with metformin.

Patients and Methods

This was a prospective study that was conducted at the OBGYN department, high risk pregnancy unit at Kasr Al Aini in period between October 2020 and October 2021.

Patients included in our study were diabetic pregnant women aged 25-40 years, either having gestational diabetes or type II pregestational diabetes. Obese pregnant women (BMI>30), pregnant 28-39 weeks, with a singleton viable fetus, eligible for elective lower segment cesarean section were candidates for our study. All patients with the following criteria were excluded from the study, those with established fetal or maternal compromise necessitating urgent delivery, associated fetal anomalies, associated hypertensive disease, kidney disease, systemic lupus erythematosus and type I diabetes. Also patients not compliant to drug therapy and those who were intolerant to metformin were excluded from our study.

The recruited patients were equally divided in to 3 groups according to their drug therapy as advised by the endocrinologist, Group 1: pregnant women using metformin in a dose of 500-2000 mg per day, Group 2: pregnant women receiving both metformin and insulin and Group 3: pregnant women receiving insulin only.

All patients were subjected to full history taking and clinical examination. The body weight was recorded at every visit in addition to the blood pressure as part of their routine ANC . All pregnant women had their routine investigations (CBC, fundus examination, complete urine analysis) and ultrasound scans done as per the local unit schedule. The blood glucose levels sheet was checked at each visit, and drug compliance was checked by the attending obstetrician and endocrinologist at the joint clinic. Also fasting and 2 hour postprandial blood sugar and HbA1C were measured at recruitment and before elective delivery. The glycemic control among the three groups was the main

outcome of our study.

Neonatal outcomes were also assessed, mainly NICU admission and clinical and biochemical outcomes. All neonates were assessed following delivery for the APGAR score at 1, 5 and 10 minutes. The cord blood was assessed for ph., lactic acid and oxygen saturation; in addition a blood sample was obtained from the neonate and assessed for the following: blood sugar and hemoglobin levels.

Statistical methods: The statistical program for the social sciences (SPSS) version 28 (IBM Corp., Armonk, New York, United States) was utilized in order to code the data and enter it. For quantitative variables, the data were summarized by using the mean & standard deviation, as well as for categorical variables, the information were summarized by using frequencies (number of cases) as well as relative frequencies (%). Quantitative parameters having a normal distribution were compared using analysis of variance (ANOVA) followed by a multiple comparisons post hoc test, whereas those with an irregular distribution were compared using the non-parametric Kruskal-Wallis test or the Mann-Whitney U test. Paired t test was employed for normally distributed quantitative parameters & non-parametric Wilcoxon signed rank test for non-normally distributed quantitative data for assessing data collected in series within each group (11). The two categorical data sets were compared using Chi-square. When the expected rate was under five (12), an exact test was performed. Significant findings have p-values under 0.05.

Discussion

Our study was a prospective study that included 189 obese pregnant women having either type II pregestational diabetes or gestational diabetes. The study had three groups according to the pharmacological treatment which was decided by the endocrinologist. They were all comparable regarding the BMI and gestational age at delivery. Thus excluding differences among groups that could be related to prematurity rather than the drug used. The significant difference in the glycemic control among the three groups could be related to the diabetes state and not to the pharmacological treatment. However the three groups showed no significant improvement in the glycemic control between presentation and delivery.

Regarding maternal outcomes and development of preeclampsia, the metformin group had a significantly lower incidence of preeclampsia compared to the metformin and insulin, and insulin only groupv14.3%, 30.2 %, 33.3% respectively, with a P value 0.0033. Several studies addressed this issue and supported the role of metformin in reducing the incidence of severe pregnancy induced hypertension (10).

Regarding neonatal outcomes, the metformin group had significantly lower incidence of neonatal acidosis compared to the insulin and metformin group and insulin only group respectively, 1.2, 2.2, 2.3. The incidence of neonatal hypoglycemia, APGAR score, O2 saturation and NICU admission was not different among the three studied groups.

In a recent meta-analysis that included 24 randomized controlled trials that addressed the use of metformin, whether alone or together with insulin in pregnant women having type II GDM; regarding its effects on short term neonatal outcomes, birthweight, and neonatal hypoglycemia and NICU admission. The use of metformin was associated with lower incidence of macrosomia, NICU admission and neonatal hypoglycemia, when compared to insulin, risk ratio [RR] 0.68; 95% CI 0.54, 0.86; p = 0.001), (RR 0.73; 95% CI 0.61, 0.88;p = 0.0009), (RR 0.65; 95% CI 0.52, 0.81; p = 0.0001). The authors concluded that metformin is a safe drug for both the mother and the neonate and helps in limiting maternal and fetal weight gain especially in women who could not use insulin safely or

have financial obstacles in using it (13).

A large double blind multi center RCT by Benham J et Al in 2021, studied the role of adjunctive use of metformin to insulin to that of insulin alone in pregnant women having type II GDM. The study was in favor of the metformin group in reducing the gestational weight gain, insulin doses, cesarean section rate, macrosomia compared to insulin alone. However, number of small for gestational age neonates was higher in the metformin group which was not clear whether it was a direct effect of metformin or secondary to improved glycemic control, they concluded that metformin could be safely used in type II GDM as long as there are no risks for SGA (14).

The Italian study group of diabetes in pregnancy stated that metformin can be used in obese and very obese pregnant women having type II GDM, as this may decrease the weight gain during pregnancy, as well as the insulin dose (15).

The Italian study group concluded their statement based on the results obtained from a former

Study in 2008. In this study, 700 women with GDM were enrolled and randomized in to

Metformin group and insulin group. Regarding the maternal effects, neither glycemic control was not different between both groups, and the development of hypertension. The gestational weight gain was less in the metformin group. Regarding the neonatal outcomes, the metformin group had significant decrease in the incidence of neonatal hypoglycemia (16).

In another meta-analysis that compared insulin, metformin and gylpuride on glycemic control and neonatal outcomes from 23 trials, the Authors found that the metformin group had lower birth weight gain (SMD − 0.17; 95%CI − 0.25, − 0.08 and maternal weight gain 0.61; 95%CI − 0.86, − 0.35 compared to the insulin group. The met analysis concluded that metformin could be as effective as insulin for maternal glucose control and effective in the prevention of maternal and neonatal complications (17).

To the best of our knowledge, this was the first study to compare metformin only, to metformin and insulin, and insulin only treatment in type II pregestational and gestational DM. It measured different maternal and fetal parameters as PIH, macrosomia, PTL and neonatal acidosis, hypoglycemia and NICU admission. The sample size was representative, however a larger sample size would be more representative.

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Results

Table 1 shows that three groups were comparable regarding the age, parity, gestational age at delivery and type of diabetes.

Table 1

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
Age	32.29	5.22	31.17	5.76	31.24	5.52	Age
gravidity	3.46	1.98	2.78	1.44	2.97	2.05	0.109
parity	2.57	1.13	2.14	1.19	2.19	1.53	0.056
BMI	32.13	1.77	32.19	1.96	32.35	2.13	0.807
G.A	37.67	0.84	37.11	0.95	37.05	1.10	0.001

		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
Type of D.M	GDM	44	69.8%	39	61.9%	29	46.0%	0.022
	PGDM II	19	30.2%	24	38.1%	34	54.0%	

Table 2 Glycemic control

The groups 2 and 3 showed significant glycemic control between presentation and delivery, compared to group 1 (metformin group).

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
FBS at presentation	119.48	30.31	121.48	37.36	133.25	43.46	0.085
2hPP at presentation	166.25	36.28	183.95	55.14	204.24	65.96	0.001**
HbA1C at presentation	6.95	0.76	7.14	0.77	7.30	1.12	0.097
Mean FBS	113.14	17.28	119.21	23.60	117.92	20.15	0.219
FBS at delivery	112.52	20.69	108.06	30.49	119.57	24.01	0.039*
Mean 2hPP	151.40	27.09	160.90	43.21	167.81	41.81	0.055
2hPP at delivery	157.25	33.24	151.51	41.16	169.22	41.86	0.036*
HbA1C at delivery	6.91	0.80	6.89	0.79	7.28	1.14	0.038*
Group 1 (metformin only)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	119.48		30.31	112.52		20.69	0.110
2hPP (mg/dl)	166.25		36.28	157.65		33.91	0.071
HbA1C (%)	6.95		0.76	6.91		0.80	0.424
Group 2 (metformin and insulin)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	121.48		37.36	108.06		30.49	0.013*
2hPP (mg/dl)	183.95		55.14	151.51		41.16	< 0.001**
HbA1C (%)	7.14		0.77	6.89		0.79	< 0.001**
Group 3 (insulin only)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	133.25		43.46	119.57		24.01	0.019
2hPP (mg/dl)	204.24		65.96	169.22		41.86	< 0.001
HbA1C (%)	7.30		1.12	7.28		1.14	0.736

Table 3: Comparison of the Glycemic control among the 3 groups, and development of preeclampsia

The 2hpp blood sugar was significantly higher in the insulin group thus explaining the need for insulin treatment in this group.

The use of metformin was associated with significantly less number of cases that developed preeclampsia.

Post-HOC pairwise comparison (P value between each 2 groups) in significant items								
			Group 1 vs Group 2		Group 1 vs Group 3		Group 2 vs Group 3	
2hPP at presentation			0.200		<0.001**		0.108	
FBS at delivery			0.325		0.121		0.012*	
2hPP at delivery			0.409		0.086		0.011*	
HbA1C at delivery			0.892		0.059		0.027*	
		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
developed P.E	yes	9	14.3%	19	30.2%	21	33.3%	0.033
	no	54	85.7%	44	69.8%	42	66.7%	

Table 4: Neonatal outcomes

There was no significant difference regarding neonatal birth weight, APGAR scores and random blood sugar levels.

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
Birth weight (gm)	3086.67	575.08	3105.56	626.76	3186.19	543.43	0.596
Neonatal RBS (mg/dl)	78.27	20.16	76.75	20.14	72.27	17.71	0.198
Apgar score 1 min	4.11	0.72	4.00	0.76	3.86	0.93	0.213
Apgar score 5 min	6.95	0.91	6.90	0.91	6.73	1.02	0.384
Apgar score 10 min	8.56	0.59	8.54	0.59	8.44	0.64	0.542

Table 5: NICU admission and biochemical parameters

The insulin group had significantly higher blood cord lactic acid and consequently significant lower ph. However no difference regarding NICU admission and other biochemical parameters.

		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
Need for M.V	Yes	2	3.2%	2	3.2%	2	3.2%	1
	NO	61	96.8%	61	96.8%	61	96.8%	
NICU admission	Yes	8	12.7%	9	14.3%	14	22.2%	0.302
	NO	55	87.3%	54	85.7%	49	77.8%	
		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Mean	±SD	Mean	±SD	Mean	±SD	
PH of cord		7.28	0.06	7.25	0.07	7.23	0.11	0.002
lactic acid		1.90	0.47	2.22	0.69	2.36	0.97	0.002
O2 saturation		32.57	6.54	32.29	6.77	32.29	6.77	0.965
Hb (g/l)		149.37	11.78	148.35	12.15	147.71	12.76	0.747
O2 contents (mmol/l)		29.11	6.55	28.64	6.62	28.49	6.54	0.857

Lactoferrin with Ferrous Gluconate versus Ferrous Gluconate for Treatment of Iron Deficiency Anaemia during Pregnancy

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Abstract

Background: Iron deficiency is the most common single-nutrient deficiency worldwide. According to the US Centers for Disease Control and Prevention (CDC) recommendations, the diagnosis of anemia during pregnancy must be based on hemoglobin (Hb) values lower than 11 mg/dl during the first and the third trimester or lower than 10.5 mg/dl during the second trimester. Ferrous gluconate that has to be administered to patients with iron deficiency anemia in large quantities due to the poor bioavailability of inorganic iron. Moreover, oral administration of ferrous gluconate causes many side effects, including gastrointestinal discomfort, nausea, vomiting, diarrhea and constipation. Lactoferrin is a multifunctional iron-binding protein possessing anti-inflammatory and anti-microbial effects.

Aim of the Study: The study aims to compare between lactoferrin with ferrous gluconate versus ferrous gluconate alone in treatment of iron deficiency anemia during pregnancy.

Patients and Methods: This was a randomized controlled clinical trial that was conducted in Ain Shams University Maternity Hospital (ASUMH) from March 2023 to November 2023 on 40 pregnant women who had iron deficiency anemia during pregnancy recruited from inpatient/outpatient antenatal clinic of ASUMH.

Results: Group B had a significant increase in hemoglobin, hematocrit and serum ferritin level, group A had significantly more nausea than group B ($p = 0.013$), while there was no significant difference between the groups in terms of constipation or non-compliance ($p > 0.05$), there is no significant difference between the groups in terms of age or gestational age.

Conclusion: In our study we compared between lactoferrin with ferrous gluconate versus ferrous gluconate in treatment of iron deficiency anemia during pregnancy. Accordingly, we found that Oral lactoferrin with ferrous gluconate is better tolerated with higher increase in mean hemoglobin and lower side effects (nausea) when compared to oral iron therapy alone.

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INTRODUCTION

Iron is a necessary trace element for all mammals and involved in many essential metabolic processes such as oxygen transport, mitochondrial respiration and enzymatic activities (1).

Anemia is characterized by a decreased quantity of red blood cells, often accompanied by diminished hemoglobin levels or altered red blood cell morphology. Anemia is pathophysiologically diverse and often multifactorial (2).

Iron deficiency (ID) is the most common micronutrient deficiency worldwide with >20% of women experiencing it during their reproductive lives. Physiological adaptation in pregnancy leads to physiological anemia of pregnancy. This is because the plasma volume expansion is greater than red blood cell (RBC) mass increase which causes hemodilution (3).

The British Committee for Standards in Hematology guidelines defines pregnancy anemia as hemoglobin level < 11 g/L in the first trimester, < 10.5 g/L in the second trimester, and < 10 g/L during the postpartum period (4).

Lactoferrin is a glycoprotein from the transferrin family consist of 691 amino acids. It is a component of exocrine secretions such as milk and saliva and is present in neutrophil granules. Lactoferrin was identified in 1939 in bovine milk and isolated in 1960 from both human and bovine milk (5).

LF is a multifunctional protein that deserves to be called a “miracle molecule”, exhibiting a number of other beneficial properties such as anti-pathogenic, anti-cancer, anti-inflammatory, immunomodulatory and DNA-regulatory activities (5).

Lactoferrin has two times higher affinity for iron than serum transferrin. Besides, it permits iron export from tissues to the blood by interplaying with ferroportin and hepcidin which are key proteins in iron homeostasis. Lactoferrin does not provoke adverse gastrointestinal side effects (6).

Oral iron supplementation is an inexpensive and effective option for treating ID in stable outpatients. The recommended dose of elemental iron for treatment of iron deficiency is 100-200mg daily. Higher doses should not be given, as absorption is saturated and side effects increased. Iron salts such as ferrous gluconate, ferrous sulfate, and ferrous fumarate remain the standard first-line therapy for treating ID (4).

The oral dose for iron deficiency anemia should be 40-80mg of elemental iron daily. Ferrous Gluconate Tablets 300mg contain 35mgof elemental iron taken 1-2times/day. If taken correctly, oral iron supplements will give a rise in Hb of 20g/l every 3 weeks.

AIM OF THE WORK

The study aims to compare between lactoferrin with ferrous gluconate versus ferrous gluconate alone in treatment of iron deficiency anemia during pregnancy.

PATIENTS AND METHODS

This was a randomized controlled clinical trial that was conducted in Ain Shams University Maternity Hospital (ASUMH) from March 2023 to November 2023 on 40 pregnant women who had iron deficiency anemia during pregnancy recruited from inpatient/ outpatient antenatal clinic of ASUMH.

Inclusion criteria:

Pregnant women with single fetus, microcytic hypochromic anemia, gestational age (14 - 35 weeks), serum ferritin level <24 ng/dl, ages eligible for study: 20 years to 40 years.

Exclusion Criteria:

Associated chronic medical disorder (CKD, liver disease, peptic ulcer and chronic blood

loss), associated bleeding disorder, anaemia requiring blood tranfusion (Hb < 7gm/dL), hypersensitivity to iron preparations, haemoglobinopathies (G6PD, thalassemias, sickle cell disease).

This study included two groups: group I: 20 patients were given ferrous gluconate 300 mg (Ferrous-Gluconate®, tab.300mg, glucofer, Egypt) two times daily, group II: 20 patients were given lactoferrin 100mg (Pravotin-sachets®,100mg, Hygint, Egypt) with ferrous gluconate twice daily.

Hematological parameters (rise in hemoglobin), (rise in serum ferritin) and the adverse effects of both drugs were studied at registration and after 4 weeks.

Study Procedures:

All patients will undergo the following:

Informed consent will be obtained from all the participants in this study before enrolling in this study and all participants will be subjected to a detailed clinical assessment including: a detailed history, general, abdominal examinations, Investigations.

1-History taking:

Personal history: name, age, occupation and address, menstrual and obstetric history: Date of LMP, expected date of delivery which will be calculated according to Naegle's rule and gestational age. In addition to history of presence of any menstrual irregularities, duration. Past History: of Anemia in previous pregnancy, other diseases like Thalassemia, sickle cell anemia, liver or renal diseases or any other condition that may affect hemoglobin.

2-Medical examination:

General: Assessment of complexion and vital data (blood pressure, pulse, capillary refill), abdominal examination to assess fundal height.

3-***Investigations*** to perform will include:

Laboratory: Complete blood count (microcytic hypochromic anemia)

Imaging: Ultrasound to assess biometry to exclude fetal growth restriction.

Women will be divided in two groups with 20 in each group, the first group will receive one tab of ferrous gluconate 300mg administered orally twice per day for 4 weeks and the second group will receive lactoferrin sachets 100mg with ferrous gluconate 300mg twice per day for 4 weeks.

Patients were assigned to take the medication orally; once daily before breakfast, and Parvotin (100 sachets were be dissolved each in ¼ glass of water and taken before breakfast). Patients were advised to avoid the intake of tea, coffee, milk, milk products, antacids and calcium preparation within 2 hours before or after iron capsules. Women will be told to record side effects as nausea, vomiting, abdominal discomfort and constipation. Women will have a blood sample (CBC) withdrawn after 4 weeks to assess rise in pregnant anemia.

Ethical Considerations:

The study gained the approval from the ethical committee of the department of Obstetrics and Gynecology, faculty of medicine, Ain Shams University. Informed consent was taken after explaining the study purpose and methods to the subjects.

Data Management and Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 25)**. Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

RESULTS

Table 1: Comparison between group A and group B regarding age and gestational age

	Group A	Group B	t test		
	Mean ± SD	Mean ± SD	t	p value	sig.
Age	32.4 ± 10.16	28.45 ± 6.39	1.47	0.151	NS
gestational age	30.47 ± 3.5	30.5 ± 3.68	-0.03	0.980	NS

This table shows that there is no significant difference between the groups in terms of age or gestational age.

Table 2: Mixed design ANOVA for Hemoglobin levels among the 2 groups

HB	Pre	Post	p value	sig.
Group A	9.59 ± 0.14	9.86 ± 0.19	0.172	NS
Group B	9.41 ± 0.14	10.09 ± 0.19	0.001	S
p value	0.359	0.416		
sig.	NS	NS		

The table shows the results of a mixed design ANOVA for hemoglobin levels among the two groups of patients. The table indicates that there was no significant difference in hemoglobin levels between the two groups before or after the treatments, group B had a significant increase in hemoglobin.

Table 3: Mixed design ANOVA for Hematocrit levels among the 2 groups

Hematocrit	Pre	Post	p value	sig.
Group A	29.77 ± 0.56	30.29 ± 0.67	0.504	NS
Group B	28.9 ± 0.56	31.77 ± 0.67	0.001	S
p value	0.278	0.124		
sig.	NS	NS		

The table shows the results of a mixed design ANOVA for hematocrit levels among the two groups of patients. The table shows that there was no significant difference in hematocrit levels between the two groups before or after the treatments, but group B had a significant increase in hematocrit from pre to post treatment.

Table 4: Mixed design ANOVA for MCV levels among the 2 groups

MCV	Pre	Post	p value	sig.
Group A	79.44 ± 1.64	82.58 ± 1.56	<0.001	S
Group B	75.53 ± 1.64	77.81 ± 1.56	0.043	S
p value	0.100	0.037		
sig.	NS	NS		

The table shows the results of a mixed design ANOVA for mean corpuscular volume (MCV) levels among the two groups of patients. The table shows that there was a significant difference in MCV levels between the two groups after the treatments, with group A having a higher MCV than group B. The table also shows that both groups had a significant increase in MCV levels from pre to post treatment, indicating that the treatments affected the red blood cell size in both groups.

Table 5: Mixed design ANOVA for MCH levels among the 2 groups

MCH	Pre	Post	p value	sig.
Group A	25.67 ± 0.71	26.85 ± 0.62	<0.001	S
Group B	24.9 ± 0.71	24.45 ± 0.62	0.035	S
p value	0.447	0.009		
sig.	NS	S		

The table show the results of a mixed design ANOVA for mean corpuscular hemoglobin (MCH) levels among the two groups of patients. The table shows that there was a significant difference in MCH levels between the two groups after the treatments, with group A having higher MCH than group B. The table also reveals that both groups had significant changes in MCH levels from pre to post, with group A increasing and group B decreasing their MCH.

