

*Issn 1110-6352*



# THE EGYPTIAN JOURNAL OF FERTILITY AND STERILITY

*Volume 28*

*Number 6*

*Nov.-Dec. 2024*

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(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 I, Hamberger L. Interaction between prostaglandins and catecholamines on cervical collagen. In: Topozada 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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## Letter from the Editor:

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*Dear colleagues,*

very interesting subjects are included in this edition. No sufficient evidence to recommend HSG as a first-line diagnostic tool for cesarean scar niche. However, in healthcare settings without ready access to hysteroscopy HSG may serve as an acceptable alternative as it is well-tolerated, cost-effective, less invasive and doesn't require special training rather than hysteroscopy, but hysteroscopy is still the valuable gold standard for detecting high-probability patients, even asymptomatic. Outpatient management of patients with PPROM is safe approach which can be adopted particularly in low-risk patients. Implementation of a perioperative surgical site infection prevention bundle was associated with a marked reduction in surgical site infection rate in patients undergoing gynecological oncology surgeries. Intraoperative placement of non-hormonal copper IUDs during caesarean delivery is a safe and effective contraceptive option with comparable complication rates to postpartum insertion. While hemoglobin levels were lower in the intrapartum group, overall outcomes support the feasibility and utility of this approach in clinical practice. Heart diseases in mothers are not absolute contraindications for pregnancy, but there were associated with serious outcomes on both the mothers and offsprings. The non-rheumatic heart diseases (mainly CHD) are associated with worse outcomes compared with the mothers with RHD. Surgical removal of endometriomas was associated with a significant decline in ovarian reserve. The decline in AFC and AMH was independent of other patient-related factors but for preoperative AMH, which affected post-operative AMH levels significantly. Patient Controlled Analgesia was better than TAP block since it covered visceral discomfort. In addition, Patient Controlled Analgesia may be administered without much difficulty, while transversus abdominis plane block requires further training as well as an intraoperative ultrasound equipment.

Best regards.

***Aboubakr Elnashar***

*MD*

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# Evaluation of the Diagnostic Role of Hysterosalpingography in Cesarean Scar Niche Diagnosed by Hysteroscopy

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## **Abstract**

**Background:** term CS niche (defect) describes the presence of hypoechoic area within the myometrium in the isthmus (lower uterine segment) with discontinuation of myometrium at the site of previous CS. Cesarean sections have increased worldwide and there is an increasing awareness of the adverse long-term sequelae associated with the procedure. The World Health Organization estimates that there are approximately 18.5 million women who undergo this procedure annually, with rates in the Western world increasing from 14.5% to 27.2% between the years 2000 and 2017.

**Aim of the Work:** To evaluate diagnostic role of hysterosalpingography (HSG) in cesarean scar niche at Early Cancer Detection and Gynecological Endoscopy Unit at Ain Shams Maternity Hospital within 6 months.

### **Patients and Methods:**

**Type of Study:** Diagnostic Accuracy Test.

**Study Setting:** Early Cancer Detection and Gynecological Endoscopy Unit at Ain Shams Maternity Hospital.

**Study Period:** 6 Months from the first of March 2022 to the end of August 2022.

**Study Population:** All women undergoing Office Hysteroscopy at Early cancer Detection and Gynecological Endoscopy Unit at Ain Shams Maternity Hospital was checked to meet the inclusion criteria for the study.

**Results:** There was not statistically significant between according to number of C.S. delivery. HSG test has low sensitivity (16%) but high PPV (100%) for detecting this condition, while the hysteroscopy has higher sensitivity (100%) but an undefined specificity and PPV since there are no true negatives. The NPV is 0% for both tests since there are no true negatives. The study results cannot provide recommendation regarding routine Hysterosalpingography examinations of CS scar defect. Women should avoid CS without medical indications and multiple abortions with uterine curettage. Nevertheless, more prospective high-quality studies are needed to establish the clinical significance of the CS scar niche and to define guidelines for the possible prevention of the CS scar niche in a subsequent pregnancy.

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**Conclusion:** no sufficient evidence to recommend HSG as a first-line diagnostic tool for cesarean scar niche. However, in healthcare settings without ready access to hysteroscopy HSG may serve as an acceptable alternative as it is well-tolerated, cost-effective, less invasive and doesn't require special training rather than hysteroscopy, but hysteroscopy is still the valuable gold standard for detecting high-probability patients, even asymptomatic.

**Keywords:** Hysterosalpingography, Cesarean Scar Niche, Hysteroscopy.

## **INTRODUCTION**

The term CS niche (defect) describes the presence of hypoechoic area within the myometrium in the isthmus (lower uterine segment) with discontinuation of myometrium at the site of previous CS <sup>(1)</sup>.

Cesarean sections have increased worldwide and there is an increasing awareness of the adverse long-term sequelae associated with the procedure. The World Health Organization estimates that there are approximately 18.5 million women who undergo this procedure annually, with rates in the Western world increasing from 14.5% to 27.2% between the years 2000 and 2017 <sup>(2)</sup>.

A cesarean scar niche, first described in 1961 when a wedge-shaped defect was noted in the uterine wall of a patient who had previously had a cesarean section during hysterosalpingography, <sup>(3)</sup> is defined as the presence of a hypoechoic area and discontinuation of the myometrium at a previous lower-segment cesarean section scar site <sup>(4)</sup>. Cesarean niche is also referred to as a cesarean scar defect, isthmocele, or a diverticulum. The presence of a cesarean scar niche is associated with gynecological symptoms such as abnormal uterine bleeding, dysmenorrhea, and subfertility, as well as potential adverse obstetrical outcomes resulting from cesarean scar pregnancy (CSP), uterine rupture, and placenta accreta spectrum (PAS) disorders <sup>(5)</sup>.

Cesarean scar defects are being more commonly reported but the incidence varied between 24 and 84%. Some women are asymptomatic, but others may have gynecologic symptoms <sup>(6)</sup> such as postmenstrual spotting, prolonged menstruation, continuous brown discharge, chronic pelvic pain <sup>(8)</sup>, and secondary infertility. These symptoms, taken together, have been closely investigated and are called cesarean scar syndrome <sup>(8)</sup>. Other problems associated with cesarean scar defect are a higher risk of complications during subsequent pregnancy, such as dehiscence, placenta previa or accrete and cesarean scar ectopic pregnancy, and difficulty with gynecologic procedures like uterine evacuation, hysteroscopy, and intrauterine device insertion <sup>(1)</sup>.

Recently, the clinical relevance of cesarean scar defects has attracted an increasing amount of attention, with more review articles published, because cesarean rates are rising worldwide. The etiology of niche related postmenstrual spotting and pain has not been fully elucidated. They are thought to be caused by retention of menstrual blood in a niche, which is intermittently expelled after most of the menstruation has ceased <sup>(4)</sup>.

Cesarean section is the most performed surgical procedure involving the uterus in the fertile women <sup>(9)</sup>, with the low transverse incision being the most common type of uterine hysterotomy. In the interpretation of HSG, awareness of the appearance of the cesarean scar defect is important in avoiding misdiagnosing the scar for underlying pathology or normal variants such as prominent cervical glands, post myomectomy diverticulum, synechiae, and focal adenomyosis <sup>(10; 11)</sup>.

## **AIM OF THE WORK**

To evaluate diagnostic role of hysterosalpingography (HSG) in cesarean scar niche at Early Cancer Detection and

Gynecological Endoscopy Unit at Ain Shams Maternity Hospital within 6 months.

## **PATIENTS AND METHODS**

**Type of Study:** Diagnostic Accuracy Test.

**Study Settings:** at Early Cancer Detection and Endoscopy Gynecological Endoscopy Unit at Ain Shams Maternity Hospital.