Table 6: Mixed design ANOVA for Ferritin levels among the 2 groups

Ferritin	Pre	Post	p value	sig.
Group A	12.3 ± 0.94	19.9 ± 2.56	<0.001	S
Group B	14.55 ± 0.94	35.15 ± 2.56	<0.001	S
p value	0.097	<0.001		
sig.	NS	S		

The table shows the results of a mixed design ANOVA for ferritin levels among the two groups of patients. The table indicates that both groups had a significant increase in ferritin levels after the treatments, but group B had a much higher increase than group A. The table also shows that there was no significant difference in ferritin levels between the two groups before the treatments, but there was a significant difference after the treatments, with group B having higher levels than group A.

Table 7: Comparison between group A and group B regarding Nausea, Constipation and Non-compliance

	Group A	Group B	Chi square		
	N (%)	N (%)	X^2	p value	sig.
Nausea	9 (45%)	2 (10%)	6.14	0.013	S
Constipation	8 (40%)	3 (15%)	3.14	0.077	NS
Non-compliance	6 (30%)	5 (25%)	0.13	0.723	NS

The table shows that group A had significantly more nausea than group B ($p = 0.013$), while there was no significant difference between the groups in terms of constipation or non-compliance ($p > 0.05$).

DISCUSSION

Anemia is defined as a condition in which the Haemoglobin (Hb) level in the body is lower than normal, which results in a decreased oxygen-carrying capacity of red blood cells to tissues (7). It affects all age groups, but pregnant women and children are more vulnerable (8).

According to the WHO guidelines, anemia in pregnancy is defined as a hemoglobin level < 11 g/dL in the first trimester and less than 10.5 g/dl in the second and third trimesters (9, 10).

In addition, according to WHO, anemia affects approximately 1.5 billion people worldwide (11). Anemia has the highest prevalence in 3 groups: children aged <5 years, pregnant women, and women of reproductive age (12).

Anemia is one of the most prevalent complications during pregnancy (13). It is commonly considered a risk factor for poor pregnancy outcomes and can result in complications that threaten the life of both mother and fetus, such as preterm birth, low birth weight (14).

Pregnancy increases maternal iron demand for three reasons. Maternal plasma and blood volumes are increased during pregnancy (15). Each extra gram of hemoglobin that the mother synthesizes requires an addition 3.46 milligram of elemental iron.

In addition, the fetus requires iron for its own metabolic and oxygen delivery needs as well as the loading of its comparatively large endogenous iron stores that will be utilized in the first six months of postnatal life (16).

There are a wide variety of iron supplements in use around the world, and their quality varies. Oral iron therapy is the treatment of choice for the most of patients with iron deficiency anemia (3,17). Conventional iron in form of ferrous sulphate is limited by gastro intestinal complaints. The use of ferrous gluconate as an alternative to these conventional ferrous salts offer less gastro intestinal upsets (18).

Lactoferrin is a naturally existing iron-binding multifunctional protein; it is present at high concentrations in human milk and in the milk of other mammals. It is also present in other body fluids such as tears, saliva, bile, pancreatic juice, genital and nasal secretions, and circulating neutrophils (19).

Therefore, oral administration of bovine lactoferrin as an iron-supplying molecule is an appealing therapeutic strategy, even if to date studies have shown conflicting results, reporting either enhancement or inhibition of intestinal iron delivery (20).

The main aim of this study was to compare between lactoferrin with ferrous gluconate versus ferrous gluconate in treatment of iron deficiency anemia during pregnancy.

This prospective randomized controlled study was conducted in Ain shams University Maternity Hospital. This study was conducted on 40 women divided into: Group I: 20 patients were given ferrous gluconate 300 mg (Ferrous-Gluconate®, tab.300mg glucofer, Egypt) two times daily. Group II: 20 patients were given lactoferrin 100mg (Pravotin-sachets®, 100mg, Hygint, Egypt) with ferrous gluconate twice daily.

In agreement with our results, Bayoumy et al., (21) who aimed to assess the compliance, efficacy and safety of lactoferrin in comparison to ferrous sulfate in Treatment of Nutritional Iron Deficiency Anemia during Second Trimester among Egyptian Ladies. They found that in Lactoferrin (N=70) group, Age (years) Mean ± SD was 26.4±4.2 with range 20.0–34.0 and the GA (in weeks) Mean ± SD was 19.3±2.7 with range 12.0–25.0. Parity Median (1st–3rd IQ) was 1.0 (0.0–2.0) with range 0.0–4.0, Parity; Primi was 20 (28.6%) while Multi was 50 (71.4%). While in Ferrous sulphate (N=70) group, Age (years) Mean ± SD was 27.4±4.5 with range 20.0–35.0 and the GA (in weeks) Mean ± SD was 19.0±2.5 with range 14.0–24.0. Parity Median (1st–3rd IQ) was 1.0 (0.0–3.0) with range 0.0–4.0, Parity; Primi was 20 21 (30.0%) while Multi was 49 (70.0%). There was no significant difference between the Lactoferrin group and ferrous sulfate group in terms of age or gestational age and as regard Parity Median (1st–3rd IQ) and Parity (Primi and Multi).

Also, Rezk et al., (22) who aimed to evaluate the efficacy and safety of lactoferrin in comparison to ferrous sulphate for the treatment of iron deficiency anemia (IDA) during pregnancy. They reported that in Group 1 (Lactoferrin group), Age was 26.4 ± 5.18, GA at inclusion was 16.32 ± 1.76 and Parity 1.42 ± 1.37. While in Group 2 (Ferrous group), Age was 26.5 ± 5.65, GA at inclusion was 16.01 ± 1.82 and Parity 1.50

± 1.29. There was no significant difference regarding age, GA and Parity between Lactoferrin group and Ferrous group.

As well, El-Nasr et al., (23) who aimed to evaluate the effectiveness, safety and acceptability of ferrous sulphate alone in comparison to combination of ferrous sulphate and lactoferrin for the treatment of iron deficiency anemia during pregnancy and their effect on neonatal iron store. Their study was conducted on 300 pregnant women from the second trimester with IDA who separated on 2 groups; ferrous sulphate group: 150 pregnant women received 150 mg of dried ferrous sulphate capsules. Combined ferrous sulphate and lactoferrin group: 150 pregnant women received combined 200 mg lactoferrin and 30 mg iron once daily for eight consecutive weeks. They found that there was no significant difference between the two groups as regard age and GA and Parity (PG and multipara).

In our study, we reported that group A had significantly more nausea than group B ($p = 0.013$), while there was no significant difference between the groups in terms of constipation or non-compliance ($p > 0.05$).

In consistent with our results, Rezk et al., (22) they reported that Gastrointestinal adverse events occurred more frequently with ferrous sulphate than the lactoferrin group.

Also, El-Nasr et al., (23) they revealed that there was statistically a significant difference between ferrous sulphate alone and combined ferrous sulphate and lactoferrin group regarding gasterointestinal side effects.

As well, Balsha et al., (24) who aimed to compare the safety, tolerability, efficacy and hematological response of lactoferrin in treatment of iron deficiency anemia during pregnancy versus ferrous sulfate capsules. They demonstrated that the adverse effects of treatment; there was a significant difference between the two groups, being the least among the lactoferrin group.

In contrast with our results, Bayoumy et al., (21) they found that Maternal adverse effects as nausea, vomiting, abdominal pain, constipation and heart burn were significantly less frequent in lactoferrin group than in ferrous sulfate group. Therefore, compliance with lactoferrin treatment was significantly higher than in ferrous sulphate group.

In our study, as regard the results of a mixed design ANOVA for hemoglobin levels between the two groups of patients, there was no significant difference in hemoglobin levels between the two groups before or after the treatments, group B had a significant increase in hemoglobin.

In consistent with our results, Bayoumy et al., (21) they found that as regard basal and follow up Hemoglobin (gm/dL), in Lactoferrin (N=70) group, Basal Hb; Mean ±SD was 9.0±0.6 ranged from 8.0 to 9.9, at Follow up Hb; Mean ±SD was 10.2±0.6 ranged from 9.1 to 11.2 and the change (after-before) in Hb; Mean ±SD 1.2±0.2 ranged from 0.2 to 1.3. There was a significant difference in Lactoferrin group before and after the treatment. While as regard basal and follow up Hemoglobin (gm/dL); in Ferrous sulphate (N=70), Basal Hb Mean ±SD was 9.1±0.6 ranged from 8.0 to 9.9; at Follow up Hb Mean ±SD was 9.6±0.6 ranged from 8.3 to 10.6 and the change (after-before) in Hb Mean ±SD 0.5±0.2 ranged from -0.5–0.8. However, they found that there was a significant difference in Ferrous Sulfate group before and after the treatment. There was non-significant difference between the two groups as regard Hb level at baseline despite, there was highly significant difference between the two groups as regard Hb level at follow up.

Also, Rezk et al., (22) they reported that in Group 1 (Lactoferrin group), Hb at enrolment was 8.15 ± 0.58, Hb after 1 month was 9.33 ± 0.37, Hb after 2 months was 10.41 ± 0.33 and Total increase in Hb was 2.26 ± 0.51. while in Group 2 (Ferrous group), Hb at enrolment

was 8.03 ± 0.702, Hb after 1 month was 8.65 ± 0.718, Hb after 2 months was 9.14 ± 0.637 and Total increase in Hb was 1.11 ± 0.22. There was no significant difference between the two groups Lactoferrin group and ferrous group as regard Hb at enrolment while there was highly significant difference between the two groups as regard Hb after treatment and in total increase in Hb.

As well, El-Nasr et al., (23) they revealed that in Group 1: Included 150 pregnant women received oral ferrous sulphate, Hb (g/dL) (Mean ±SD) at Basal was 8.79±0.86, after 1m was 9.42±0.87, after 2M was 10.02±0.91 and Total increase of Hb level was 2.25±0.80. In Group 2: Included 150 pregnant women received oral combined lactoferrin and ferrous sulphate, Hb (g/dL) (Mean ±SD) at Basal was 8.84±0.85, after 1m was 9.82±0.84, after 2M was 10.78±0.84 and Total increase of Hb level was 3.87±0.91. There was no significant difference between the two groups as regard Hb at basal measurement while there was highly significant difference between the two groups as regard Hb after treatment and in total increase in Hb.

Moreover, Balsha et al., (24) they demonstrated that in Lactoferrin (N=95) group, Hb (g/dL) (Mean ±SD) at basal was 9.4±0.9 with range of 7.2–10.9, after treatment was 10.9±1.0 with range of 8.8–13.5 and the elevation in Hb was 1.5±0.5 with range of 0.3–2.7. While in Ferrous sulphate (N=93) group, Hb (g/dL) (Mean ±SD) at basal was 9.5±0.8 with range of 7.1–10.8, after treatment was 10.3±0.8 with range of 7.9–12.3 and the elevation in Hb was 0.8±0.4 with range of 0.2–1.7. There was no significant difference in Hb level at basal measurement between the two groups while the change in hemoglobin level after treatment; there was a significant difference between the two groups, being higher in the lactoferrin group.

In our results, as regard the results of a mixed design ANOVA for hematocrit levels between the two groups of patients, there was no significant difference in hematocrit levels between the two groups before or after the treatments, but group B had a significant increase in hematocrit from pre to post treatment.

In consistent with our results, Bayoumy et al., (21) they found that as regard basal laboratory findings in Lactoferrin (N=70) group, HCT (%); Mean ±SD was 28.5±2.2 ranged from 22.6 to 34.0. While in Ferrous sulphate (N=70), HCT (%); Mean ±SD was 28.1±2.7 ranged from 21.3 to 34.3 these values indicated that there was no significant difference as regard HCT (%) between the two groups.

Also, El-Nasr et al., (23) they revealed that in Group 1: Included 150 pregnant women received oral ferrous sulphate, HCT (Mean ±SD) at basal was 29.39±2.27, after 1m was 31.42±2.40, after 2M was 33.09±2.53 and Total increase of HCT level was 5.66±1.68. In Group 2: Included 150 pregnant women received oral combined lactoferrin and ferrous sulphate, HCT (Mean ±SD) at basal was 28.99±1.87, after 1m was 32.23±1.85, after 2M was 34.94±1.73 and Total increase of HCT level was 8.31±2.01. There was no significant difference between the two groups as regard HCT at basal measurement while there was highly significant difference between the two groups as regard HCT after treatment and in total increase in HCT.

In our findings, as regard the results of a mixed design ANOVA for mean corpuscular volume (MCV) levels between the two groups of patients, there was a significant difference in MCV levels between the two groups after the treatments, with group A having a higher MCV than group B. Our results also showed that both groups had a significant increase in MCV levels from pre to post treatment, indicating that the treatments affected the red blood cell size in both groups.

In supporting our results, Bayoumy et al., (21) they found that as regard basal laboratory findings in Lactoferrin (N=70) group, MCV; Mean ±SD was 72.1±6.5 ranged from 54.6 to 88.6. While in Ferrous sulphate (N=70),

MCV; Mean ±SD was 71.1±5.6 ranged from 54.0 to 82.0. There was no significant difference as regard MCV between the two groups.

Also, El-Nasr et al., (23) they revealed that in Group 1: Included 150 pregnant women received oral ferrous sulphate, MCV (Mean ±SD) at basal was 69.36±2.46, after 1m was 71.78±2.60, after 2M was 73.59±2.67 and Total increase of MCV was 6.34±1.3. In Group 2: Included 150 pregnant women received oral combined lactoferrin and ferrous sulphate, MCV (Mean ±SD) at basal was 68.84±2.095, after 1m was 72.44±2.05, after 2M was 75.27±2.09 and Total increase of MCV was 9.87±2.03. There was no significant difference between the two groups as regard MCV at basal measurement while there was highly significant difference between the two groups as regard MCV after treatment and in total increase in MCV.

In our findings, as regard the results of a mixed design ANOVA for mean corpuscular hemoglobin (MCH) levels among the two groups of patients, there was a significant difference in MCH levels between the two groups after the treatments, with group A having higher MCH than group B. In addition, we revealed that both groups had significant changes in MCH levels from pre to post, with group A increasing and group B decreasing their MCH.

In agreement with our results, Bayoumy et al., (21) they found that as regard basal laboratory findings in Lactoferrin (N=70) group, MCHC; Mean ±SD was 23.3±2.8 ranged from 17.6 to 30.4. While in Ferrous sulphate (N=70), MCHC; Mean ±SD was 23.5±2.8 ranged from 18.0 to 32.1. There was no significant difference as regard MCHC between the two groups.

In the present study, as regard the results of a mixed design ANOVA for ferritin levels between the two groups of patients. We demonstrated that both groups had a significant increase in ferritin levels after the treatments, but group B had a much higher increase than group A. We also found that there was no significant difference in ferritin levels between the two groups before the treatments, but there was a significant difference after the treatments, with group B having higher levels than group A.

In consistent with our results, Bayoumy et al., (21) they found that as regard basal laboratory findings in Lactoferrin (N=70) group, Serum ferritin; Mean ±SD was 10.8±3.3 ranged from 4.0 to 23.0. While in Ferrous sulphate (N=70), Serum ferritin; Mean ±SD was 10.7±3.2 ranged from 4.0 to 17.0. There was no significant difference as regard Serum ferritin between the two groups.

Also, El-Nasr et al., (23) they reported that in Group 1: Included 150 pregnant women received oral ferrous sulphate, Serum ferritin level (ng/mL) Mean ±SD was 136.65±4.02. while in Group 2: Included 150 pregnant women received oral combined lactoferrin and ferrous sulphate, Serum ferritin level (ng/mL) Mean ±SD was 161.87±30.34. Therefore serum ferritin level was significantly increased with combined ferrous sulphate and lactoferrin group than ferrous sulphate alone.

As well, Balsha et al., (24) they revealed that in Lactoferrin (N=95) group, Serum ferritin (ng/dL) (Mean ±SD) at basal was 9.2±1.3 with range of 6.5–11.9, after treatment was 13.7±1.4 with range of 10.1–17.3 and the elevation in Serum ferritin was 4.5±0.5 with range of 3.3–5.7. While in Ferrous sulphate (N=93) group, Serum ferritin (ng/dL) (Mean ±SD) at basal was 9.3±1.2 with range of 6.5–11.9, after treatment was 10.6±1.2 with range of 7.6–14.0 and the elevation in Serum ferritin was 1.3±0.5 with range of 0.6–2.4. There was no significant difference in Serum ferritin level at basal measurement between the two groups while the change in serum ferritin level after treatment; there was a significant difference between the two groups, being higher in the lactoferrin group.

CONCLUSION

In our study we compared between lactoferrin with ferrous gluconate versus ferrous gluconate in treatment of iron deficiency anemia during pregnancy. Accordingly, we found that Oral lactoferrin with ferrous gluconate is better tolerated with higher increase in mean hemoglobin and lower side effects (nausea) when compared to oral iron therapy alone.

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Role of Administration of Sublingual Misoprostol Before Open Myomectomy

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Abstract

Background: Uterine fibroids are considered the most prevalent benign tumors in women. open myomectomy is the conventional management for large or numerous fibroids. However, hemorrhage is one of the most prevalent consequences in open myomectomy cases. Misoprostol, an analog of prostaglandin E1, is widely used in obstetrics and is capable of increasing uterine contraction and decreasing hemorrhage. Our aim was to assess the impact of sublingual intake of Misoprostol before myomectomy to minimize blood loss during surgery.

Methods: A randomized controlled clinical trial was conducted on 150 women within their reproductive age with symptomatic fibroids who are planned for open myomectomy. They were randomized into "study" and "control" groups to receive either one dose of Misoprostol sublingually (400 mcg) or placebo before myomectomy. The operative time, intraoperative blood loss and the effect of blood loss on hematocrit and hemoglobin levels were assessed.

Results: The operative time among the Misoprostol group was significantly shorter than the placebo group (58.80±4.51 vs 71.08±10.62 minutes,$p<0.001$). Additionally, the blood loss in the suction apparatus and the total blood losses among the Misoprostol group were significantly reduced compared to the control group (279.16±44.61 vs 340.55±66.71 ml , $p<0.001$).

Conclusion: A sublingual dose of Misoprostol (400 mcg) one hour before surgery significantly reduces the intraoperative blood loss and the operation time during myomectomy.

Keywords: Myomectomy; Misoprostol; Blood loss.

INTRODUCTION

Uterine fibroids, "leiomyomas" or "myomas", are the most prevelant benign uterine tumors, occurring in >70% of women (1). Fibroids consist of smooth muscle, fibroblasts, and a significant quantity of fibrous extracellular matrix, all contributing to the pathogenetic process (2).

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In 20–50 % of affected cases, uterine fibroids are asymptomatic. The most prevalent symptom reported by women with fibroids is heavy menstrual bleeding; however, other gynecological symptoms include pelvic pressure and discomfort, extended menstrual bleeding, and bleeding outside of menstrual cycles. Anemia could be developed due to excessive bleeding. Increased frequency, incontinence, and hesitation are among the urinary symptoms that may be associated with fibroids (3).

It could be diagnosed clinically by recognizing a solid, multilobular uterus or solid, palpable lumps protruding from the uterus (1). However, transvaginal ultrasonography achieves higher sensitivity (90%) and specificity (87%) for diagnosis, which increased up to 100% and 98%, respectively, with adding sonohysterography (4).

Myomectomy on laparotomy or "open myomectomy" has been the conventional form of conservative surgical management for large uterine myomas in women who wish to preserve their uterus or fertility. Indeed, it has been the only conservative surgical option for treating fibroids until the development of laparoscopic and hysteroscopic techniques (5,6).

Blood loss associated with myomectomy is the most frequent adverse consequence. The need for blood transfusion ranges between 4 and 20% of myomectomy patients. To prevent blood loss during open myomectomies, several techniques have been developed, including ligating the uterine arteries temporarily, infiltrating vasopressin inside the myomas, applying Misoprostol or dinoprostone intravaginally, using pro-fibrin/thrombin agents, or using tourniquet around the cervix or infundibulopelvic ligaments (7).

Misoprostol is a prostaglandin E1 analog. It is widely used in obstetrics for cervical ripening, induction of labor, management of postpartum hemorrhage and termination of second-trimester pregnancies. Misoprostol is capable of increasing uterine contraction and decreasing hemorrhage (8,9). Recently, it has been tested in randomized controlled studies to reduce blood loss during myomectomy. Therefore, we conducted our study to assess the role of sublingual intake of Misoprostol before myomectomy in reducing blood loss during surgery.

METHODS

A randomized controlled clinical trial was conducted in the Obstetrics and Gynecology Department at Kasr El Aini Hospitals, Cairo University and the Obstetrics and Gynecology Department at EL-Menshawy General Hospital. It included 150 women at reproductive age with symptomatic fibroids who are planned for open myomectomy. The Research Ethics Committee (REC), Faculty of Medicine, Cairo University has approved this study under registration number (MS-70-2022). The included women had signed written informed consent before participating in the study after being informed of its purpose. All participants had the right to withdraw from the study without being adversely impacted regarding the medical care they should receive.

The inclusion criteria were women within their reproductive age with symptomatic fibroids and planned for open myomectomy. Women were excluded in case of age younger than 20 years, history of previous pelvic or abdominal surgery excluding cesarean section, bleeding or coagulation disorders, allergy to Misoprostol, medical disorders such as hypertension, diabetes, cardiac or pulmonary diseases, liver diseases or ischemic heart disease, and anemia (Hemoglobin [Hb] < 8 g/dL).