**Study Period:** 6 Months from the first of March 2022 to the end of August 2022.

**Study Population:** All women undergoing Office Hysteroscopy at Early cancer Detection and Gynecological Endoscopy Unit at Ain Shams Maternity Hospital was checked to meet the inclusion criteria for the study.

**Inclusion Criteria:** age more than 18 years, previous history of cesarean delivery, cesarean scar niche confirmed by Hysteroscopy and premenopausal status.

**Exclusion Criteria:** pregnancy, contrast allergy, active pelvic infection and medical history interfering with HSG.

**Sampling Method:** convenience sampling method.

**Sample Size:** sample size was calculated using PASS program, setting the type-1 error ( $\alpha$ ) at 0.05 and the power ( $1-\beta$ ) at 0.8. Results from previous study (Dalfo et al., 2004), showed that HSG had a sensitivity of 81.2% and a specificity of 80.4%, in comparison with hysteroscopy. Calculation according to these values produced a sample size of 50 cases.

**Ethical Considerations:** our study received the approval of the local Ethical Committee of Faculty of Medicine, Ain Shams University. The protocol was discussed by the ethical scientific committee for approving the study a written informed consent was obtained from all participants before starting the procedure after explanations the steps and the potential complications of each diagnostic modality. Study Population was selected regarding the

appropriate inclusion and exclusion criteria.

**Study Procedures:** *After a written consent was taken, the recruited women were subjected to the following:* careful and detailed history, personal history: Age, name, residence, occupation, socioeconomic standard, and special habits of medical importance, menstrual cycle history, detailed obstetric history with taken the number of spontaneous abortions (causes, gestational age if possible) and past medical history: history of cardiac problems, history of diabetes mellitus, hypertensive disorders, chest diseases, renal diseases, blood diseases or bleeding tendency and surgical intervention, dilatation and curettage and the occurrence of post-operative complication.

**Physical examination, Including:** general examination, vital data (temperature, blood pressure, respiratory rate, pulse), chest and cardiac examination, abdominal examination and pelvic examination.

**Office hysteroscopy procedure:** Technique: the hysteroscopic examination was performed using a rigid 30-degree hysteroscope with a 4 mm diameter diagnostic sheath (Karl Storz Endoscope, Turrilingen, Germany). High-intensity cold light source and fiber optic cable were used to illuminate the uterine cavity. Normal saline solution was used to distend the uterine cavity with flow between 200 and 350 ml/min, at 30-40 mmHg. Patient was placed in the dorsal lithotomy position, after the patient was asked to empty her bladder. The thighs should be at a 90-degree angle to the pelvis to create enough space for the surgeon to manipulate the hysteroscope.

The patient perineum should be just past the edge of the table. Normal saline was used for uterine distension connected to the inflow channel on the sheath with intravenous tubing.

A vaginal wash with saline solution was performed without placing speculum. Before the hysteroscope and sheath insertion into the external os, the sheath was flushed to

remove the air. The tip of the hysteroscope was positioned in the vaginal introitus, the labia being slightly separated with fingers. The vagina was distended with saline. The scope was driven to the posterior fornix to readily visualize the cervix and slowly backwards to identify the external cervical os. When this became visible, the scope was carefully moved forward to the internal os and then the uterine cavity with least possible trauma. The uterine cavity was systematically explored by rotating the fore-oblique scope to identify any anomaly in the uterine walls and/or the right and left tubal ostia. At this stage it is crucially important to avoid lateral movements as much as possible to reduce patient discomfort to a minimum. After that, the scope was removed, and the patient was asked to remain in the dorsal position for a few minutes to avoid vasovagal attack.

**Niche criteria in Hysteroscopy:** cesarean scar niche appears as a pouch-like anatomic defect on the anterior wall of the isthmus or of the cervical canal its superior third or less frequently at its mean inferior third. Niche location essentially depends on the site of the cesarean section, as patients with the defect in the higher part of the cervix previously underwent elective cesarean section, whereas in those in whom cesarean section was done in presence of cervical modifications, isthmocele is localized in the lower part of the cervical canal.