The participants were randomized to receive either a single dose of sublingual Misoprostol (400 mcg) or placebo using identical sealed envelopes prepared by the investigator. After enrollment, each participant was allowed to choose one envelope to determine the assigned group.

All women were subjected to detailed medical history and clinical examination to ensure adherence to inclusion criteria. On the day of the operation, the medication, either a single dose of sublingual Misoprostol (400 mcg) or placebo, was given one hour before the procedure. The primary outcome is to assess the role of receiving a single dose of sublingual Misoprostol (400 mcg) one hour before open myomectomy in reducing the estimated intraoperative blood loss.

We estimated the intraoperative blood loss by measuring the blood volume in the suction machine reservoir and calculating the weight difference of the surgical swabs. The difference of the surgical swabs (in grams) was translated to ml by using the blood density formula (1.050g/ml). To assess the impact of blood loss on hematocrit (Hct) and Hb levels, the patient's Hct and Hb were measured preoperatively and 24 hours postoperatively.

Sample size: Sample size was calculated by comparing intraoperative total blood loss between women undergoing myomectomy treated with sublingual Misoprostol or placebo. As reported in a previous publication by Alhalaby (2021), the mean±SD of total intraoperative blood loss in the Misoprostol group was 308±33 ml, while in the control group, it was 404.4±49.1 ml (10). Accordingly, the proper sample size was 75 women in each group to detect a real difference in blood loss of 30 ml with 95% power and α error of 0.05 using Student's t-test for independent samples. The sample size was calculated using "PS: Power and Sample Size Calculation" software, version 3.0.11 for Microsoft Windows "William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA".

Statistical methods: Data was analyzed using the statistical package for the Social Sciences (SPSS) version 25 "IBM Corp., Armonk, NY, USA". Numerical data were presented in mean ± standard deviation or median and range. Categorical data were presented in frequencies and percentages. P-values < 0.05 were considered statistically significant.

RESULTS

Our study included two groups of patients; the "Control Group" included 75 women who underwent myomectomy without pre-operative intake of sublingual Misoprostol, and the "Study Group" included 75 women who had sublingual Misoprostol given prior to myomectomy. Demographic characteristics of all participants in both groups showed no statistically significant differences "Table 1".

The pre-operative assessment showed no statistically significant differences between both groups regarding the following parameters: the number of myomas (P=0.080), the size of the largest myoma (P=0.373), the site of myoma whether intramural, subserous, or both (P=0.080), pre-operative Hct levels (P=0.121). However, pre-operative Hb levels were significantly higher among the placebo group than the Misoprostol group (p<0.001) "Table 2".

Regarding intra-operative assessment, the operative time was significantly shorter among the Misoprostol group than the placebo group (58.80±4.51 vs 71.08±10.62 minutes,p<0.001). In addition, the blood loss in suction and the total blood losses were significantly higher among the placebo group than the Misoprostol group (340.55±66.71 Vs 279.16±44.61 ml ,p<0.001 for suction and 483.21±76.06 Vs 420.39±53.49 ml, p<0.001 for total blood losses).

However, the weight of the surgical swabs showed no statistically significant differences between both groups "Table 3".

The post-operative assessment showed no significant difference between both groups regarding post-operative Hb level (P=0.601). However, the Hb deficit was significantly higher among the control group than the study group (1.30±0.59 Vs 0.45±0.36 g/dL p<0.001). Post-operative Hct percent was significantly higher among the study

group than the control group (p=0.028).The percentage of Hct deficit was significantly higher among the control group than the study group (2.27±1.15 Vs 0.49±0.33 p<0.001) "Table 4".

DISCUSSION

Uterine fibroids are considered the most prevalent benign tumors in women. Typically, they are asymptomatic; however, 20-50% of afflicted patients develop symptoms such as menorrhagia, pelvic discomfort or pressure, or urinary problems (11,12). In women who want to keep their fertility, open myomectomy is the conventional management for large or numerous fibroids. However, hemorrhage is one of the most prevalent consequences in open myomectomy cases (13).

As few studies evaluated the role of Misoprostol in reducing blood loss during myomectomy, we conducted this study to assess the impact of sublingual Misoprostol on reducing blood loss and the operation time during open myomectomy. This study is a randomized controlled clinical trial on 150 women who underwent open myomectomy and randomly received either a single dose of sublingual 400 mcg Misoprostol (75 patients) or placebo (75 patients). We found that a single sublingual 400 mcg dose of Misoprostol one hour before myomectomy significantly reduces blood loss and operation time.

In agreement with the current study, Alhalaby et al. (2021) performed a study on 50 Egyptian women to assess the impact of receiving a single dose of vaginal Misoprostol preoperatively. They reported that the blood loss in the Misoprostol group was less than in the placebo group (308±32.66 vs. 404.4±87; P<0.001). In addition, the Misoprostol group showed a shorter operative time than the control group (56.8±3.12 vs. 78.6±10.6; P<0.001). The post-operative Hb and Hct levels were lower among the placebo group when compared to Misoprostol. Hb and Hct deficits were significantly higher among the placebo group than the Misoprostol group (10).

The beneficial effect of Misoprostol was also evaluated by two randomized controlled studies: Ragab et al. (2014), who studied the effect of the intra-vaginal administration and Abbas et al. (2019), who studied the effect of the sublingual administration. In both studies, it was observed that the larger dose of Misoprostol decreased blood loss and operative time much more than the lesser dose, with no rise in post-surgical fever, concluding that higher doses of Misoprostol (400 mcg twice, 1 and 3 hours before surgery) were more beneficial (14,15).

In a recent study by Sharami et al. (2020), Hb and Hct were evaluated 4 and 24 hours after myomectomy in the study and placebo groups. They also assessed the amount of blood loss, duration of operation, complications, and need for transfusion or hysterectomy. The study revealed that receiving a rectal dose of 400 mcg of Misoprostol before the operation significantly reduces blood loss (P<0.001). However, it did not affect the operative time, incidence of complications, need for transfusion or hysterectomy, or post-operative Hb and Hct levels at 4 and 24 hours after surgery (P>0.05) (16).

Mohamed et al. (2019) studied 94 randomly enrolled female candidates for myomectomy. The study group received a dose of Misoprostol (400 mcg) rectally one hour before surgery. The blood loss during surgery was significantly lower in women who received rectal Misoprostol than in the placebo group (460.8±155.2 mL vs. 815.4±187.7 mL). Additionally, the Misoprostol group showed a significantly higher post-operative Hb and Hct and a significantly shorter operative time. There was no significant difference between groups regarding the need for blood transfusion (17).

Abdel-Hafeez et al. (2015) also came in concordance with the current study. In their randomized trial, intra-operative blood loss was significantly lower in women receiving

rectal Misoprostol than in the control group (574±194.8 mL vs. 874±171.5 mL). Additionally, the deficit in post-operative Hb was significantly lower in the Misoprostol group than in the control group (1.7±0.4 g/dL vs. 2.1±0.5 g/dL). Abdel-Hafeez et al.also found that operation time in the Misoprostol group was 76.8±15.8 minutes compared to 94.8±22.8 minutes in the placebo group (18).

Niroomand et al. (2015) also assessed intraoperative blood loss, the post-operative need for blood transfusion, and the pre-operative and post-operative Hb levels. His results revealed that the mean pre-operative and post-operative Hb levels were not significantly different between the Misoprostol and the placebo groups. However, the mean operative time and estimated blood loss were significantly higher in the placebo group. In addition, about 9 patients (22.5 %) in the placebo group needed a blood transfusion, while there was no need for a blood transfusion in the Misoprostol group (P=0.001) (19).

Another study by Vahdat et al. (2015) confirmed the efficacy of sublingual Misoprostol during abdominal myomectomy. Post-operative Hb level (6 hours after surgery) was significantly higher in the Misoprostol group (9.8±0.8 vs. 9.1±0.9, P=0.003), while the Hb level after 24 hours showed no significant difference between both groups (10.50±0.56 vs. 10.24±0.58, P=0.066). Additionally, no significant difference was found between both groups regarding anemia and the need for blood transfusion after surgery (20).

Wali et al. (2021) performed a meta-analysis (including eight studies) about using Misoprostol for open myomectomy. They concluded that using Misoprostol prior to surgery was significantly linked to a reduction in blood loss, a decrease in Hb drop, a decrease in the need for blood transfusion, and a reduction in operating time. The duration of the post-operative stay and post-operative pyrexia did not differ (21).

Contrary to the current study, Wetherell et al. (2022) conducted a similar study in Australia on two randomized groups to receive Misoprostol. Both groups were matched in age and uterine fibroid criteria regarding number and size. Wetherell et al. reported no significant difference between Misoprostol and placebo regarding total blood loss (306 ml±281 ml vs. 325±352 ml; P=0.83) (22). However, these results could be attributed to the fact that this study was exploratory and was performed on a much lower sample size.

Finally, the role of Misoprostol intake before myomectomy in reducing blood loss during surgery could be attributed to the decrease in the vascularity and perfusion of uterine myomas. Khalaf et al. (2020) depended on uterine Doppler to evaluate the effect of Misoprostol, and they found that Misoprostol significantly decreases the vascularity and perfusion of uterine fibroids whether administered rectally or sublingually one hour before open myomectomy (23).

CONCLUSION

Our study revealed that a single dose of Misoprostol (400 mcg) sublingually one hour before the operation is significantly effective in reducing blood loss and operation time during myomectomy. No study has yet been conducted to prove the best route for Misoprostol administration before abdominal myomectomy; therefore, we recommend further studies comparing the different routes of Misoprostol administration.

DECLARATIONS

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

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

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Table 1: Demographic characteristics of all participants

	Control Group "n=75"	Study Group "n=75"	P-value
Age (years)	34.40±4.72 34 (25 - 44)	33.45±4.83 33 (25 - 45)	0.227
Parity	1.55±0.81 1 (0 - 3)	1.65±1.05 2 (0 - 4)	0.486
Previous Cesarean section	1 (0 - 3)	1 (0 - 4)	0.738
Previous normal delivery	0 (0 - 3)	0 (0 - 3)	0.583
Number of abortions	1 (0 - 4)	1 (0 - 4)	0.939

Table 2: Pre-operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Number of myomas	1.73±0.78 2 (1 - 4)	1.97±0.88 2 (1 - 4)	0.080
Size of largest myoma (cm)	6.76±0.66 6.7 (5.6 - 8.3)	6.65±0.84 6.5 (5.4 - 8.4)	0.373
Type of fibroids **- Intramural** **- Subserous** **- Both**	 54 (72 %) 7 (9.33 %) 14 (18.67 %)	 45 (60 %) 12 (16 %) 18 (24 %)	0.268
Pre-operative hemoglobin (g/dL)	11.80±1.14 11.8 (9.4 - 13.8)	11.05±1.17 10.9 (9.2 - 14)	<0.001
Pre-operative Hematocrit (%)	41.18±2.80 41.6 (34 - 45.7)	40.43±3.12 40.4 (33 - 45.6)	0.122

Table 3: Operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Operation time (minutes)	71.08±10.62 70 (54 - 91)	58.80±4.51 59 (50 - 68)	<0.001
Blood loss in suction (mL)	340.55±66.71 330 (210 - 510)	279.16±44.61 280 (210 - 380)	<0.001
Weight difference of swabs (gm)	149.80±19.40 142 (137 - 212)	148.29±24.93 137 (132 - 207)	0.680
Total blood loss (mL)	483.21±76.06 475 (350 -712)	420.39±53.49 417 (336 - 577)	<0.001

Table 4: Post-operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Post-operative hemoglobin (g/dL)	10.50±1.15 10.6 (8 - 12.6)	10.60±1.22 10.3 (8.7 - 13.5)	0.601
Hemoglobin difference (g/dL)	1.30±0.59 1.3 (0.4 - 5.2)	0.45±0.36 0.4 (-2.1 - 1.1)	<0.001
Post-operative Hematocrit (%)	38.91±2.34 39.2 (32.4 - 42.8)	39.93±3.11 40 (32.3 - 45.1)	<0.001
Hematocrit difference (%)	2.27±1.15 2.4 (-5.7 - 3.9)	0.49±0.33 0.5 (-1.3 - 1.6)	<0.001

Assessment of Primary Cesarean Section Incision Site Early in The Purpureum to Predict Subsequent Consequences.

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Short running title:

Assessment of Cesarean Section scar defect

Conflict of interest Statement:

Declarations of interest none

Abstract

Aim: To assess primary cesarean scar after 6 weeks post-delivery to describe its characteristics using two-dimensional transvaginal ultrasound.

Methods: This cross-sectional study was performed at Mansoura University Hospitals, Mansoura, Egypt from the beginning of March 2020 to March 2021. Eighty women underwent primary cesarean section fulfilled the inclusion criteria were examined by TVUS to evaluate cesarean scar after 6 weeks from delivery. The main outcome was measurement of residual myometrial thickness (RMT), while the secondary outcome was niche measurement (depth, width, site, shape).

Results: The mean age of included cases was 24.63 ± 6.23 years. The mean GA at delivery was 37.21 ± 2.50 weeks. The cephalic presentation was predominant in 68.75% of females. Maternal indications for CS were reported in 50% of females, fetal indications in 46.3%, while unreliable indications were shown in 3.7%. The mean niche depth was 1.16 ± 0.46 cm. The mean niche width was 1.48 ± 1.17 cm. The mean site (From incision to internal os) was 0.21 ± 0.43 cm. The mean RMT was 0.84 ± 0.55 cm. The mean RMT-OS was 1.8 ± 1.82 cm. Triangular shape of niche was the most common shape in 72.5% of females. Circular shape of niche was detected in 17.5 % of females, both oval shape and polygonal shape were 5 %, each. No significant differences were observed between level of experience of main surgeon, closure of visceral or parietal peritoneum & state of labor and RMT. Also, no significant difference was found between level of experience of main surgeon and site & shape of niche.

Conclusion: Caesarean section scar in women after 6 weeks from primary CS assessed by using 2D-TVUS was not affected by the site of CS incision, surgeon's experience, visceral or parietal peritoneum closure and labor stage at the time of CS.

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Introduction

In most countries, the most common obstetric procedure is the cesarean section (CS), which is becoming more and more popular. This procedure could result in late scar dehiscence, which could cause uterine rupture in a later pregnancy. Serious complications like as wound dehiscence and wound evisceration are linked to maternal death rates of 12 and 30 percent, respectively [1]. The approximately 60% population-based percentage of CS conducted in Egypt in 2014 significantly surpasses the WHO-recommended threshold of 10-15% [2]. Despite the fact that the observed increase in Egypt's CS rate over time is consistent with findings from other national and international research, this increase positions Egypt as the nation with the highest CS done globally [3]. A number of studies have been conducted with varying degrees of success to assess the relationship between the measurement of the lower uterine segment (LUS) and the risk of uterine rupture or dehiscence [4, 5]. The cesarean scar defect (CSD) (also known as niche or isthmocele) is the most frequent issue following cesarean delivery (CD); it has been referred to by several names in the literature, including pouch, niche, and isthmocoele. It is described as a triangular-shaped area of myometrial thinning or uterine scar dehiscence that continues into the endometrial cavity [6]. If the TVUS evaluation shows that RMT is less than 2.2 mm, or if the incision depth is at least 50 or 80% of the anterior myometrium, the CSD is deemed severe [7].

The incidence of a severe complication, such as uterine rupture during a subsequent pregnancy, is only 2%, but if the CSD is deemed severe, this percent can rise to 5% [8]. The frequency of CS scar abnormalities ranges from 24–70% in a routine ultrasonography evaluation of a non-pregnant uterus in women with a history of at least one CS. Owing to the overall number of CS cases and the frequency of CS scar abnormalities, this is a medical issue that primarily affects women [9]. It was discovered that two-dimensional transvaginal ultrasonography (2D-TVUS) was a reliable technique for measuring scar thickness. Additionally, it was discovered that colored Doppler was helpful in determining the scar's vascularity [10]. The LUS is seen on ultrasound as a two-layered structure made up of the comparatively hypoechoic myometrial layer and the echogenic visceral-parietal reflection, which extends from the bladder's interior inward and includes the bladder's musculosa and mucosa (the outer layer) [11].

Patients and Methods

This a cross-sectional study was conducted from March 2020 to March 2021 in Obstetrics and Gynecology department in Mansoura University Hospitals, Mansoura, Egypt. The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. MS.20.03.1085) and conducted according to the ethical standards of Declaration of Helsinki. During the study period, we examined 80 women underwent primary CS by 2D-TVUS to evaluate CS scar after 6 weeks to describe its characteristics and to evaluate impact on the subsequent events. All participants were interviewed, received sufficient information about the protocol of the study, and then counseled to be enrolled.

The main inclusion criteria were women underwent primary CS done for either maternal indications as: obstructed labor, failure to progress and medical disorders or fetal indications as malpresentation, multiple pregnancy, fetal distress, fetal anomalies and neonatal weight >3500 grams. Immunocompromised patients (chronic diseases, autoimmune conditions as (lupus, rheumatoid arthritis), asthma, extended use of biologics, disease-modifying antirheumatic

medications, and corticosteroids, active treatment for solid tumor and hematologic malignancies), patients with bleeding diathesis (inherited as hemophilia & Von Willebrand disease or acquired as thrombocytopenia & kidney failure), patients with Hb level< 10gm / dl and patients who had infection (if +ve C-reactive protein, chorioamnionitis, long period of premature rupture of membrane, fever) were excluded. Every patient who was enrolled in the study gave their informed consent and was given the option to leave the study at any time for any reason. All participants were submitted to complete history taking, obstetric history, medical history, previous surgical procedure, caesarean section indications (maternal or fetal). Recording of state of labour (in labour or not in labour), early CS complications and operative details as: (dissection peritoneal reflection, uterine incision, closure, blood loss, pre- and post-operative hemoglobin & hematcrit). Data were collected from medical records and recorded in the intraoperative sheet. In addition, ultrasonographic assessment of niche (site, width, shape), residual myometrial thickness (RMT), RMT-OS, distance proximal & distal to incision, uterine and cervical length & width.

Ultrasound examination was done at 6 weeks after the cesarean delivery using LOGIQ F6 ultrasound machine, (General Electric Medical Systems, China) with a 7 MHz transvaginal 2D probe by the candidate. For the diagnosis of CS defect (niche) we depended on the definition of the presence of defect at least 2 mm in depth. CS defect was considered large when the depth of the defect was more than 50% total myometrial thickness.

Women with half-empty bladder lied in a lithotomy position during the examination. Then, complete visualization of the uterus in sagittal plane. To locate the potential niche and CS scar, LUS was closely inspected. We measured the distance between CS scar and cervical internal os. Also, the uterine position whether ante-flexed or retro-flexed was documented. When a niche was found, in the midsagittal plane; RMT measured from the serosa covering the uterus to the niche apex, depth (D), distance from niche apex to the base of the niche and width (W) measured in the widest diameter of the hypoechoic area of niche base was measured. We excluded intrauterine device and the endometrium from the niche measurements (figure, 1). In women without a scar defect, RMT was measured from the endometrial boundary to the serosal surface at the level of the CS scar [12]. The thinnest RMT in the sagittal plane should typically be found, while it can also be found farther laterally.

Statistical analysis and data interpretation

Sample size was calculated by the use of G*power version 3.0.10 to depending on pregnancy outcome of pregnancy scar taking birth weight as the primary outcome, sample size of 80 patients was needed with effect size (0.47) retrieved from previous research [7], with error =0.05 and power = 80.0%.

We using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) after revision of data. Paired samples t-test, Chi-Square test, Monte Carlo test, Kruskal Wallis, Fisher's exact test were used and P value <0.05 was set significant.

Results

The mean age of the studied females was 24.63 ± 6.23 years. The mean gestational age at delivery was 37.21 ± 2.5 weeks. The cephalic presentation was predominant in 68.75% of females followed by breech presentation (20%) and 11.25% had multiple pregnancies. The median number of gravidities, parities, abortions was 1, 2 & 1, respectively. There is 1.3% of females with previous still birth. Hypertension (HTN) was the most common reported

associated medical condition in 20% of cases followed by preeclampsia (7.5%) then diabetes mellitus (DM) and deep vein thrombosis (DVT) in 2.5%, each. Bronchial asthma (BA), hepatitis C virus (HCV), hyperthyroidism and mitral valve replacement & aortic regurgitation (MVR + AR) were shown in 1.3% for each of them. Manual vacuum aspiration (MVA) was conducted in 3.8 % of females, ovarian cystectomy in 2.5 % and hysteroscope & myomectomy in 1.3% of cases for each of them, table (1).

Maternal indications for CS were reported in 50% of females, fetal indications in 46.3%, while unreliable indications were shown in 3.7%. There were 22.5% of females in labor upon examination, table (2). The lower segment CS was performed in 96.3% of females as stated by the surgeons while as noticed by the observer, lower segment CS was performed in 75% of females. In addition, upper segment CS was performed in 3.8% of females as stated by the surgeons, while the observer noticed that the upper segment CS was performed in 25% of female. Dissection peritoneal reflection was performed in 27.5% of females. Transverse uterine incision and double layer closure were performed in all females except one. Extension of incision was performed in 1 female only. Peritoneal closure visceral was performed in 51.2% of females, while peritoneal closure parietal was performed in 65% of females, table (3).

Sparing endometrium during suturing was performed in 1 female only as decided by the surgeon and the observer. The only case which was closed by using single layer closure was 18 years old, pregnant ± 36 weeks, twin (cephalic-breech), patient was not in labour with closed cervix during CS. Level of experience of main surgeon > 3 years and there was agreement between main surgeon and observer about site of incision and transverse incision at lower segment. It was smooth caesarean with no intraoperative complications. Closure of both visceral and parietal peritoneum. The niche depth was 1.69 cm, niche width was 1.2 cm, site of niche (distance between niche and internal os was nearly zero), the shape was triangular. The RMT was 0.4 cm (figure, 2), the mean RMT-OS was 0.3 cm, the distance proximal incision was 1.7 cm, the distance distal incision was 1.9 cm, the distance incision uterovesical fold (UVF) of peritoneum was 1.27 cm, the length of uterus was 8.26 cm, the uterine width was 4.3 cm, the cervical length was 3 cm and the cervical width was 2 cm, table (3).

The mean amount of blood loss was 351.25 ± 76.30 ml. Complications were reported in 5% of cases. The mean preoperative and postoperative hemoglobin level were 11.28 ± 1.08 gm/dl and 10.96 ± 1.14 gm/dl, respectively. There was a decrease in the postoperative hemoglobin as compared to the preoperative values, but this decrease didn't achieve a statistically significant difference. The mean preoperative and postoperative hematocrit level were 35.13 ± 3.22 % and 34.41 ± 3.52 %, respectively. There was a decrease in the postoperative hematocrit as compared to the preoperative values, but this decrease didn't achieve a statistically significant difference, table (3).

The mean niche depth was 1.16 ± 0.46 cm. The mean niche width was 1.48 ± 1.17 cm. The mean site (From incision to internal os) was 0.21 ± 0.43 cm. The mean RMT was 0.84 ± 0.55 cm. The mean RMT-OS was 1.8 ± 1.82 cm. The mean distance proximal to incision was 1.97 ± 0.56 cm. The mean distance distal to incision was 1.9 ± 1.05 cm. The mean length of uterus was 8.43 ± 1.67 cm. The mean width of uterus was 4.88 ± 1.40 cm. The mean cervical length was 3.10 ± 0.47 cm. The mean of cervical width was 2.61 ± 0.41 cm. Triangular shape was more prevalent in 72.5% of females, circular shape (17.5 %), oval shape and polygonal shape were detected in 5 %, each, table (4).

No significant difference between level of experience of main surgeon and RMT < 1 cm ($p = 0.123$), site of niche ($p = 0.163$) or shape of niche ($p = 0.198$) was observed, table (5).

No significant difference was observed between closure of visceral peritoneum and RMT ($p = 0.352$) or closure of parietal peritoneum and

RMT (p = 0.346). Additionally, no statistically significant difference was found between state of labour and RMT (p = 0.797). table (6).

Discussion

The existence of a uterine niche, which is defined as any uterine dimpling 2 mm or more at the cesarean scar site that could be observed by ultrasound, specially with increase of CS [13]. There is little data connecting the existence of CS scar abnormalities on US scan to the function of the uterus during a subsequent pregnancy, yet they may be clinically significant. It is crucial to distinguish between uterine scar dehiscence and a full rupture of the uterine wall. Whereas the former presents a significant risk to both the mother and the fetus, the latter is not linked to a significant risk for either [14].

We evaluated the scar 6 weeks after CS. At that point, the scar is always discernible. At 6 weeks postpartum, the uterus has not fully involute, and scar healing at the uterotomy incision is still in progress.

It has been reported that cesarean scar defect (CSD) presence does not change from 6 weeks to 1 year; however, the scar shape may change owing to maturation [15]. TVUS allowed the CS scar to be seen in all women. In 26.8% of the instances, a fully healed hysterotomy scar was found; in the other patients (73.2%), the scar niche (a hypoechoic triangle) was visible [16].

Previously, non-reassuring fetal heart rate tracings (NFHRT) (40%), labor arrest (31%), and maternal request (11%) are the three primary indicators for CS. In 10% of all CDs, multiple gestations and possible macrosomia were detected. Of the women with CS, only 1% had pre-eclampsia [17]. The most common reason for CS (59.5%) was found to be maternal illness and fetal problems; labor troubles came in second (27.8%). Gestational diabetes and gestational hypertension were examples of maternal diseases.

A transverse lower cut made on the uterine muscle is the most common technique for carrying out a CS [18]. Better healing of the uterine scar is suggested by the double-layer with unlocked first-layer omitting the decidua approach, which was linked to larger myometrium thickness overall, myometrium thickness remaining, and healing ratio [19]. Additionally, according to the conclusions of other scientists, this approach can potentially result in a decrease in severe obstetric issues related to scar tissue [20].

AbdelMooty et al. [21] showed that niche prevalence was 84% of participants. 71% had a triangular niche (which was in accordance to our findings), 26% a semicircular niche, and 3% a droplet niche.

The niche and RMT measurements in previous researches were different, for example, the median RMT was 8 mm, the median niche depth 7.2 mm, the median niche width was 10.4 mm according to Glavind et al. [22]. Moreover, the mean niche depth was 3.3 mm after double-layer closure [23]. The mean height and base of the niche in the primary CS group was 4.63 mm and 6.05 mm, respectively and the mean RMT was 8.16 mm [24]. The differences could be explained due to variations in sample size, different inclusion criteria (primary CS or repeated CS) and the timing of ultrasound assessment post-delivery.

In this study, we didn't find significant difference between level of experience of main surgeon and RMT, site of niche (from incision to internal os) or shape of the niche.

Similarly, in previous studies, no significant relationship between RMT and surgeon's experience (resident vs specialist) was observed [6, 25]. Other researchers came to the conclusion that surgical experience considered a risk factor for the creation of a niche, and that a surgeon with higher experience (a gynecologist as opposed to a trainee) may be more likely to develop a niche due to inadequate approximation and

tissue handling which was different from our results [26].

Our findings showed that no significant variance between closure of visceral & parietal peritoneum and RMT. In the literatures, the double-layer uterine closure is associated with a greater RMT and healing ratio, suggesting that this technique is associated with better uterine scar healing [18]. According to certain theories, the uterine niche's growth and the ensuing negative consequences connected to CS may be related to the uterine incision closure procedure [27]. It was suggested that the surgical have an impact on the RMT and uterine scar healing. Nevertheless, there isn't a recommendation supported by evidence for the closure procedure, and it is unclear which approach to use for uterine closure [28]. According to earlier research, double-layer closure had a thicker RM and a reduced incidence of major defects. But there is still no conclusive analysis about other clinical outcomes [29].

Earlier research evaluating the CS scar shape in connection to the stage of labor, cervical dilatation, and station of the presenting fetal portion was prognostic of the formation of large niches, with RMT $\leq$ 2.2 mm, which was dissimilar to our findings. It's interesting to note that as cervical dilatation increased, so did the proportion of women with huge niches. 50% of the women with large niches experienced cervical dilatation of more than 8 cm [30]. In addition, in other study, compared to women without cervical dilatation and women in the first stage of labor, the mean RMT value was considerably lower in women who had the CS performed in the second stage of labor [31]. RMT value was significantly lower in women who had the CS performed in the second stage of labor [32]. These variations could be a result of various study designs.

The authors can specify that the primary limitations of this study are limited number of samples and incorporating the instances from a single facility as the latter couldn't reflect the variation in the surgeon preferences. Also, the follow up at a single time point could decrease the power of the results. The study also is a single arm study which couldn't provide efficient comparison of the obtained results.

Conclusion

Caesarean section scar in women after 6 weeks from primary CS assessed by using 2D-TVUS was not impacted by the location of the incision, the experience of the surgeon, the closure of the visceral or parietal peritoneum, or the stage of labor at the time of the C-section.

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Tables' legend:

Table (1): Demographic and basic data in the study participants.

Variables		Study cases (n= 80)
Age (years)	Mean ± SD	24.63 ± 6.23
	Median (min-max)	23 (17 - 42)
GA (years)	Mean ± SD	37.21 ± 2.50
	Median (min-max)	38 (29 - 42)
Gravidities	Median (min-max)	1 (1 - 6)
Parities	Median (min-max)	2 (0 - 4)
Abortion	Median (min-max)	1 (0 - 4)
Still-birth	Median (min-max)	1
Presentation		**Number (%)**
Breech		16 (20%)
Cephalic		55 (68.75%)
Multiple pregnancy		9 (11.25%)
Medical history		
DM		2 (2.5%)
HTN		16 (20%)
Preeclampsia		6 (7.5%)
PPH		0 (0%)
BA		1(1.3%)
DVT		2 (2.5%)
HCV		1 (1.3%)
Hyperthyroidism		1 (1.3%)
MVR + AR		1 (1.3%)
Surgical history		
MVA		3 (3.8%)
Hysteroscope		1 (1.3%)
Myomectomy		1 (1.3%)
Ovarian cystectomy		2 (2.5%)

Cont inuous data expressed as mean ±SD and median (range). Categorical data expressed as Number (%).

NB: Preterm, Ectopic/VM and Early neonatal death were not reported in the cases.

Abbreviations: BA: Bronchial asthma; DM: Diabetes mellitus; DVT: Deep vein thrombosis; GA: Gestational age; HCV: Hepatitis C virus; HTN: Hypertension; PPH: Postpartum haemorrhage; MVA: Manual vacuum aspiration; MVR: Mitral valve replacement; AR: Aortic regurgitation.

Table (2): Indications for CS and state of labor in the study participants.

Variables	Study cases (n= 80) Number (%)
Indication for CS	
Maternal	40 (50%)
Fetal	37 (46.3%)
Unreliable indications	3 (3.7%)
Patient in labour	
No	62 (77.5%)
Yes	18 (22.5%)

Categorical data expressed as Number (%).

Abbreviations: CS: Cesarean section.

Table (3): Operative details of the study cases.

Variables	Study cases (n= 80) Number (%)
Incision by surgeon	
Lower segment	77 (96.3%)
Upper segment	3 (3.8%)
Incision noticed by observer	
Lower segment	60 (75%)
Upper segment	20 (25%)
Dissection peritoneal reflection	
No	58 (72.5%)
Yes	22 (27.5%)
Uterine incision	
Transverse	80 (100%)
Extension	
No	79 (98.8%)
Yes	1 (1.2%)
Closure	
Double	80 (100%)
Peritoneal closure visceral	
No	39 (48.8%)
Yes	41 (51.2%)

Peritoneal closure parietal			
No		28 (35%)	
Yes		52 (65%)	
First layer surgeon			
Full thickness		79 (98.8%)	
Spare endometrium		1 (1.2%)	
First layer observer			
Full thickness		79 (98.8%)	
Spare endometrium		1 (1.2%)	
Blood loss (ml)	Mean ± SD	351.25 ± 76.30	
	Median (min-max)	325 (250 - 550)	
Items	Preoperative (n= 80)	Postoperative (n= 80)	Test of significance
Hemoglobin (gm/dl)	11.28 ± 1.08	10.96 ± 1.14	t = 1.814 P= 0.176
Hematocrit (%)	35.13 ± 3.22	34.41 ± 3.52	t = 2.260 P= 0.082
Complications			
No		76 (95%)	
Yes		4 (5%)	

t: Paired samples t-test
Continuous data expressed as mean ±SD and median (range)
Categorical data expressed as Number (%)
NB 1: Complications were in form of uterine injury.

Table (4): Ultrasonographic data in the study cases.

Variables		Study cases n= 80
Niche depth (cm)	Mean ± SD	1.16 ± 0.46
	Median (min-max)	1.17 (0 – 2.3)
Niche width (cm)	Mean ± SD	1.48 ± 1.17
	Median (min-max)	1.21 (0.29 – 8)
Site (From incision to internal os) (cm)	Mean ± SD	0.21 ± 0.43
	Median (min-max)	0 (0 – 1.48)
RMT (cm)	Mean ± SD	0.84 ± 0.55
	Median (min-max)	0.76 (0 – 3.7)
RMT – OS (cm)	Mean ± SD	1.8 ± 1.82
	Median (min-max)	1.75 (0 – 12)
Distance proximal to incision (cm)	Mean ± SD	1.97 ± 0.56
	Median (min-max)	1.97 (0.71 – 3.31)
Distance distal to incision (cm)	Mean ± SD	1.9 ± 1.05
	Median (min-max)	1.7 (1.1 – 7.9)
Uterine length (cm)	Mean ± SD	8.43 ± 1.67
	Median (min-max)	8.65 (3.65 – 11.25)

Uterine width (cm)	Mean ± SD	4.88 ± 1.40
	Median (min-max)	4.57 (3.24 – 11.9)
Cervical length (cm)	Mean ± SD	3.10 ± 0.47
	Median (min-max)	3 (2.28 – 4.06)
Cervical width (cm)	Mean ± SD	2.61 ± 0.41
	Median (min-max)	2.58 (1.95 – 3.73)
	Number (%)	
Shape of niche		
Circular	14 (17.5%)	
Oval	4 (5%)	
Polygonal	4 (5%)	
Triangular	58 (72.5%)	

Continuous data expressed as mean ±SD and median (range).

Categorical data expressed as Number (%).

Abbreviations: RMT: Residual myometrial thickness measured from measured from the serosa covering the uterus to the niche apex.

Table (5): Relation between level of experience of main surgeon and RMT, site of niche (from incision to internal os) and shape of the niche.

Experience	**More than 1year** [N=16]	**More than 2 years** [N=39]	**More than 3 years** [N=19]	**More than 5 years** [N=6]	**Test of Sign.**
RMT					
RMT < 1 cm	11 (68.8%)	30 (76.9%)	18 (94.7%)	6 (100%)	MC = 5.773 P = 0.123
RMT ≥ 1 cm	5 (31.2%)	9 (23.1%)	1 (5.3%)	0 (0%)	
Site of niche (from incision to internal os)	0 (0 – 1.48)	0 (0 – 1.4)	0 (0 – 1.48)	0 (0 – 0.4)	KW = 5.126 P = 0.163
Shape of the niche					
Triangular	9 (56.3%)	30 (76.9%)	15 (78.9%)	44 (66.7%)	MC = 12.278 P = 0.198
Circular	2 (12.5%)	7 (17.9%)	3 (15.8%)	2 (33.3%)	
Oval	2 (12.5%)	1 (2.6%)	1 (5.3%)	0 (0%)	
Polygonal	3 (18.8%)	1 (2.6%)	0 (0%)	0 (0%)	

MC: Montecarlo test; KW: Kruskal Wallis: RMT: Residual myometrial thickness.

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

Note: Experience > 1 year: mid senior resident; > 2 years: senior resident; > 3 years: level of assistant lecturer; > 5 years: level of consultant.

Table (6): Relation between closure of peritoneum & state of labor with RMT.

Visceral peritoneum	**Not closed** [N=39]	**Closed** [N=41]	**Test of Sign.**
RMT < 1 cm	31 (79.5%)	34 (82.9%)	$\chi^2 = 0.203$ P = 0.352
RMT ≥ 1 cm	8 (20.5%)	7 (17.1%)	
Parietal peritoneum	**Not closed** [N=28]	**Closed** [N=52]	**Test of Sign.**
RMT < 1 cm	22 (78.6%)	43 (82.7%)	$\chi^2 = 0.212$ P = 0.346
RMT ≥ 1 cm	6 (21.4%)	9 (17.3%)	
RMT	**Not in labor** [N=62]	**In labor** [N=18]	**Test of Sign.**
RMT < 1 cm	50 (80.6%)	15 (83.3%)	FET = 0.066 P = 0.797
RMT ≥ 1 cm	12 (19.4%)	3 (16.7%)	

χ^2: Chi square test
FET: Fisher's exact test
RMT: Residual myometrial thickness

Figures' legend:

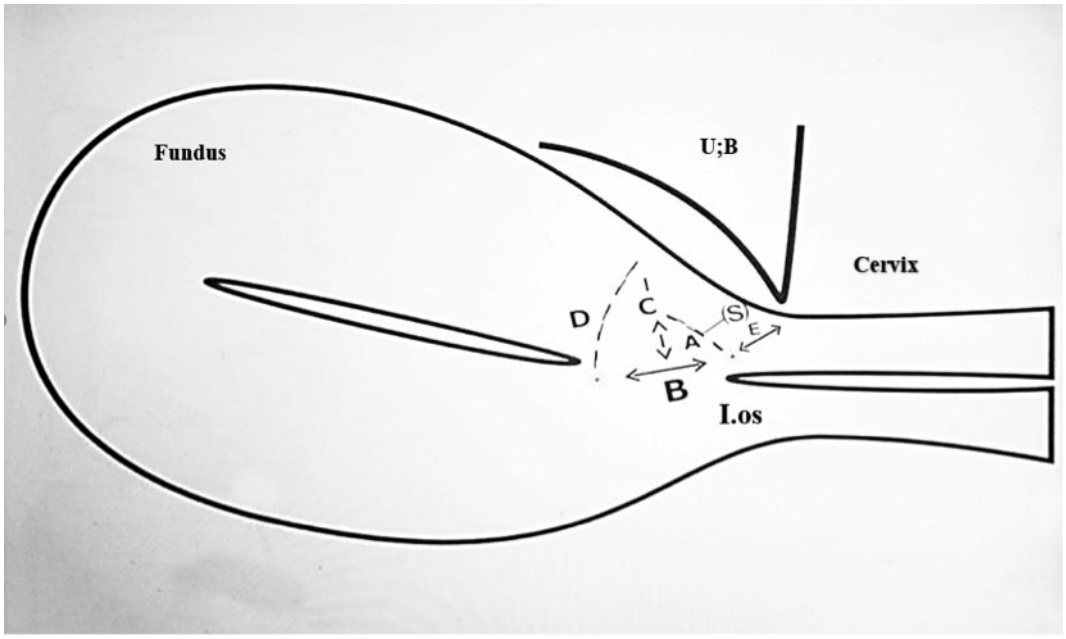

Figure (1): Transvaginal-2d- ultrasound six weeks post-partum

1- Niche (A) Depth (B) Width.
2- RMT(c) (Distance between RMT & I. OS).
3- Depth of myometrium proximal to incision (D).
4- Depth of myometrium distal to incision (S).
5- Distance between I. OS & UV fold of peritoneum (E).

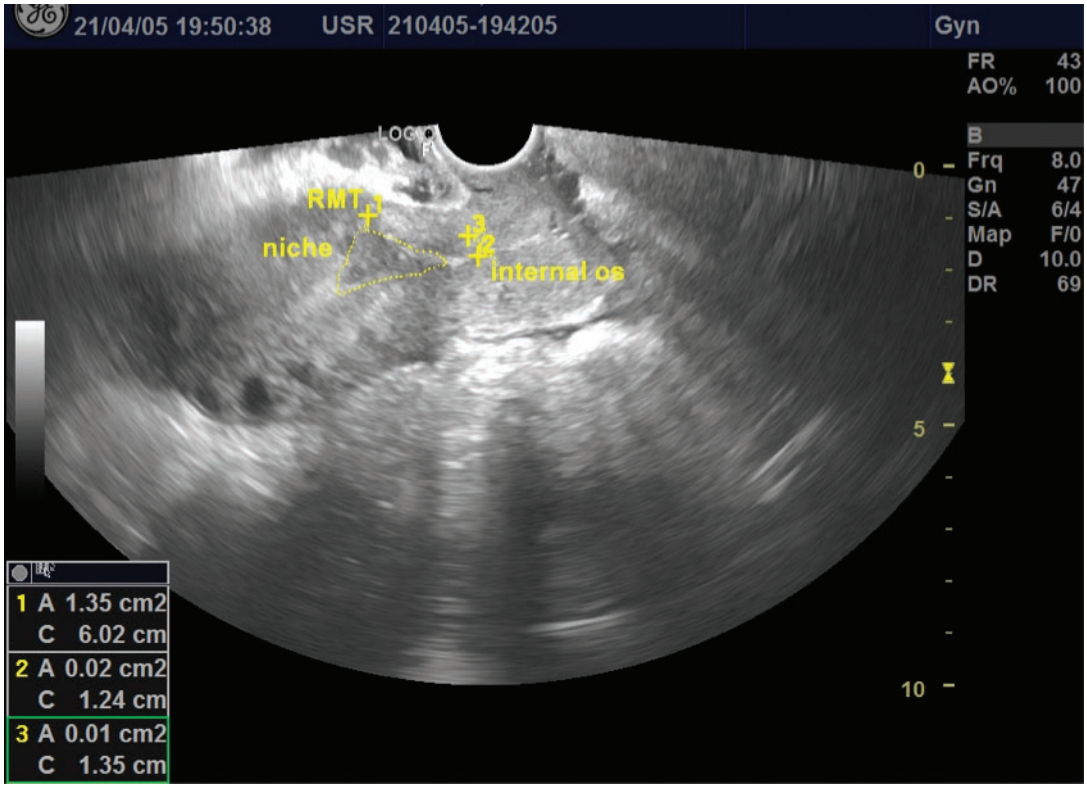

Figure (2): Triangular shaped niche at the level of internal os, AVF uterus 2D-TVUS in sagittal plane.