**HSG procedure:** (Ryan G Steward, 2021, Medscape) HSG was done at The Diagnostic Radiology Unit at Ain Shams Maternity Hospital. Hysterosalpingography was performed by radiologist of the diagnostic radiology unit. HSG was done between the 6th and 11th days of menstrual cycle (Day 1 is the first day of menstrual bleeding). Patient in lithotomy position. The uterine position was determined by a pelvic examination. The hystero-graphy placed into the cervical canal, and the radio opaque material dissolved

in 10-20 cc water and injected into the uterine cavity slowly with the assistance of fluoroscopy. An x-ray examination was performed twice: first, in the filling period of the uterine cavity by contrast material, and second in the spreading period of the abdomen.

**Niche criteria in HSG x-ray film:** A diverticulum or a pouch-like anatomic defect located at the site of previous caesarean delivery scar at the lower uterine cavity, uterine isthmus, or upper endocervical canal in patients with history of cesarean delivery.

**Data management and statistical Analysis:** data were collected, tabulated, and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and Med Calc 13 for windows (Med Calc Software, Ostend, Belgium). Qualitative data were described using number and percent and were compared by Chi2 test. Quantitative data were described using mean, standard deviation (SD), median, range, and interquartile range (IQR). The diagnostic value indices including the specificity, sensitivity, positive and negative predictive values as well as accuracy for the results were calculated. The significance of the obtained results was judged at the (0.05) level.

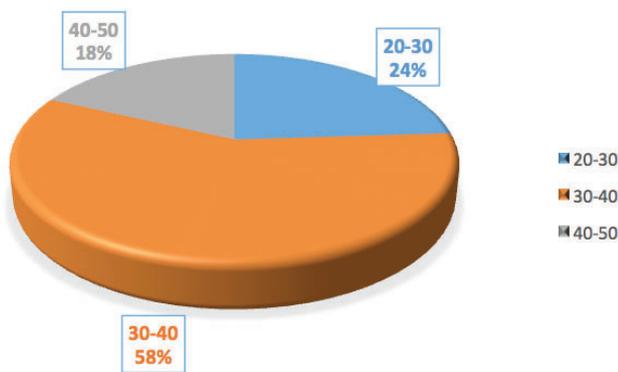
**The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:**  $P > 0.05$ : Non-significant (NS).  $P < 0.05$ : Significant (S).  $P < 0.01$ : Highly significant (HS).

## **RESULTS**

This study was carried out on fifty patients. The age ranged between (21 -47) years with mean  $\pm$  SD ( $34.7 \pm 5.8$ ) years. the majority of patients was ranged between (30-40) years and (20-30) years by 58% and 24% respectively as shown in Table (1), Figure (13).

**Table (1): The Distribution of all studied cases according to Demographic characters:**

Age in years:		
Min. – Max.	21 – 47 years	
Mean ± SD	34.7 ± 5.8	
Median (IQR)	35.0 (31.0 – 38.75)	
Age categories: (n=50)		
	20-30	12 (24.0%)
	30-40	29 (58.0%)
	40-50	9 (18.0%)

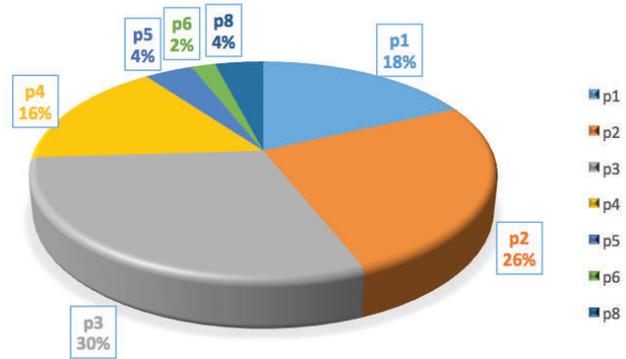


**Figure (1):** The Distribution of all studied cases according to Age categories

As a regard of parity, the parity distribution in all cases was diagnosed as p3 in 30% (15 patients), p2 in 26% (13 patients), p1 in 18% (9 patients), p4 in 16% (8 patients), p5 in 4% (2 patients) and p8 in 4% (2 patients) as shown in Table (2), Figure (14).