Value of Laparoscopy in Diagnosis of Endometriosis in Unexplained Infertility

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Abstract

The presence of endometrial tissue outside of the endometrium and myometrium is referred to as pelvic endometriosis. Deep infiltrative endometriosis is the presence of endometrial implants, fibrosis, and muscle hyperplasia that extend more than 5 millimetres into the peritoneum (DIE). The most precise treatment for assessing tubal pathologic abnormalities and other hidden intra-abdominal causes of infertility is diagnostic laparoscopy, according to most experts. Diagnostic laparoscopy may be useful in the infertility work-up programme before moving on to intrauterine insemination (IUI) treatment since IUI requires ideal conditions for the ovum pick-up and its transport mechanism.

Aim of the Work : The aim of this study was to evaluate the value of laparoscopy in diagnosis of endometriosis in cases of unexplained infertility.

Methods : This observational cross section study included 24 cases of unexplained infertility diagnostic laparoscopy done for all of them.

Results: Laparoscopic findings in studied patients, 9 patients (37.5%) showed endometriosis, 8 patients (33.3%) showed adhesions and 7 patients (29.2%) showed no laparoscopic findings. endometriosis grade detected by laparoscopy in studied patients. 1 patient (11.1%) showed endometriosis grade I, 2 patients (22.2%) showed endometriosis grade II, 2 patients (22.2%) showed endometriosis grade III and 4 patients (44.4%) showed endometriosis grade IV.

Conclusion: It is concluded that endometriosis is a common diagnosis in women with unexplained infertility and chronic pelvic pain. Laparoscopy should be indicated when diagnosis is suspected, together with tissue sampling and histopathologic examination.

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Introduction

The presence of stroma and endometriotic glands outside the uterus is referred to as endometriosis. Peritoneal, ovarian, and deep infiltrating endometriosis are the three forms of endometriosis that have been histologically

identified. Deep infiltrating endometriosis is defined as penetrating the surrounding tissues by more than 5 mm(1)

In the painful abdominopelvic region, endometriosis patients also exhibit enhanced responsiveness to noxious and benign somatic stimulation (referred to as "hyperalgesia" and "allodynia," respectively), such that a significant negative correlation is seen between patient-rated abdominopelvic pain intensity (e.g., visual analogue scale) and pressure (or "force") threshold (2).

The most frequent medical intervention involves the suppression of menstruation with combined oral contraceptive tablets, progestins, and GnRH agonists, frequently in conjunction with painkillers. The need for more potent disease modifying drugs and precise noninvasive diagnostic technologies for endometriosis is acknowledged on a global scale (3).

The lack of illuminating biomarkers, the frequent onset of symptoms at a young age, and the clinical overlap with other diseases all contribute to the frequent delay in diagnosis. It has been projected that between 5 and 10 years after the onset of symptoms, definitive visual identification of lesions after surgery takes place (4).

The current gold standard for determining the presence and severity of endometriosis is operational real-time laparoscopic results utilizing uniform staging systems. According to recent guidelines, histopathologic analysis is advised for diagnostic confirmation; nevertheless, because non-standardized and unblended assessment caused bias to prior studies, its true value has not been clearly measured(5).

Aim of Work

The aim of this study was to evaluate the value of laparoscopy in diagnosis of endometriosis in cases of unexplained infertility.

Patients & Methods

This observational cross section study was conducted at the Obstetrics and Gynecology department of Benha University Hospitals from May 2023 to November 2023.

This Study was approved by the ethics committee of Benha Faculty of Medicine and The review board in OB/GYN. Department. Written Informed consent was obtained from all participants prior to commencing the study.

This study enrolled 24 patients who attended Benha University Hospitals with complaint of unexplained infertlity. All patients included in this study underwent diagnostic laparscopy at our hospital.

Inclusion criteria:

- Women age between 20 and 40 year.
- Infertility
- Normal ovulatory cycles
- Partner’s semen sample containing at least 1.5 ml for semen volume , 39 million per ejaculate for total sperm number, 15 million per ml for semen concentration , 40% for total motility , 32% for progressive motility, 58% for vitality and 4% normal form for sperm morphology according to World Health Organization criteria (2012) .
- Hystrosalpingiography (HSG) if it was performed we check it to assess uterine cavity and tubal patency.

Exclusion criteria

- Endometriosis surgery has previously been performed.
- Endometriosis treatment received in the nine months prior.
- Using a partner's sperm for intrauterine insemination or ovulatory medication therapy within the past month.
- oophorectomy or salpingectomy;
- Other medical or surgical treatment for

infertility in the previous three months.

- Previous pelvic inflammatory illness

All patients were subjected to the following:

A) Full history was taken included medical history of chronic and acute disease.

B) the patients were examined generally, abdominally and locally.

Investigations:

- Routine investigations were performed as CBC , blood group , ALT ,AST, Serum creatinine and Coagulation profile .
- Laparoscope used for diagnosis of endometriosis in unexplained infertility cases and also used for staging the grade of endometriosis also if present.

Results

The mean age of studied patients was 30.0± 6.1 years with minimum age of 20 years and maximum age of 40 years (range 20 – 40). The mean duration of infertility in studied patients was 5.79± 2.72 years with minimum duration of 1 years and maximum duration of 10 years (range 1 – 10).All studied patients (100%) had regular menstrual cycle with no cases of irregular cycles (table 1). Serum CA 125 in studied patients: The mean serum CA 125 of studied patients was 81.42± 17.41 with minimum CA 125 of 48 and maximum CA 125 of 107 (range 48 – 107) (table 2) . Laparoscopic findings in studied patients: 9 patients (37.5%) showed endometriosis, 8 patients (33.3%) showed adhesions and 7 patients (29.2%) showed no laparoscopic findings (table3). Endometriosis grade detected by laparoscope in studied patients: 1 patient (11.1%) showed endometriosis grade I, 2 patients (22.2%) showed endometriosis grade II, 2 patients (22.2%) showed endometriosis grade III and 4 patients (44.4%) showed endometriosis grade IV (table 4).

Table (1): age and Duration of infertility and menstrual cycle in studied patients.

Variables		Studied patients (N = 24)
Age (years)	Mean±SD Range	30.0±6.1 (20 – 40)
Duration of infertility (years)	Mean±SD Range	5.79±2.72 (1 – 10)
Menstrual cycle	Regular Irregular	24 (100%) 0 (0%)

Table (2): serum CA125 in studied patients.

Variables		Studied patients (N = 24)
CA 125	Mean±SD Range	81.42 ±17.41 (48 – 107)

Table (3):Description of laparoscopic findings in studied patients.

Variables		Studied patients (N = 24)
Laparoscopic findings	Endometriosis Adhesions No finding	9 (37.5%) 8 (33.3%) 7 (29.2%)

Table(4):Description of endometriosis grade detected by laparoscope in studied patients.

Variables		patients (N = 9)
Endometriosis	Grade I Grade II Grade III Grade IV	1 (11.1%) 2 (22.2%) 2 (22.2%) 4 (44.4%)

Discussion

In our study laparoscopic diagnosis of endometriosis was reported in 37.5% of cases. 1 patient (11.1%) showed endometriosis grade I , 2 patients (22.2%) showed endometriosis grade II , 3 patients (22.2%) showed endometriosis grade III and 4 patients (44.4%) showed endometriosis grade IV. Biopsy was taken from suspected patients and the diagnosis of endometriosis was confirmed by histopathological examination. Therefore, meticulous histopathological confirmation should still be the first step in laparoscopic diagnosis and treatment of suspected endometriosis. Also in our study founded by laparoscopy that 33.3% of cases suffer from adhesions and no laparoscopic findings detected in 29.2% of cases.

Positive cases of endometriosis had a statistically significant range of menstrual disturbances including dysmenorrhea, whereas there was no significance as regards menorrhagia or dyspareunia. Dysmenorrhea should direct the attention to the possibility of endometriosis. Moreover, endometriosis was more common in patients with a history of previous surgery (e.g. cesarean section, myomectomy, and ovarian cystectomy), especially when uterine cavity was opened, which may be a predisposing factor. Another explanation is that some of these operations were originally performed to treat some endometriotic lesions but patients did not have a confirmed diagnosis of endometriosis.

The most common pelvic pathology in our study was severe endometriosis by 44.4% , whereas in the study of Bhandari et al. (2019) showed that most common pelvic pathology was minimal endometriosis by 24.2%. Also in this study laparoscopic findings showed that 48.4% of cases suffer from endometriosis, 17.8% adhesions and no laparoscopic findings in 47.9% of cases and this variation may be explained by long period of infertility.(6)

In study of Gajendra et al. (2017) showed that most common pelvic pathology was minimal endometriosis by 66.44% as in the study of Bhandari et al. (2019) , Whereas in our study the most common pelvic pathology was severe endometriosis by 44.4%. Also in Gajendra et al. (2017)study laparoscopic findings showed that 44.11% of cases suffer from endometriosis and no laparoscopic findings in 55.89% of cases.(6,7)

In study of Gajendra et al. (2017) pelvic inflammatory disease was excluded which is similar to our study as in our study we excluded any history of PID , but also in this study they exclude any adhesions due to previous surgeries or infections.(7)

Endometriosis was more common in patients with a history of previous surgery (e.g. cesarean section,myomectomy, and ovarian cystectomy), especially when uterine cavity was opened, which may be a predisposing factor. Another explanation is that some of these operations were originally performed to treat some endometriotic lesions but patients did not have a confirmed diagnosis of endometriosis. In our study 66.6% of cases of endometriosis have history of cesarean section .

Laboratory findings showed marked variance

as regards CA125 between positive and negative cases, which could be considered a good noninvasive test for diagnosing endometriosis. In our study the mean serum CA 125 of studied patients was 81.42±SD 17.41, whereas in Other study mean serum CA125 was 28.3±SD 22.8.(8)

Other investigators showed that laparoscopic findings was 33% of cases suffer from endometriosis, 7% adhesions and no laboratory findings in 12% of cases.(8)

While Katke RD (2019) laparoscopic findings was 22% of cases suffer from endometriosis, 14% adhesions and no laboratory findings in 46 % of cases.(9)

While Koji RD (2017) laparoscopic findings was 51.2% of cases suffer from endometriosis, 41.5% adhesions and no laboratory findings in 7.3 % of cases.(9)

In our study endometriosis grade detected by laparoscope in studied patients. (11.1%) showed endometriosis grade I, (22.2%) showed endometriosis grade II, (22.2%) showed endometriosis grade III and (44.4%) showed endometriosis grade IV.

In other studies grades of endometriosis was : (24.2%) showed endometriosis grade I, (27.1%) showed endometriosis grade II, (3.7%) showed endometriosis grade III and (0%) showed endometriosis grade IV. (6).

In other studies grades of endometriosis was : (66.44%) showed endometriosis grade I, (21.1%) showed endometriosis grade II, (7.7%) showed endometriosis grade III and (6.66%) showed endometriosis grade IV. (7)

In other studies grades of endometriosis was : (51.2%) showed endometriosis grade I, (21.1%) showed endometriosis grade II, (0%) showed endometriosis grade III and (0%) showed endometriosis grade IV. (8)

In other studies grades of endometriosis was : (39.44%) showed endometriosis grade I, (18.1%) showed endometriosis grade II, (21.7%) showed endometriosis grade III and (21.66%) showed endometriosis grade IV. (9)

Conclusion

It is concluded that endometriosis is a common diagnosis in women with unexplained infertility and chronic pelvic pain. Laparoscopy should be indicated when diagnosis is suspected, together with tissue sampling and histopathologic examination.

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Gestational and Postpartum Urinary Incontinence at Mansoura University Hospital

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Abstract

Background: Adult women of all ages are frequently affected by urinary incontinence (UI), which can have a detrimental effect on quality of life. Although the cause of UI is complex, several major risk factors include aging, obesity, and unfavorable obstetric events. The genesis of UI has been linked to pregnancy and childbirth. The impact of childbirth on the risk of UI is still up for debate, despite numerous research showing a clear, short-, medium-, and long-term correlation between UI and vaginal delivery.

Objective: To study the prevalence and risk factors of urinary incontinence in nulliparous women in Mansoura university hospitals , the prevalence of postpartum urinary incontinence and the effect of mode of delivery on the prevalence postpartum urinary incontinence.

Patients and Methods: The present study was a cross sectional study at Mansoura university hospitals (MUH) including nulliparous pregnant women. 105 Pregnant women asked to answer a questionnaire. urine leakage that occurs involuntarily during effort, exertion, sneezing, or coughing is known as SUI leakage; urine leakage that occurs involuntarily during effort, exertion, or right before urgency is known as UUI leakage; and urine leakage that occurs involuntarily during exertion, effort, sneezing, or coughing is known as MUI leakage.

Results: The study also questioned change in urination style, complaints related to the urinary system frequency of urination during follow up and illustrates that there is statistically significant increase in frequency of urination from 5.7% ranging from 11-15 times/day that increased to 11.4% ranging from 11 to 15 times/ day in second trimester then become 31.4% from 11 to 15 times/ day then decrease of frequency of urination to 5.7% from 11 to 15 , 1% more than 15 times/day that decreased to 7.6% from 5 to 10 and 92.4% from 0 to 5 at 3 months. .A statistically significant increase in frequency of nocturnal urination during follow up from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up. For first trimester;

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51.4% none , 22.9% twice , 17.1% once and 8.6% three times. .A statistically significant increase incidence of burning during micturition during follow up from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up. significant change in amount of urine during follow up from first trimester to one month ($p<0.001$) and from first trimester to 3 months follow up ($p=0.002$).

Conclusion: Urinary incontinence is one of the common disorders during pregnancy and postpartum period which can affect quality of women's life significantly. The effect of mode of delivery C.S 77.1% and vaginal delivery 22.9%. a non-statistically significant relation between urinary incontinence during follow up and age , period of gestation and mode of delivery among studied cases ($p>0.05$).

Introduction:

Numerous anatomical and functional conditions fall under the category of pelvic floor dysfunctions (e.g., hyper-function: defecatory dysfunction, sexual dysfunction, and voiding dysfunction; hypo-function: urine incontinence, fecal incontinence, and pelvic organ prolapse).

As a result, these prevalences may be underestimated because the majority of epidemiological studies rely on self-report data, which may skew the true incidence of pelvic floor dysfunctions.

According to epidemiological studies, pelvic floor dysfunction is linked to unfavorable obstetric occurrences. The physiological and structural changes that occur during pregnancy have been linked to lower urinary tract symptoms (LUTSs) both during and after childbirth. In Brazil, LUTSs were found in 63.8% of expectant mothers. (1) Nevertheless, those symptoms are temporary and go away a few months after delivery, therefore no additional research is needed.

Urinary incontinence (UI) is described as "the complaint of any involuntary leakage of urine" in the most recent definition provided by the International Continence Society (ICS). Even though UI is not a fatal ailment, it is a prevalent, bothersome, and costly condition that significantly lowers a woman's quality of life. (2)

To improve the management and treatment of impacted patients, physicians and health researchers have looked at the factors influencing the prevalence of UI in great detail in recent years.

However, because there are significant methodological discrepancies among the studies, it is challenging to derive precise prevalence numbers from the literature. (3, 4) The fact that women experience UI more frequently than males does not change the significance of circumstances like pregnancy in contributing to UI.

Consequently, The purpose of this research was to look into the prevalence of UI in nulliparous women and to give a summary of the risk variables that are connected to UI. additionally, to study the frequency of postpartum urine incontinence and the impact of delivery mode on the frequency of postpartum urine incontinence.

AIM OF THE WORK

The purpose of this research is to examine the prevalence of postpartum urine incontinence and its relationship to the mode of delivery, as well as the risk factors and prevalence of urinary incontinence in nulliparous women attending Mansoura University Hospitals.

PATIENTS AND METHODS

Study Area and design: This was a cross sectional study, carried out on 106 nulliparous women who came to obstetrics and gynecology department in Mansoura University Hospitals. Mansoura University Hospital is Referral teaching hospital.

Study Population:

Inclusion Criteria: Pregnant women aged 18 –40 years. Nulliparous pregnant. Nulliparous pregnant with: Change in urination style, such as straining to urinate, difficult urination, discontinuous urination, and more frequent urination than before pregnancy. Urinary tract complaints include pain and burning sensations, which could indicate an infection. Changes pertaining to the bladder, such as the sensation of fullness within the bladder, were evaluated.

Exclusion Criteria: Those suffering from systemic diseases like diabetes mellitus. A state of obesity. elevated blood pressure. bladder system issues, individuals who have undergone prior pelvic floor surgery.

Sample Size: Sample size was 105 nulliparous women.

Study design and steps:

Pregnant women will be asked to answer a questionnaire including information on maternal age, parity height, pre-pregnancy weight, education

The study used this questionnaire three times during different periods of gestation (first, second, third) trimester. The study queried about complaint of involuntary loss of urine on effort or physical exertion or sneezing or coughing (SUI), strong, sudden need to urinate (UUI), and complaint of features of both SUI and UUI. Change in urination style may be reported as, urination more frequently than before pregnancy, discontinuous urination, difficult urination, straining for urination. Complaints related to the urinary system are pain and burning sensation which may denote urinary tract infection. Changes pertaining to the bladder, such as the sensation of fullness within the bladder, were evaluated.

Ethical Consideration:

The hospital's ethical committee approved this study, and patients gave their informed consent after being fully told about the study's objectives, risks, and procedures. The study approved by the Ethics Committee of Faculty of Medicine, Mansoura University. The following sufficient safeguards are in place to protect participant privacy and data confidentiality: Each participant received a code number, and their address and name were stored in a unique file. The patient's identity will be kept confidential while the study is being conducted. The study's findings were only applied in a scientific manner; no other purposes were pursued.

The benefits of the study to the subjects included in the study:

The appropriate diagnosis and management of disease.

Statistical analysis

Version 22 of the statistical software for social sciences, or SPSS, will be used to examine the data. Quantitative data will be expressed as mean and standard deviation for normally distributed data and median and range for non-normally distributed data after being evaluated for normalcy using the Kolmogrov-Smirnov test. Qualitative data will be presented as number and percent. Depending on the type of data, the relevant statistical test will be used; the following tests are recommended: For a categorical variable, use Chi-Square. For continuous variables, there is the Mann Whitney U test and the Student t test.

RESULTS

Table (1): demographic characteristics and obstetric history of the studied cases

n=105	%
Age/years (mean±SD)	29.95±6.63
Period of gestation/weeks Median (min-max)	20(5-38)

Mode of delivery **Vaginal** **CS**	 24 81	 22.9 77.1

Table (2) mean age of the study group is 29.95 ±6.63 , median period of gestation is 20 weeks and 77.1% of the study group delivered by C.S and 22.9%delivered vaginally.

Table (2): changes in frequency of micturition during follow up among studied cases.

Frequency of urination	n	%
First trimester **5-10** **11-15**	n=35 33 2	 94.3 5.7
Second trimester **5-10** **11-15**	n=35 62 8	 88.6 11.4
3rd trimester **5-10** **11-15** **>15**	 70 33 2	 66.7 31.4 1.9
48 h **0-5** **5-10** **11-15** **>15**	 11 59 29 6	 10.5 56.2 27.6 5.7
One month **0-5** **5-10** **11-15** **>15**	 79 19 6 1	 75.2 18.1 5.7 1.0
3 months **0-5** **5-10**	 97 8	 92.4 7.6
test of significance	Friedman test =116.71 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Type (2):demonstrates frequency of urination during follow up and illustrates that there is statistically significant increase in frequency of urination from 5.7% ranging from 11-15 times/day that increased to 11.4% ranging from 11 to 15 times/ day in second trimester then become 31.4% from 11 to 15 times/ day then decrease of frequency of urination to 5.7% from 11 to 15 , 1% more than 15 times/day that decreased to 7.6% from 5 to 10 and 92.4% from 0 to 5 at 3 months.

Table (3): changes in frequency of nocturnal urination during follow up among studied cases.

Nocturnal urination	n	%
First trimester	n=35	
none	18	51.4
1	6	17.1
2	8	22.9
3	3	8.6
Second trimester	n=70	
none	39	55.7
1	9	12.9
2	9	12.9
3	13	18.6
3rd trimester	n=105	
none	20	19.0
1	37	35.2
2	28	26.7
3	20	19.0
48 h		
none	31	29.5
1	30	28.6
2	26	24.8
3	18	17.1
One month		
none	77	73.3
1	17	16.2
2	6	5.7
3	5	4.8
3 months		
none	102	97.1
1	1	1.0
2	2	1.9
test of significance	Friedman test =70.98 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Table (3) illustrates frequency of nocturnal urination during follow up among studied cases .A statistically significant increase in frequency of nocturnal urination during follow up from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up. For first trimester ; 51.4% none , 22.9% twice , 17.1% once and 8.6% three times , for second trimester ; 55.7% none , 18.6% three times , 12.9% twice and 12.9% once , for third trimester ; 35.2% once, 26.7% twice, 19% three times and 19% none. For 48H ; 29.5% none, 28.6% once , 24.8% twice and 17.1% three times . For one month ; 73.3% none, 16.2% once , 5.7% twice and 4.8% three times . For three month ; 97.1% none, 1.9% twice and 1% once.

Table (4): changes in frequency of burning during micturition during follow up among studied cases.

burning during micturition	n	%
First trimester **No** **Yes**	n=35 3 32	 8.6 91.4
Second trimester **No** **Yes**	n=70 2 68	 2.9 97.1
3rd trimester **No** **Yes**	n=105 4 101	 3.8 96.2
48 h **No** **Yes**	 10 95	 9.5 90.5
One month **No** **Yes**	 73 32	 69.5 30.5
3 months **No** **Yes**	 101 4	 96.2 3.8
test of significance	Friedman test =119.14 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Table (4) demonstrates frequency of burning during micturition during follow up among studied cases .A statistically significant increase incidence of burning during micturition during follow up from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up. Burning during micturition is detected among 91.4% at first trimester , 97.1% for second trimester, 96.2% for third trimester 90.5% for 48 H, 30.5% for one month and 3.8% for third months follow up.

Table (5): changes in urinary incontinence during follow up among studied cases.

urinary incontinence	n	%
First trimester	n=35	
Absent	1	2.9
Urge	14	40.0
Stress	8	22.9
Mixed	12	34.3
Second trimester	n=70	
Absent	1	1.4
Urge	24	34.3
Stress	10	14.3
Mixed	35	50.0
3rd trimester	n=105	
Urge	50	47.6
Stress	16	15.2
Mixed	39	37.1
48 h		
Absent	2	1.9
Urge	45	42.9
Stress	22	21.0
Mixed	36	34.3
One month		
Absent	38	36.2
Urge	23	21.9
Stress	32	30.5
Mixed	12	11.4
3 months		
Absent	97	92.4
Urge	2	1.9
Stress	6	5.7
test of significance	Friedman test =104.51 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Table (5) illustrates frequency of urinary incontinence during follow up among studied cases .A statistically significant increase in incidence of urinary incontinence during follow up from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up. Urinary incontinence is distributed as following .For first trimester ; 40% urge , 34.3%mixed , 22.9% stress & 2.9% absent. For second trimester ; 50% mixed , 34.3%urge , 14.3% stress & 1.4% absent. For third trimester ; 47.6% urge , 37.1%mixed and 15.2% stress. For 48h ; 42.9% urge , 34.3%mixed , 21% stress and 1.9% absent. For one month ; 36.2% absent , 30.5% stress, 21.9% urge and 11.4% mixed. For three months ; 92.4% absent , 5.7% stress, 1.9% urge.

Table (6): changes in amount during follow up among studied cases .

Amount	n	%
First trimester **Droplet** **Stream**	n=35 17 18	 48.6 51.4
Second trimester **Droplet** **Stream**	n=70 25 45	 35.7 64.3
3rd trimester **Droplet** **Stream**	n=105 25 80	 23.8 76.2
48 h **Droplet** **Stream**	 28 77	 26.7 73.3
One month **Droplet** **Stream**	 20 85	 19.0 81.0
3 months **Droplet** **Stream**	 7 98	 6.6 93.3
test of significance	Friedman test =35.58 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Table (6) illustrates amount of urination during follow up among studied cases . A statistically significant change in amount of urine during follow up from first trimester to one month (p<0.001) and from first trimester to 3 months follow up (p=0.002).Stream urination changed from 51.4% at first trimester to 64.3% at second trimester , 76.2% at third trimester , 73.3%at 48 hours , 81% at one month and 93.3% at 3 months .

Table (7): changes in bothering in daily life during follow up among studied cases.

Bothering in daily life	n	%
First trimester	n=35	
None	2	5.7
Slight	29	82.9
Some	4	11.4
Second trimester	n=70	
None	4	5.7
Slight	27	38.6
Some	34	48.6
severe	5	7.1
3rd trimester	n=105	
Slight	22	21.0
Some	38	36.2
severe	45	42.9
48 h		
None	7	6.7
Slight	21	20.0
Some	34	32.4
severe	43	41.0
One month		
None	61	58.1
Slight	21	20.0
Some	12	11.4
severe	11	10.5
3 months		
None	98	93.3
Slight	6	5.7
Some	1	1.0
test of significance	Friedman test =105.42 p<0.001*	
within group significance	p1<0.001* , p2<0.001*, p3<0.001*, p4<0.001* p5<0.001*	

Table (7) demonstrates bothering in daily life during follow up among studied cases .A statistically significant high grade of bothering is detected during follow up from first , second to third trimester , while statistically significant increase is detected after that for 48 h to one & three months. For first trimester ; 11.4% have some bothering that increased to 48.6% some bothering and 7.1% sever bothering at second trimester then increased to 41% severe bothering at 48 hours , 10.5% severe bothering at one month that improved at 3 months to be only 1% some bothering .

DISCUSSION

A common postpartum consequence is urinary incontinence (UI), a health problem linked to a lower quality of life for women worldwide. The majority of occurrences of urine incontinence (UI) are caused by stress. (5)

The trauma experienced after delivery is one of the main risk factors for SUI in women, however the etiology of this condition is complex. Many SUI women eventually develop persistent UI because they are unable to heal during the postpartum period. (6).

Urge urinary incontinence (UUI), which affects 36% of the individuals in the study, is one of the several types of involuntary urine leaking that can coexist with SUI. Even though symptoms could be severe, very few patients decide to get medical attention. (7)

Vaginal delivery and labor involving vacuum extraction or forceps are thought to significantly increase the prevalence of postpartum SUI, according to numerous research. On the other hand, it is established that cesarean delivery—particularly an elective one—protects against postpartum SUI. (8)

The variables linked to the emergence of postpartum SUI in diverse groups, however, still need to be assessed. There are differences in the short- and long-term factors influencing postpartum SUI. (9)

Therefore, the current study aimed to assess the prevalence and risk factor of urinary incontinence in nulliparous women in Mansoura hospital and prevalence of postpartum urinary incontinence. The current study included 105 nulliparous pregnant women.

The current study showed that the mean age of the studied cases was 29.95 ±6.63, median period of gestation was 20 weeks ranging from 5 to 38 and mode of delivery 77.1% Cesarean section and 22.9 vaginal delivery.

Similarly, Lima et al. (10) study showed that the average age of prim parous women was 22.9 ± 3.9 years old and in contrast to our study mode of delivery was spontaneous vaginal in 352 (70.4%) cases ,instrumental vaginal 25(5%) cases and cesarean section in 125(24.6%) cases attributed increase rate of cesarean section in Egypt .

As opposed to our investigation, Rajavuori et al. (11) reported that 428 (78.2%) of the cases had spontaneous vaginal delivery, 43 (7.9%) had instrumental vaginal delivery, and 76 (13.9%) had cesarean section delivery. A varied sample size may be the cause of the discrepancy.

The current study demonstrated the frequency of urination during follow up showing statistically significant increase in frequency of urination (11-15) from 5.7% in first trimester that increased to 11.4% in second trimester then become 31.4% in third trimester then decrease of frequency of urination (11-15) to 27.6% after 48 hour postpartum, decrease to 5.7% one month postpartum and 7.6% from (5-10)daily at 3 months postpartum.

According to Yates (12), who concurred with our findings, the uterus compresses the bladder throughout the first and third trimesters, making this period of time the most prevalent for urine frequency, which increases until term. The main causes include increased renal blood flow (RBF), increased GFR, hypervolemia (fluid overload), and the effects of hormonal changes. It is most likely solely affected by the pressure inside the uterus in the latter weeks of pregnancy.

According to Hee P, Lose G, Beier-Holgersen R, Engdahl E, Falkenlove P, uroflowmetry, residual urine (RU) measurements (ultrasonography), frequency of urination, the voiding pattern following a "normal" vaginal delivery, and 51 primiparous women, these tests were carried out at the first postpartum voiding and on the third and fifth postpartum days. The immediate postpartum period saw a considerable decrease in the adjusted (for

volume differences) peak flow rate.

The current study illustrated a statistically significant increase the frequency of nocturnal urination during follow up among studied cases from first to second trimester then 3rd trimester then decrease for 48 hours , one month and 2 months follow up.

The current study illustrated a statistically significant increase frequency of burning during micturition during follow up among studied cases from first to second trimester then 3rd trimester then decrease for 48 hours, one month and 2 months follow up.

Changes in the urinary tract during pregnancy make women more vulnerable to infection. Compression of the ureters from the gravid uterus causes ureteral dilatation. Progesterone's hormonal effects can also relax smooth muscles, which can result in dilatation and urine stasis, as well as an increase in vesicoureteral reflux. (13)

Interestingly, the current study illustrated a statistically significant increase in the frequency of urinary incontinence during follow up among studied cases from first to second trimester then 3rd trimester then decrease for 48 hours, one month and 2 months follow up post-delivery.

In harmony with our results, Sangsawang et al. (14) reported that the third trimester had the highest prevalence, which was followed by the second and first trimesters. In the first trimester, only 13–19% of cases were reported. While the prevalence in the second trimester was similar at 19.2%, the third trimester had a noticeably greater prevalence: 37.5 %.

When Wesnes et al. (15) reported questionnaire data from the Norwegian Institute of Public Health's Norwegian Mother and Child Cohort Study, they discovered that SUI was the most prevalent type of UI, occurring in high prevalence in both nulliparous and multiparous women (31% and 42%, respectively).

Also, Mørkved et al. (16) from Norway discovered that 42% of pregnancies ended in SUI. The same study found that 8 weeks after delivery, 38% of women experienced SUI.

Furthermore, the prevalence of UI declines throughout the postpartum phase, according to Thom et al. (17). For six months after giving birth, 27.4% of parous women may experience UI; only a small percentage of women get spontaneous remission.

The current study illustrated a statistically significant change in amount of urination during follow up among studied cases from first trimester to one month ($p<0.001$) and from first trimester to 3 months follow up ($p=0.002$).

The current study demonstrated a statistically significant high grade of bothering during follow up from first, second to third trimester, while statistically significant increase was detected after that for 48 h to one & three months.

Remarkably, the current study illustrated statistically significant positive correlation between age and frequency of urination at first trimester among studied cases ($r=0.348$, $p=0.04$) and statistically significant positive correlation between age and bothering in daily life at first trimester ($r= 0.366$, $p=0.03$).

The current study demonstrated statistically significant positive correlation between period of gestation and nocturnal urination at third trimester ($r=0.371$, $p=0.001$) and also at 48 h ($t=0.402$, $p=0.001$).

The current study demonstrated statistically significant positive correlation between age of the studied cases and burning during micturition at third trimester ($r=0.211$, $p=0.03$) and also at 48 h ($t=0.219$, $p=0.025$). But, period of gestation had statistically significant negative correlation with burning during micturition at first trimester ($r=-0.370$, $p=0.029$).

The current study showed statistically significant positive correlation between age

of the studied cases and urinary incontinence at first & third trimester (r=0.377, p=0.026 & r=0.196, p=0.046). But, period of gestation had statistically significant negative correlation with Urinary incontinence after 48 h (r=-0.207, p=0.034). However, the current study showed a non-statistically significant relation between urinary incontinence during follow up and age (in second trimester or at 48 hr or 1 or 3 month) and mode of delivery among studied cases (p>0.05).

Wang et al. (9) demonstrated, in line with our findings, that age at gestation was still a risk factor for postpartum SUI, based on seven studies involving 11,441 participants. The results suggested that older gestational ages would be associated with a higher risk for pregnant women. The findings on age at gestation were therefore trustworthy.

Also in similarity with our findings, Lima et al. (10) discovered no connection, either in the primiparous or multiparous groups, between urine incontinence and vaginal or caesarean deliveries and incontinence.

Additionally, Lima et al. (10) discovered that stress urine incontinence affected both primiparous and multiparous women, with a higher frequency of occurrence during the third trimester of gestation (period of gestation).

In Rajavuori et al. (11) study, the rate of cesarean sections was just 14%, and there were no appreciable variations in postpartum UI between the techniques of birth.

Cesarean delivery offers protection against UI, particularly prior to menopause, according to research on delivery modes. The pelvic floor's anatomical changes following vaginal delivery make a woman more vulnerable to UI. (18) This risk is significantly increased by instrumentally assisted vaginal delivery because of the additional pelvic floor injury from abrasions and mechanical stress. (19)

The current study demonstrated non statistically significant correlation between age, period of gestation, mode of delivery and amount of urination among the studied cases during follow up (p>0.05).

There are several reasons for the disparities in the results of the aforementioned research, such as variations in the duration of follow-up, diverse patient groups, patient selection, and small sample sizes.

CONCLUSION

Pregnant women who experience urine incontinence have a number of risk factors for this disease, including age, gestational age, birth mode, and urinary tract infection. The third trimester of pregnancy was when this symptom occurred most frequently.

It was feasible to draw the conclusion from the current study that there was no significant relationship between the occurrence of urine incontinence during pregnancy and parity or mode of delivery.

Therefore, more research is required to confirm this relationship on its own. Nonetheless, it is well recognized that avoiding or even lessening these symptoms toward the end of pregnancy and even after delivery requires a pelvic muscle strengthening program.

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Integrated prediction model before conservative management of placenta accreta spectrum : hospital based cohort study.

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Abstract

Introduction: The increase in the rate of caesarean sections has led to increase of potentially life threatening complications such as placenta accreta, low-lying placenta and rupture uterus, as well as, surgical morbidity. Placenta accrete spectrum is a condition of abnormal placental invasion on which the placenta invades beyond the decidua basalis. Morbidly adherent placenta represents a spectrum of disorders characterized by abnormal penetration of the placenta into the uterine wall.

Objectives: this hospital based cohort study was conducted at obstetrics and gynecology department at mansoura university hospitals from September 2022 to September 2023 aiming to formulate ascoring system to assess the degree of placenta accrete spectrum before decision of conservative management of placenta accrete spectrum.

Methods: Pregnant females in the third trimester of pregenancy with history of past cesarean section and diagnosed to have placenta accrete with 2D ultrasound and we intend to do conservative management, full history was taken, investigation, ultrasound and Doppler was done.

Results: Integrated score is highly sensitive for prediction of placenta accreta spectrum (71.9%) and specificity 64.9% and cut off level is 8.5 also positive predicitive value is 63.9% and negative predicitive value is 72.7% and accuracy of the score is 68.1% .

Conclusion: The study's implications for practice are profound. The integrated scoring system, by combining various parameters and ultrasound criteria, has the potential to aid clinicians in assessing PAS severity before choosing management strategies. This is particularly relevant when considering conservative approaches. The study's findings and the consistency of results with other related research enhance the credibility and applicability of the prediction model. In practice, the prediction model can assist healthcare professionals in identifying high-risk cases of PAS, allowing for informed decisions about conservative management options.

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Introduction

The incidence of the PAS has been elevating from a reported occurrence of one case in 30,000 deliveries in 1950 to one case in 2500 deliveries in 1997. This marked elevation has been due to the increase in caesarean section delivery rates allover the world . Recent studies showed marked increase in CS rate in Egypt (1). The association between cesarean section & placenta accreta may be due to malrepair of the endometrium (2). placenta accreta spectrum may occur after any procedure that causes some damage to the endometrium, including dilatation and curettage, manual removal of the placental tissue, uterine artery embolization, and also doing myomectomy.(3). Additional risk factors include maternal age, high parity , IVF techniques, and a diagnoses of placenta accrete spectrum in a previous pregnancy(4).

TVS has been done to evaluate the uterine scar site in non-pregnant women. The scar site can be detected in relation to the uterovesical junction (5). Antenatal diagnosis of PAS allows for multidisciplinary planning and delivery before the onset of labor and/or vaginal bleeding. This approach has decreased maternal morbidity rates, including less bleeding, fewer transfusion requirements and intraoperative bladder injuries as well as improve fetal outcome (6).

The depth of placental invasiveness is one of the most important factors that affect maternal outcome. Therefore, in order to decide the best strategies for the management of placenta accrete spectrum, acorrect assessment of the degree of the invasion at the time of delivery, stratification of women according to this, and correlation between prenatal imaging, intra-operative aspects and pathological aspects are of importance when comparing data from different studies (7).

Patients & Methods

Study design:

We conducted a cohort study

Place: Mansoura university hospitals, obstetric& gynecology deparement

Time: September 2022 to September 2023

Sample size: The calculated sample size of the study was 31 participants for each group at 5% level of significance and 80%, using the power of the study following formula (8).

$$n=\frac{Z^2*p*(1-P)}{d^2}$$

Where:

Z = 1.96 for 95% confidence level.

p = Expected total accuracy of placenta accrete index score in prediction of placenta accrete group was 98% based on (9)

d = precision (Margin of error) = 0.05

The sample size was elevated to **40 participants for each group** to compensate for insufficient data and to increase the power of the study.

Patient

Inclusion criteria:

1. Pregnant females in third trimester of pregnancy (28 -40 week).
2. Pregnant females with history of at least one cesarean section .
3. Pregnant females diagnosed to have placenta previa accreta by 2D trans vaginal ultrasound assessment(placenta previa situated at anterior uterine wall about 2 cm from the internal os) .
4. Pregnant females undergo conservative management at delivery.

Exclusion criteria:

1. Pregnant females with no history of previous cesarean deliveries

2. Pregnant females under go cesarean section hysterectomy.
3. Pregnant females diagnosed to have posteriorly situated placenta previa.

Methods

» **Clinical assessment :**

In the form of full history taking(personal history &obstetric history , Number of past CS deliveries , Previous history of placenta previa, Past or current history of medical disorders (DM, heart disease, HTN, renal ,hepatic impairment).

» General examination was done and vital signs was assessed and recorded.

» An abdominal examination was performed and the fetal heart rate will be recorded.

» Routine investigations including CBC, urine analysis, liver function tests & kidney function tests.

» Ultrasound evaluation for PAS was done with grayscale and color

Doppler imaging using (GE Logiq P5, General Electric, USA) ultrasound device with a transabdominal array probe 3.5 MHZ. Scanning was performed with a moderately filled bladder. The diagnosis of placenta previa was confirmed if the placenta situated within 2 cm from the internal cervical os but did not cover it. Meanwhile, anterior placenta previa was diagnosed if any portion of the placenta was anterior and the placental tissue covering the internal cervical os.

» Detailed assessment looking for ultrasound signs of PAS was done which include:

A:loss of the retroplacental clear zone, the smallest myometrial thickness in sagittal plane.

B: presence of lacunar spaces

Its grading into_____ 0-3 and bridging vessels using color Doppler Lacunar spaces were graded as follows: grade (0) = not present, grade (1) =1-3 present and generally small, grade (2) = 4-6 present and tending to be larger and more irregular and grade (3) = many throughout the placenta and appearing large and bizarre.

C:bladder wall interruption

D:placental Wall bulge

E: exophytic focal mass mostly into urinary bladder

» Doppler assement including

A: vesicouterine hypervascularity

B: presence of sub placental hypervascularity

C: bridging vessels passing from placenta to myometrium or adjacent organs

D: lacunae feeder vessels

• Intraoperative assessment according to FIGO classification for placenta accreta spectrum

Grade 1: Abnormally adherent placenta (placenta creta)

At time of laparotomy

» No evidence of separation with giving synthetic ecobolics such as oxytocin and gentle controlled cord traction

» Attempts of manual removal of the placenta results in heavy bleeding from the placenta implantation site that require mechanical or surgical procedures

» Macroscopically, the uterus shows no distension at the placental bed ,no placental tissue is seen invading through the surface of the uterus, and there is no neovascularity or there is little neovascularity.

Grade 2: Abnormally invasive placenta (Increta)

At time of laparotomy

» Abnormal macroscopic findings at the placental implantation site: bluish/purple colouration, distension (placental “bulge”)

» Significant amounts of neovascularity (dense tangled bed of vessels running parallel

craniocaudially in the uterine serosa)

» Uterine serosa not invaded by placental tissues

» gentle cord traction results in the dimple sign , the uterus pulled inwards but without separation of the placenta.

Grade 3: Abnormal invasive placenta (Percreta)

Grade 3a: Limited to the uterine serosa

Clinical criteria

At laparotomy

» Abnormal macroscopic findings on the uterine serosa (as above) and serosa is invaded by the placental tissues.

» No invasion to any other organ, such as the back of the bladder (a clear surgical plane can be identified between the uterus and the bladder)

Grade 3b: With urinary bladder invasion

Clinical criteria

• At time of laparotomy

» Placental villi are invading into the bladder walls .

» Clear surgical plane cannot be identified between the bladder and uterus

Grade 3c: With invasion of other pelvic tissue/organs

Clinical criteria

At laparotomy

Placental villi invade into the broad ligament, vaginal walls, pelvic sidewalls or any other pelvic organs (with or without invasion of the bladder)

The gold standared for scoring was histopathological examination of a biopsy that was taken from placental bed& it was classified into (according to figo clacification of PAS 2019):

Grade 1: Abnormally adherent placenta (placenta adherenta or creta)

Histologic criteria

- Microscopic examination of the placental implantation site samples from hysterectomy specimen shows wide areas of absent decidua between villous tissue and myometrium with placental villi attached directly to the myometrium.
- The final diagnosis cannot be made only on just delivered placental tissue nor on random biopsies of the placental implantation sites.

Grade 2: Abnormally invasive placenta (Increta)

Histologic criteria

- Hysterectomy specimen or partial myometrial removal of the increta area shows placental villious tissue present inside the muscle fibers and sometimes inside the lumen of the deep uterine vessels (radial or arcuate arteries).

Grade 3: Abnormally invasive placenta (Percreta)

Grade 3a: Limited to the uterine serosa Histologic criteria

- Hysterectomy specimens showing that placental tissue inside or reaching the uterine serosa

Grade 3b: With urinary bladder invasion Histologic criteria

- Hysterectomy specimens showing placental tissues reaching the uterine serosa and invading the bladder wall tissue or urothelium.

Grade 3c: With invasion of other pelvic tissues/organs Histologic criteria

- Hysterectomy specimen showing placental tissues reaching the uterine serosa and invading pelvic tissues/organs (with or without invasion of the bladder)

Patients were divided into two groups:

1. Study group was 40 patients diagnosed to have placenta previa &placenta accreta spectrum.
2. Control group was 40 patients diagnosed placenta previa without placenta accreta spectrum.

scoring system:

The scoring system icluded five items each was given a score 1or score 2

Items	Score 1	Score 2
Number of cesarean sections:	If one cesarean delivery .	If > one cesarean delivery.
Number of lacunae:	Grade 0&1	Grade 2&3
Retroplacental Clear zone:	Present	Absent
Doppler assessment:	Hypervascularity of placental lacunae alone.	Hypervascularity between placenta and bladder with bridging vessels in between.
Intraoperative evaluation:	Intraoperative easy access to dissection plane between bladder and placenta.	Intraoperative difficult access to dissection plane between bladder and placenta.

Management plan was:

Preoperative management:

Counseling:

Cases with suspected placenta accreta was counseled about potential risks and complications.

Cases with placenta accreta are at increased risk for hemorrhage, massive blood transfusion, bladder, ureteric injury, infection, need for intubation, prolonged hospital stay, ICU admission, need for reoperation, thromboembolic complications and death. Considerations should involve comparative possibility for hysterectomy and subsequent infertility (10).

Timing of delivery:

According to our local protocol:

Time of delivery was at (34-36 week) if associated with history of reccurent bleeding.

Time of delivery was at 37 week if not associated with history of reccurent bleeding.

Anesthesia for delivery:

General anasthesia or regional anasthesia planned with anesthesia team.

Intraoperative management:

Patients was subjected to one of the conservative methods of PAS according to multi desplaniery team assessment.

Conservative management includes the following techniques:

1 ..|One-step conservative surgery approach for placenta accreta spectrum (PAS) disorders:

1. Upper uterine segment incision and delivery of the fetus.
2. Removal of all myometrial tissue which is invaded and the all placenta in one piece with previous local vascular control.
3. Surgical maneuvers fo ensuring r hemostasis.
2. Myometrial suturing in 2 planes.
3. Bladder wall repair if needed.

2 ..Stepwise surgical approach for (PAS) disorders:

1. Combined an early uterotonics intravenously just before fetus delivery
2. Transverse upper uterine incision at the superior border of the placenta without cutting through the placenta.
3. Delivery of the fetus
4. The uterus is exteriorized and compressed against the symphysis pubis by assistant (transient bilateral kink of uterine arteries).
5. Bilateral ligation of the anterior division of the internal iliac artery .

6. Placental tissue complete extraction (delayed after pelvic devascularization).

4. Proper identification of the lower uterine segment by the index and ring fingers after identification of internal cervical os by the middle finger of the left hand.

5. Repair of the uterine incision.

3combined approach.

*if un controlled bleeding occur cesarean hysterectomy will be done.

Outcome measures:

Primary outcome: was to formulate a cut off level score at which success rate developed to preserve the uterus in cases of PAS.

Secondary outcome :

Complication rate:

- bladder injury rate
- bleeding rate
- blood transfusion volume.
- Intestinal injury rate
- ICU admission rate
- hosipital stay length.
- Thromboembolic complications rate .
- Maternal Mortality rate.

Statistical analysis

The collected data were coded, processed and analyzed using SPSS program (Version 26) for windows. The appropriate statistical tests was used when needed. P values less than 0.05 (5%) was considered to be statically significant.

Ethical consideration:

- Study protocol was submitted for approval by IRB
- Approval of the mangers of the health care facilities in which the study were conducted
- Informed consent was obtained from each participant sharing in the study.

Confidentiality and personal privacy was respected in all levels of the study. Collected data were not used for any other purpose.

Results

Table (3): Demographic and baseline obstetric data among studied group

	Placenta accreta (n=32)	No placenta accreta (n=37)	Unsatisfactory (n=11)	P value
Age (Years) Mean ± SD	30.81± 5.73	30.11± 4.47	30.27± 6.88	P1=0.569
Age (Years) Min-Max	22-43	20-40	18-41	P2=0.799 P3=0.926
Gravidity Median(range)	**5 (2-7)**	**3 (2-8)**	**4 (2-9)**	P1=0.005* P2=0.852 P3=0.05*
Parity Median(range)	**3 (1-5)**	**2 (1-5)**	**3 (1-5)**	P1=0.003* P2=0.536 P3=0.214
Number of cesarean sections Median(range)	**3 (1-5)**	**2 (1-5)**	**3 (1-5)**	P1=0.003* P2=0.536 P3=0.198
Abortion Number(percent) Yes No	 12 (37.5%) 20 (62.5%)	 12 (32.4%) 25 (67.6%)	 4 (36.4%) 7 (63.6%)	P1=.659 P2=0.946 P3=0.808

Preterm Number(percent) Yes No	0 (0%) 32 (100%)	2 (5.4%) 35 (94.6%)	1 (9.1%) 10 (90.9%)	P1=0.495 P2=0.238 P3=1.0
Place of first section Number(percent) MUH Outside MUH	4 (12.5%) 28 (87.5%)	5 (13.5%) 32 (86.5%)	3 (27.3%) 8 (72.7%)	P1=1.0 P2=0.252 P3=0.361
Previous pregnancy complications Number(percent)				
PET CS scar ectopic Gestational diabetes Gestational diabetes & PET Pulmonary embolism Vesicular mole Rupture uterus IUFD No	1 (25.0%) 1 (25.0%) 1 (25.0%) 1 (25.0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 28 (87.5%)	3 (42.9%) 0 (0%) 0 (0%) 0 (0%) 1 (14.3%) 1 (14.3%) 1 (14.3%) 1 (14.3%) 30(81.1)	0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 11 (100%)	P1=0.623 P2=0.646 P3=0.838

MUH... Mansoura university hospitals.

PET...pre eclampsia.

IUFD...intrauterine fetal death.

The table (3) shows that median gravidity is 5(2-7)in placenta accreta more than placenta non accreta 3(2-8). P1=0.005 and median parity is 3(1-5) in Placenta accreta more than placenta non accrete 2(1-5) P1=0.003. Median number of cesarean sections is significant in Placenta accrete 3(1-5) than placenta non accrete 2 (1-5) P1=0.003.

Table (5): Ultrasound & doppler criteria among the studied groups:

	Placenta accreta (n=32)	No placenta accreta (n=37)	Unsatisfactory (n=11)	P value
Ultrasound criteria				
Clear zone ***Number(percent)*** Lost Present	29 (90.6%) 3 (9.4%)	30 (81.1%) 7 (18.9%)	11 (100%) 0 (0%)	P1=0.261 P2=0.558 P3=0.119
Lacunae grade ***Number (percent)*** Grade 1 Grade2 Grade3	3 (9.4%) 16 (50.0%) 13 (40.6%)	10 (27.0%) 21 (56.8%) 6 (16.2%)	4 (36.4%) 5 (45.5%) 2 (18.2%)	P1=0.036* P2=0.093 P3=0.896
Bladder wall interruption ***Number (percent)*** Yes NO	7 (21.9%) 25 (78.1%)	2 (5.4%) 35 (94.6%)	1 (9.1%) 10 (90.9%)	P1=0.043* P2=0.347 P3=1.0
Placental pulge ***Number (percent)*** Yes No	4 (12.5%) 28 (87.5%)	2 (5.4%) 35 (94.6%)	1 (9.1%) 10 (90.9%)	P1=.405 P2=1.0 P3=1.0

Focal exophytic mass ***Number (percent)*** Yes No	 1 (3.1%) 31 (96.9%)	 2 (5.4%) 35 (94.6%)	 0 (0%) 11 (100%)	P1=1.0 P2=1.0 P3=1.0
Doppler criteria				
Uterovesical hypervascularity ***Number (percent)*** Yes No	 27 (84.4%) 5 (15.6%)	 18 (48.6%) 19 (51.4%)	 7 (63.6%) 4 (36.4%)	P1=0.002* P2=0.145 P3=0.382
Subplacental hyprtvascularity ***Number (percent)*** Yes No	 30 (93.8%) 2 (6.2%)	 30 (81.1%) 7 (18.9%)	 9 (81.8%) 2 (18.2%)	P1=0.161 P2=0.558 P3=0.956
Bridging vessels ***Number (percent)*** Yes No	 19 (59.4%) 13 (40.6%)	 14 (37.8%) 23 (62.2%)	 6 (54.5%) 5 (45.5%)	P1=0.074 P2=0.779 P3=0.324
Lacunae feeder vessels ***Number (percent)*** Yes No	 26 (81.2%) 6 (18.8%)	 28 (75.7%) 9 (24.3%)	 11 (100%) 0 (0%)	P1=0.576 P2=0.122 P3=0.07

The table (5) shows that Lacunae grade 3 is more significant in Placenta accrete (40.6%) than placenta withour accreation (16.2%) than unsatisfactory group(18.2%) P1=0.036 and bladder wall interruption is more significant in Placenta accreta (21.9%) more than placenta without accreation (5.4%) P1=0.043 also uterovesical hypervascularity is more significant in Placenta accreta (84.4) than placenta without accreation

Table (6): Intraoperative intervention among the studied groups :

	Placenta accreta (n=32)	No placenta accreta (n=37)	Unsatisfactory (n=11)	P value
Surgical procedures				
Surgical technique ***Number (percent)*** *Resection of lower uterine segment & cervicoisthmic sutures	 15 (46.9%) 17 (53.1%)	 9 (24.3%) 28 (75.7%)	 8 (72.7%) 3 (27.3%)	P1=0.05* P2=0.138 P3=0.003*
Bilateral uterine artery ligation ***Number(percent)***	32 (100%)	37 (100%)	11 (100%)	-
Internal iliac artery ligation ***Number(percent)*** Yes	 12 (37.5%) 20 (62.5%)	 7 (18.9%) 30 (81.1%)	 4 (36.4%) 7 (63.6%)	P1=0.085 P2=0.946 P3=0.227
Intra operative complications				
Intra operative complications ***Number(percent)*** Intra operative complications Yes No	 **11 (34.4%)** 21 (65.6%)	 **7 (18.9%)** 30 (81.1%)	 **4 (36.4%)** 7 (63.6%)	P1=0.145 P2=1.0 P3=0.227

Intra operative complications ***Number(percent)*** Blood loss Bladder injury Bladder injury & blood loss	 9 (81.8%) 1 (9.1%) 1 (9.1%)	 4 (57.1%) 3 (42.9%) 0 (0%)	 3 (75%) 1 (25%) 0 (0%)	P1=0.146 P2=1.0 P3=0.474
Bladder dissection ***Number(percent)*** Easy Difficult	 18 (56.2%) 14 (43.8%)	 32 (86.5%) 5 (13.5%)	 7 (63.6%) 4 (36.4%)	P1=0.005* P2=0.668 P3=0.088
Amount of blood loss Median (range)	1500 (400-5000)	1000 (300-4000)	2000 (800-6400)	P1=0.011* P2=0.539 P3=0.007*
Intraoperative blood transfusion Median (range)	2.5 (1-8)	2 (0-7)	3 (2-10)	P1=0.006* P2=0.178 P3=0.001*

The table(6)shows that Resection of lower uterine segment and cervicoisthmic sutures is more significant in Placenta accreta (46.9%) than placenta without accreation (24.3%) P1=0.05 and difficul bladder dissection is more significant in Placenta accreta (43.8%) than placenta without accreation (13.5%) P1=0.005 also amount of blood loss is more significant in Placenta accrete (median 1500 ml) than placenta without accreation (median 1000 ml) P1=0.011 and intraoperative blood transfusion is more significant in Placenta accrete median 2.5 (1-8) than placenta without accretion median2 (0-7) P1=0.006

Table (7) intraoperative evaluation of placenta accrete according to FIGO stages:

	Placenta accreta (n=32)	No placenta accreta (n=37)	Unsatisfactory (n=11)	P value
Grade 1	2 (6.2%)	13 (35.1%)	2 (18.2%)	P1=0.001*
Grade 2	14 (43.8%)	19 (51.4%) V	4 (36.4%)	P2=0.374
Grade 3a	13 (40.6%)	5 (13.5%)	3 (27.3%)	P3=0.057
Grade 3b	3 (9.4%)	0 (0%)	1 (9.1%)	
Grade 3c	0 (0%)	0 (0%)	1 (9.1%)	

The table (7)shows that intraoperative FIGO grade 3 a is more significant in Placenta accreta (40.6%)than placenta without accreation (3.5%)P1= 0.001.

Table (8): Pre and post -operative Hb &ICU & hospital stay among the studied groups

Placenta accreta (n=32)		No placenta accreta (n=37)	Unsatisfactory (n=11)	P value
Preoperative Hb Mean ± SD	10.63±1.08	10.77±1.04	11.04±1.23	P1=0.591 P2=0.298 P3=0.466
Postoperative Hb Mean ± SD	11.08±1.19	11.07±1.43	10.38±0.98	P1=0.994 P2=0.089 P3=0.140

Postoperative ICU admission number-percent) Yes No	2 (6.2%) 30 (93.8%)	1 (2.7%) 36 (97.3%)	1 (9.1%) 10 (90.9%)	P1=0.471 P2=1.0 P3=0.410
Hospital stay (Days) Median (range)	10.5 (4-26)	11 (4-40)	10.5 (8.5-12)	P1=0.842 P2=0.171 P3=0.289

Preoperative Hgb shows no significance by statistical analysis as in placenta accreta mean 10.63 and placenta without accreation 10.77 and unsatisfactory 11.04, also postoperative Hgb shows no significance by statistical analysis as in placenta accreta mean 11.08 and placenta without accreation 11.07 and nonsatsifactory 10.38.

Postoperative ICU admission shows no significance in placenta accreta 2(6.2%) and placenta without accreation (2.7%) also days of hospital stay show no significance in placenta accreta median 10.5 and placenta without accreation median 11.

Table (9): Proportion of placenta accreta and no accreta cases according to histopatholpgy

	The studied group (n=80)	
	No	**%**
Placenta accrete(number -percent) **• Grade 1** **• Grade 2** **• Grade 3**	**32** 16 13 3	**40.0** 50.0 40.6 9.4
No placenta accrete (number-percent)	**37**	**46.2**
Unsatisfactory cases(number-percent)	**11**	**13.8**

Proportion of placenta accreta in studied groups according to histopathology is 30 case (40%) ... placenta figo grade 1 ===16 case & placenta figo grade 2 ==13 case & figo grade 3==3 cases .

Placenta non accrete number 37 case (46.2%),also unsatisfactory 11 case (13.8%).

Integrated score is more significant in Placenta accrete median 9 (5-10) than placenta without accreation median 8 (6-9) than unsatisfactory median 8 (7-10) P1<0.001

Table (10): Integrated score among the studied groups

Integrated score	**Placenta accreta (n=32)**	**No placenta accreta (n=37)**	**Unsatisfactory (n=11)**	**P value**
Mean ± SD	8.97± 1.06	7.92±0.98	8.54±0 .93	P1<0.001*
Median	9.0	8.0	8.0	P2=0.248
Range	5-10	6-9	7-10	P3=0.067

Table (11): Receiver operating characteristics curve (ROC) for prediction of placenta accrete by integrated score.

AUC	**95% CI**	**Cutoff**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
0.778	0.67 0.89	8.5	71.9%	64.9%	63.9%	72.7%	68.1%

AUC: Area under the curve, CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value.

Integrated score is highly sensitive for prediction of placenta accreta spectrum (71.9%) and specificity 64.9% and cut off level is 8.5 also positive predicitive value is 63.9% and negative predicitive value is 72.7% and accuracy of the score is 68.1% .

Discussion

The current study assesses the diagnostic accuracy of its integrated scoring system through Receiver Operating Characteristics (ROC) curve analysis. The findings demonstrate a considerable sensitivity (71.9%) in predicting the presence of placenta accreta spectrum while preserving a specificity of 64.9%. The calculated cut-off level of 8.5 on the integrated score served as a threshold for distinguishing between different levels of risk. Further its positive predictive value, correctly predicts the presence of placenta accreta, was 63.9%, while the negative predictive value, was 72.7%. The overall accuracy of the integrated score was estimated at 68.1%, further affirming its potential to provide a reliable assessment of placenta accrete. Furthermore, the Area under the Curve (AUC) value of 0.778 in the ROC analysis signifies the integrated score's ability to discriminate between placenta accreta and non-accreta cases.

Similar analyses are conducted in some studies. They also use ROC curve analysis to evaluate their scoring systems' performance in predicting PAS. Our integrated scoring system's sensitivity (71.9%) is relatively lower than the sensitivities reported in some other studies (e.g., Mahboobeh fard: 83.3%, Yisu GAO: 91.84%, Abd El-Gaber Ali: 92.3%). This suggests that your system may have a higher likelihood of false negatives, meaning it might miss some cases of PAS (11). The specificity of your integrated scoring system (64.9%) is also less than the specificities in other studies (e.g., Yisu Gao: 87.27%, Abd El-Gaber Ali: 94.1%). Moreover, the accuracy of your integrated scoring system (68.1%) is within the range reported by other studies (e.g., Mahboobeh fard: 82.6%, Vajiheh Marsoosi: 86.54%)(12). Another research has validated the Placenta Accreta Index (PAI) as a reliable predictor of placenta accreta syndrome (PAS). The PAI's sensitivity (87%) and specificity (77%) are significant factors in assessing the efficacy of predictive models(13). The effectiveness of the PAI in predicting PAS supports the utilization of a scoring system like ours for accurate prediction. Furthermore, other studies underscore the importance of incorporating ultrasound features in predicting PAS(14).

The current study highlights the significance of ultrasound and Doppler criteria in predicting PAS severity. Parameters such as lacunae grade, bladder wall interruption, and uterovesical hypervascularity were found to be significantly more pronounced in the placenta accreta group, implying their potential as markers for identifying PAS. Other study reinforces this notion, indicating that several ultrasound criteria, including absence of retroplacental clear zone, abnormal placental lacunae, and hypervascularity, can accurately diagnose placenta accreta and its variants(15). Keita Hasegawa's findings align with this by showcasing that PAI > 2 is a useful cut-off point for predicting PAS. Notably, the presence of severe placental lacunae and thin myometrial thickness further supports the role of these ultrasound criteria in identifying PAS(16). These findings align with the current study's results, which highlight the significance of similar ultrasound and Doppler criteria in differentiating between PAS and non-accreta cases. Others have placed considerable emphasis on the predictive capacity of ultrasound and Doppler markers in identifying placenta accreta spectrum (PAS) and predicting outcomes in their researches. Their study delved into the value of ultrasound markers in prognosticating major intraoperative blood loss in PAS cases. The parameters they identified, including the quantity of lacunae, subplacental hypervascularity, and tortuous vascularity with chaotic branching, as well as the presence of bridging vessels(17), align with the Doppler assessment parameter in the predictive model of the present study.

The current study introduces an integrated scoring system comprising five parameters

to predict PAS severity. These parameters include cesarean sections, lacunae grade, retroplacental clear zone, Doppler assessment, and intraoperative evaluation. Several other studies, also integrate multiple ultrasound parameters to predict PAS outcomes. These parameters include abnormal lacunae, bladder wall interruption, myometrial thickness, placental location, bridging vessels, and more (18). The association of these parameters across studies suggests a consensus on the significance of specific ultrasound markers in predicting PAS severity. The current study's scoring system reflects this consensus by incorporating similar parameters. Moreover, some studies focus on incorporating specific ultrasound features like lacunae, bladder wall interruption, uterine-bladder serous interface disruption, placental bulge, placental location, and hypervascularity into their scoring systems(19). These shared ultrasound features confirm the significance of such markers in predicting PAS and support the consistency of findings across studies.

Conclusions and implications for practice

In conclusion, the present study's findings serve to underscore the strong association between multiple previous cesarean sections and the presence of PAS thereby increasing the risk of this condition. Additionally, the predictive model is supported by gravidity, parity, and cesarean count, which are significant predictors. Furthermore, the identification of ultrasound and Doppler criteria as crucial indicators for predicting PAS severity is noteworthy. The significant differences observed between the placenta accreta and non-accreta groups in parameters such as lacunae grade, bladder wall interruption, and uterovesical hypervascularity highlight the potential of these markers in identifying cases of PAS and emphasize the importance of ultrasound evaluations in predicting severity.

The present study's introduction of an integrated scoring system evinces its effectiveness in the stratification of placenta accrete cases, while also demonstrating its potential to augment clinical decision-making. The scoring system's capacity to distinguish between PAS and non-accreta cases, as well as its sensitivity and specificity values, corroborate its usefulness. Furthermore, the established risk stratification cut-off level and Area AUC value serve to further underscore the scoring system's discriminative efficacy and clinical applicability.

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Age Related Antral Follicle Count Nomogram for Egyptian Women

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Declarations of interest:

The authors declare that they have no competing interests.

Abstract

Objectives : To investigate relation between antral follicle count (AFC) and chronological age to determine normal values for AFC in women with regular menstrual cycles.

Study design : A Cross-sectional study was conducted on 575 women aged from 18–48 years with regular menstrual bleeding at EL-Shatby Maternity University Hospital to assess the AFC, scanning was performed in the early follicular phase. the results were compared with previous nomogram.

Results: 575 normal menstruating females were categorized into 5 groups according to their ages and TVUS was done in the early follicular phase to detect the AFC. There's significant linear decline in mean AFC along different age groups in normal menstruating women with significant decline after age 38 years, There's a negative linear relationship between age and AFC in all studied centiles in normal menstruating women.

Conclusion: the first step in providing patients with scientifically based counselling is the creation of a nomogram of AFC values for assisted reproductive technologies and also for the natural conception chance and pregnancy outcome.

Key words: Antral follicle count; Nomogram; Ultrasonography.

INTRODUCTION

The ovarian reserve (OR) can be defined as the number and quality of the remaining follicles and oocytes in both the ovaries at a given age.[1] Decrease in the follicles number under a threshold level results in irregular cycles and eventually menopause therefore decrease in their quality leads to poor reproductive outcome.

Folliculogensis starts in early fetal life reaching a maximum number of 6 to 7 million at 20 weeks, concurrently with the process of atresia. At time of birth, the number of follicles that are available range from 1 to 2 million. After puberty, a

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number of follicles was selected, one of them grows to be the dominant follicle and rest become degenerated and undergo apoptosis. The atrophied follicles cannot regenerate again. Due to the gradual depletion of primordial follicles number, the antral follicular count (AFC) decreases and the accelerated decrease in numbers after remaining of less than 25,000 primordial follicles.[2, 3]

After the age of 31 years the female fecundity declines and accelerated after the 37 years , and by age of 41 years leading to sterility [4] The degree of decrease differs considerably between females of the same age.

An indirect indicator of a woman's remaining follicular pool is provided by ovarian reserve tests(ORT) [5] .An ideal tests should be easy to conduct and repeatable, an optimal ORT should enable the distinction between women who have a normal ovarian response and those who do not.[6]

ORTs are divided in to clinical by Age, Menstrual cycle characteristics. Biochemical: including FSH, E2, Inhibin B, AMH. And Ultra sonographic: by AFC, Ovarian volume and Ovarian blood flow. Or Dynamic using Clomiphene citrate challenge test or Gonadotropin agonist stimulation test or Exogenous FSH ovarian response test.

Ovarian antral follicles can be identified and counted using transvaginal ultrasound. [7, 8]

Since the availability of a test to evaluate the true ovarian reserve is not present, AFC is accepted as a good representive marker. [9, 10]AFC is regularly assessed in women of reproductive age, for different reasons as in infertility and work-up of assisted reproduction technique. [11] In prediction of the risk of menopause.[12, 13] to detect the suspicion of ovulatory dysfunction as a consequent of hyperandrogenism anovulation[14, 15] and in other specific clinical situations.[7, 16]

It is a non-invasive easy technique [17] that could be used as a marker for the ovarian reserve of each ovary distinctly.[14]

AFC and AMH evidently have the same accuracy in providing information as regards OR and in prediction of ovarian stimulation response.[14, 18-22] AMH assessment has restrictions because of the lack of international standardization [18, 21] and high-priced costs; A consistent automated test together with standardization should improve the assay's ability to predict ovarian response.[22]

One of the prominent advantage of AFC over AMH is that, the observer can evaluate many other significant aspects of the ovaries, like their position and the presence ovarian lesions as chocolate cysts or other lesions, and assessing the functional ovarian reserve by AFC, further more gaining important information as regards the fallopian tubes and the uterus. Combining both of AMH and AFC enhance the prediction of excessive ovarian stimulation response , but no prediction to poor ovarian response.[20]

AFC can be done any time in the menstrual cycle. Nevertheless, investigator should put in mind that in early follicular phase counting of follicles is more easier, and decreases the possibility of the presence of a corpus luteum or ovarian cysts, which might conceal some antral follicles.[7, 18]

AFC can predict both poor and exaggerated ovarian response [20, 23] and therefore, it is useful to categorize optimal gonadotropin dosage. [11, 23-25] AFC < 5–7 is related to small number of oocytes retrieved[26, 27] and decreased pregnancy rate.[28] A total AFC ≥ 20 is associated with high ovarian response and increase the risk of (OHSS). [18, 29-31]

AFC may help in prediction of menopausal age, AFC ≤ 4 being associated with high risk of menopause within 7 years (35%) when compared to other women with AFC > 4 (13%). [12, 13].

AIM OF THE WORK

To investigate the relationship between AFC and chronological age to establish normal values for AFC in women that have regular menstrual cycles.

PATIENTS

The study involved females that attend the outpatient clinic of El Shatby Maternity University Hospital for preconception counseling, contraception counseling, gynecological checkup or for infertility evaluation. Five hundred (575) women were selected with eligibility criteria: having regular menstrual cycle (length 25-35 days) with <5 days' difference between cycles, female age range from 18 -48 years, and presence of both ovaries .and all the antral follicles of 2–10 mm in diameter were included.

Females were excluded if age <18 years or >48years, had a history of taking hormones in the past six months, history of chocolate cyst cystectomy or detection of a current one or any ovarian surgery, history of pelvic inflammatory disease (PID), history of chronic systemic disease, metabolic or immunological disease, patients with poor ultrasound visualization of the ovaries, presence of at least one functional ovarian cyst >25mm.Women (n) will be categorized into 5 groups based on age:

i. 18-28 years **(n = 120)**

ii. 29-33 years **(n = 138)**

iii. 34-38 years **(n = 104)**

iv. 39-43 years **(n=113)**

v. 44-48 years **(n = 100)**.

METHODS

Cross-sectional study was conducted, informed consent from all women were taken, all patients have attended the clinic in their follicular phase of the menstrual cycle between day 2 and 4 to avoid the effect of intra-cycle variation, trans-vaginal sonography using MINDRAY DP-2200 ultrasound machine was done using two dimensional imaging with transvaginal transducer with a minimum frequency 7 MHz, to detect AFC in order to present AFC nomogram for general population for every age group in normal menstruating women, also to compare our data with previous studies in Normal women (La Marca et al)[32]

By using a systematic process for antral follicles counting:[31]

First Identify the ovary by Exploring the dimensions in two planes by performing a scout sweep and decide on the direction of the sweep to measure the size of follicles and count them, then measuring the largest follicle in two dimensions. If the largest follicle is less than 10 mm in diameter start to count from the outer ovarian margin of the sweep to the opposite margin and consider every round or oval transonic structure within the ovarian margins to be a follicle repeating the procedure with the other ovary and finally combine the number of follicles in each ovary to obtain the AFC.

If the largest follicle is greater than 10 mm in diameter a further detection of the size range of the follicles by measuring each sequentially smaller follicle, in turn, until a follicle with a diameter of less than 10 mm is found then performing a total count as described before regardless of follicle diameter finally, subtract the number of follicles of greater than 10 mm from the total follicle count.

STATISTICAL METHODS

Data were fed to the computer and analyzed using IBM SPSS software package version 21.0. (Armonk, NY: IBM Corp) The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using mean and standard deviation. Significance of the obtained results was judged at the 5% level. The used tests were Student t-test, Pearson coefficient and Bland Altman plot

For agreement with other study Bland Altman plot was used and one sample t test (between the difference and zero) (if significant then there is fixed bias).

The Bland Altman statistical method was used to measure the limits of agreement between our study and previous studies. The difference between the two studies per centile was calculated and plotted against the mean of the two studies per centiles separately. Then the limits of agreement were calculated as d ±2 SD where 'd' is the mean of the difference between the two studies and 'SD' is the standard deviation of the difference [33].

RESULTS

There's significant linear decline in mean AFC along different age groups in normal menstruating women with significant decline after age 38 years as shown in Table (1), There's a negative linear relationship between age and AFC in all studied centiles in normal menstruating women. and on detecting values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women as shown in Table (2) and represented in figure (1)

On using Bland altman's plotting between our study and la marca study[32], there was positively correlated (there's an agreement) to the other study, which means that centiles in both studies decline by the same interval per year. As shown in Table (3) and figure (2).

DISCUSSION

This study was to investigate the relationship between AFC and age on a large general population. Most of studies have investigated AFC in patients with known fertility or infertile patients.

On planning this study, we scheduled to include number of healthy women aged between 18- 48 years with regular menstrual cycle (length 25-35 days) with less than five days difference between cycles and with the presence of both ovaries, These women have attended the clinic for ultrasound examination for estimation of Antral follicular count using transvaginal sonography.

The results of our study have confirmed that there is an age related decrease in AFC. With (R^2 =0.32 for normal women), which mean 32% from change in AFC is related to age. Like previous studies there was numerous discrepancy in AFC in different age groups, and age alone have explained the decrease in AFC.

As regard normal menstruating women, the study revealed that the median of AFC was 0.4 follicle per year which was similar to La Marca et al[32] who have found that there was age related decline in AFC with median decline also 0.4 follicle per year.

In our study we found that there was significant negative linear relationship between age and AFC along different age groups in normal menstruating women, these findings was similar to La marca et al [32]who also reported a negative linear relationship between age and AFC in normal women.

In contrast Almog et al[34] have reported a biphasic linear correlation reflecting two different rates of antral follicle count loss by age for most percentiles in normal healthy women, This difference might be related to the features of the study population.

However, the highest rate of follicle loss was between age of 18 and 30. These results confirm previous reports of age related decrease in AFC among normal women.

Regarding the impact of aging on AFC, the literature contains scant and unclear evidence. Scheffer et al [17] described a biphasic pattern of AFC reduction as it decreased by 4.8% per year before the age of 37 years, then declined to11.7% after this threshold .The same dataset had a 2 second analysis and a model with linear decline in AFC till the age of 43 years followed by an exponential decrease with asymptote at zero was used to explain the data. The conventional linear model provided the most accurate match to the AFC in all other studies investigating the correlation between age and AFC. We also aimed to establish the normal values

for AFC in normally menstruating women using IBM SPSS statistics program version 21. we estimated centiles for AFC all over the female reproductive period in normal healthy women for the first time, a nomogram reporting normal and interquartile values for AFC, age by age, throughout the reproductive period has been provided.

By subjective comparison between our data and La Marca et.al. 's data, it was observed that our centiles are slightly higher than LaMarca 's et al [32]centiles which may be due to racial or ethnic variety of different population.

Bland Altman's plot [33] is a statistical analysis, based on the quantification of the agreement between two quantitative measurements by studying the mean difference and constructing degree of agreement.

We have used it to study the degree of agreement between our study and la Marca in normal menstruating women, by calculating [1] correlation coefficient(r) which when positively significant (<0.001) means the two groups correlated to each other and [2] Mean difference between both groups which is represented as fixed bias which is present due to different studied population number or different characteristics.

When the centiles of our study and other study La Marca et al[32]were plotted according to Bland Altman plotting in normal menstruating women, there was found that all points were situated at the mean ± 1.96 which explain that our study was positively correlated(there's an agreement) to the other study, which means that centiles in both studies decline by the same interval per year.

CONCLUSIONS

AFC is the most common measured variable that is connected to ovarian function. However, because there were no normal data up to this point, the interpretation of the measurement was mostly dependent on the operator's unique experience. Therefore, the first step in providing patients with scientifically based counselling is the creation of a nomogram of AFC values, to give a clear idea regarding their potential fertility for assisted reproductive technologies as well as for spontaneous conception and the outcome of pregnancy, particularly in the event of ovarian disease such as endometriomas, which are more likely to be linked to decreased AFC.

Conflict of interest

There is no conflict of interest.

Table (1): The descriptive value for AFC that are stratified according to female age

Female age	N	AFC Mean ± SD.
18 – 28	120	15.77 ± 3.83
29 – 33	138	14.34 ± 3.61
34 – 38	104	13.17 ± 4.45
39 – 43	113	9.43 ± 3.80
44 – 48	100	4.08 ± 1.92

SD: **Standard deviation**

Table (2) Values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women

Our data

Age (years)	5th	25th	50th	75th	95th
18	10	14.75	15.5	18.5	20
19	10	14.5	17.5	20.25	22
20	15	17	18	19.75	21
21	7	12.75	15.5	20	22
22	12	14.5	16.5	18.5	20
23	14	16	18	20	20
24	12	15.5	17	17	17
25	5	7.5	13.5	18.5	22
26	11	12	17	20	22
27	7	13	15	17	22
28	7	8.5	14.5	18	18
29	10	14.5	16	17.5	20.5
30	7	13	15	17	23
31	6.05	12	15	16	20.95
32	7	13	14.5	15	20.9
33	6.15	8.75	12.5	15	22.1
34	6.2	10	14	18	22
35	6.05	8.75	13.5	16.5	21.95
36	5	9.5	15	15.5	20
37	5	9	13	15	18.7
38	7	7	13	13	19
39	5	11.5	12	14.5	16
40	3.2	7	8	11	14.8
41	5	6.25	8.5	11.75	19.8
42	3.15	4.75	7.5	9.25	20.25
43	5	6	7	10	11
44	3.1	5	6	7	9
45	2	3.5	4	5	7.7
46	1.05	2	4	5	6
47	1	2	3	4	5
48	1	2	2.5	3.25	5.85

LaMarca et al data

Age (y)	5th	25th	50th	75th	95th
16	6.2	11.6	16.6	22.6	33.2
17	6.0	11.4	16.2	22.1	32.4
18	5.9	11.1	15.8	21.5	31.6
19	5.7	10.8	15.4	21.0	30.8
20	5.6	10.5	15.0	20.5	30.0
21	5.4	10.2	14.6	19.9	29.2
22	5.3	10.0	14.2	19.4	28.4
23	5.1	9.7	13.8	18.8	27.6
24	5.0	9.4	13.4	18.3	26.8
25	4.8	9.1	13.0	17.7	26.0
26	4.7	8.8	12.6	17.2	25.2
27	4.6	8.6	12.2	16.6	24.4
28	4.4	8.3	11.8	16.1	23.6
29	4.3	8.0	11.4	15.5	22.8
30	4.1	7.7	11.0	15.0	22.0
31	4.0	7.4	10.6	14.4	21.2
32	3.8	7.1	10.2	13.9	20.4
33	3.7	6.9	9.8	13.4	19.6
34	3.5	6.6	9.4	12.8	18.8
35	3.4	6.3	9.0	12.3	18.0
36	3.2	6.0	8.6	11.7	17.2
37	3.1	5.7	8.2	11.2	16.4
38	2.9	5.5	7.7	10.6	15.6
39	2.8	5.2	7.3	10.1	14.8
40	2.6	4.9	6.9	9.5	14.0
41	2.5	4.6	6.5	9.0	13.2
42	2.3	4.3	6.1	8.4	12.4
43	2.2	4.1	5.7	7.9	11.6
44	2.0	3.8	5.3	7.3	10.8
45	1.9	3.5	4.9	6.8	10.0
46	1.7	3.2	4.5	6.3	9.2
47	1.6	2.9	4.1	5.7	8.4
48	1.4	2.7	3.7	5.2	7.6
49	1.3	2.4	3.3	4.6	6.8

Table (3): Comparison between our study and La Marca study using Bland altman's plotting

Centile	Age (years)	Our study	Other study	T	P
5th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	1.0 – 15.0 6.61 ± 3.68 6.15 **↑2.95 ± 2.60** 0.863*(<0.001*)	1.40 – 5.90 3.66 ± 1.35 3.70	6.310*	<0.001*
25th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	2.0 – 17.0 9.73 ± 4.43 9.50 **↑2.86 ± 2.45** 0.891*(<0.001*)	2.70 – 11.10 6.87 ± 2.55 6.90	6.507*	<0.001*
50th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	2.50 – 18.0 12.32 ± 4.75 14.0 **↑2.56 ± 2.11** 0.906*(<0.001*)	3.70 – 15.80 9.76 ± 3.68 9.80	6.763*	<0.001*
75th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	3.25 – 20.25 14.41 ± 5.17 16.0 **↑1.06 ± 2.09** 0.916*(<0.001*)	5.20 – 21.50 13.35 ± 4.96 13.40	2.811*	0.009*
95th	Min. – Max. Mean ± SD Median **Mean difference** **r (p)**	5.0 – 23.0 17.76 ± 5.54 20.0 **↓1.84 ± 4.94** 0.735*(<0.001*)	7.60 – 31.60 19.60 ± 7.27 19.60	2.076*	0.047*

t: Paired t-test for comparing between the two techniques (if significant there is a difference)
r: Pearson coefficient
*: Statistically significant at $p \leq 0.05$

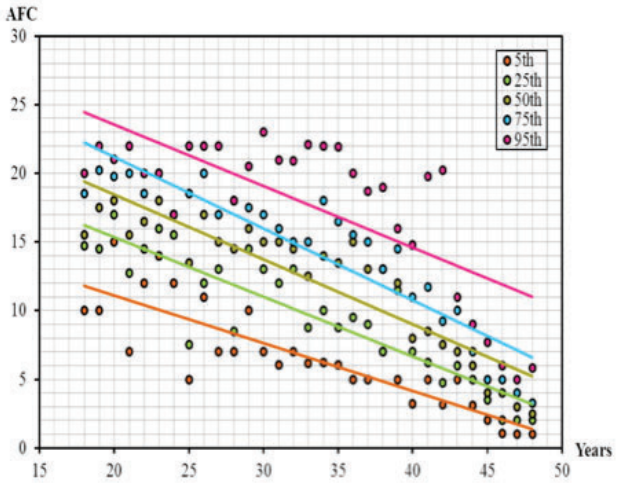

Figure (1): Values of 5th, 25th, 50th, 75th and 95th centiles as a function of age in normal menstruating women which proved that there's a negative linear relationship between age and AFC.

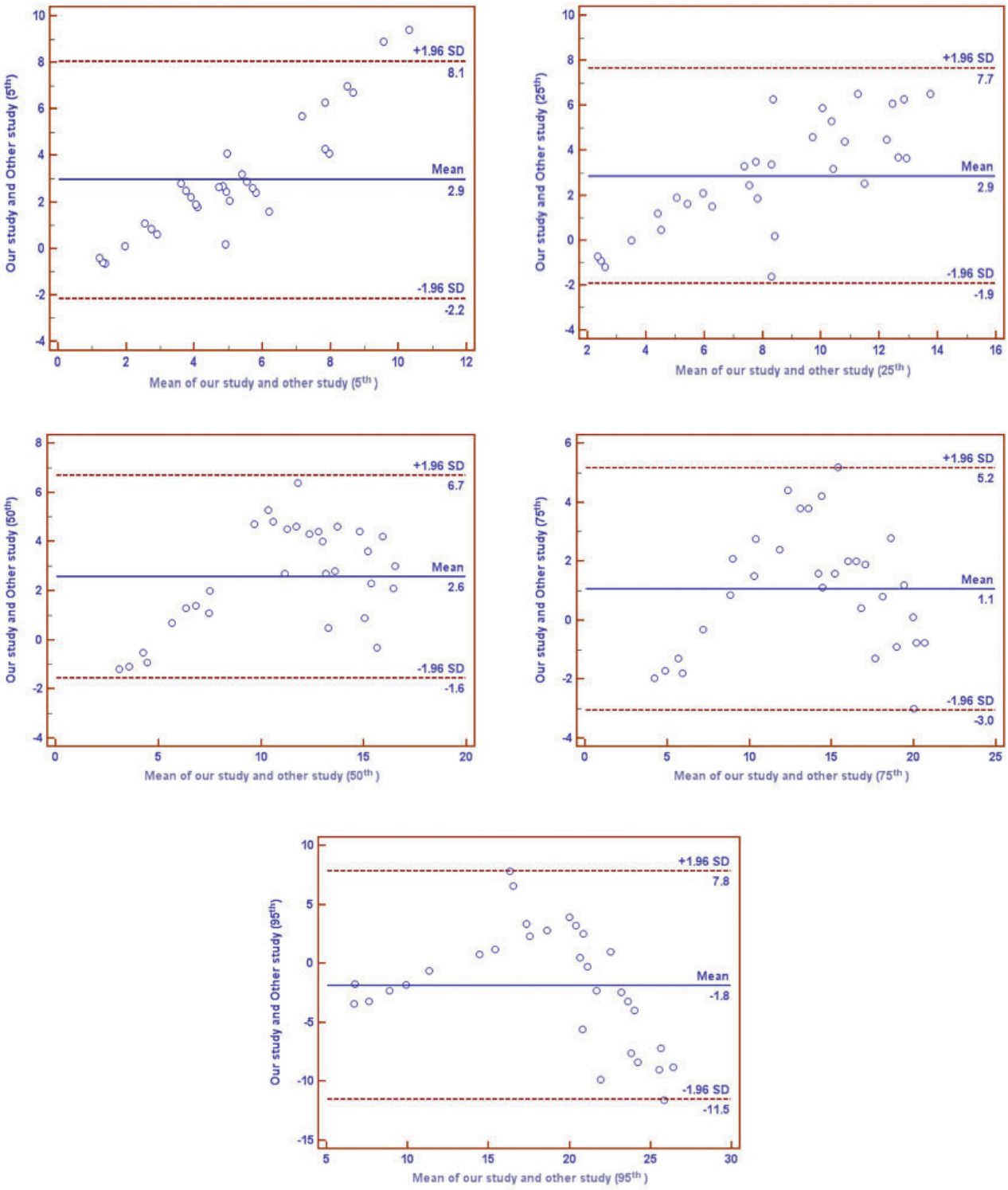

Figure (2): Comparison between our study and La Marca study concerning (5th 25th 50th,75th ,95th).

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