**Table (2): The Distribution of all studied cases according to Parity:**

Parity: (n=50)		
	p1	9 (18.0%)
	p2	13 (26.0%)
	p3	15 (30.0%)
	p4	8 (16.0%)
	p5	2 (4.0%)
	p6	1 (2.0%)
	p8	2 (4.0%)

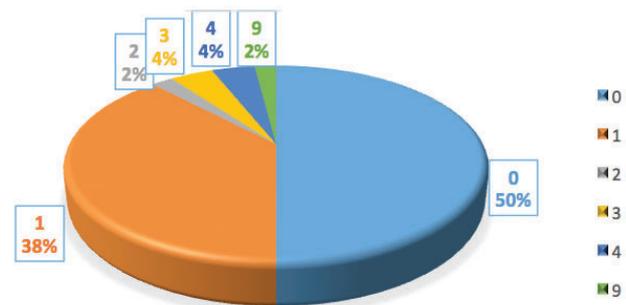


**Figure (2):** The Distribution of all studied cases according to Parity

The distribution of gravity in all studied cases was shown in Table (3), Figure (15), the most common gravity was 0 in 50% (25 patients) and 1 in 38% (19 patients).

**Table (3): The Distribution of all studied cases according to Gravity:**

Gravity: (n=50)		
	0	25 (50.0%)
	1	19 (38.0%)
	2	1 (2.0%)
	3	2 (4.0%)
	4	2 (4.0%)
	9	1 (2.0%)

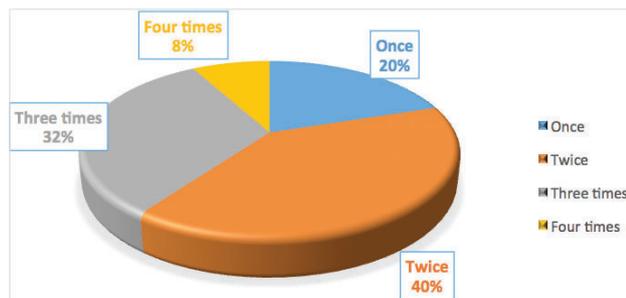


**Figure (3):** The Distribution of all studied cases according to Gravity

According to the number of caesarian delivery, 20 patients (40%) delivered twice, 16 patients (32%) delivered three times, 10 patients (20%) delivered once while 4 patients (8%) delivered four times as shown in Table (4), Figure (16).

**Table (4): The Distribution of all studied cases according to Number of caesarian delivery:**

Number of C.S. delivery: (n=50)		
Once	10	(20.0%)
Twice	20	(40.0%)
Three times	16	(32.0%)
Four times	4	(8.0%)



**Figure (4):** The Distribution of all studied cases according to the number of caesarian delivered

As a regard of HSG niche diagnosis, among 50 patients, 8 patients (16%) were diagnosed as positive while 42 patients (84%) were diagnosed as negative as shown in Table (5), Figure (17).

**Table (5): The Distribution of all studied cases according to HSG niche diagnosis:**

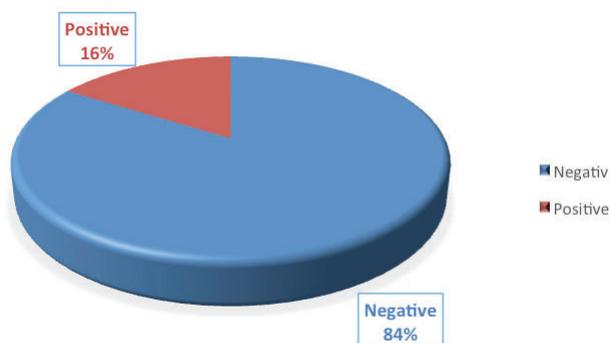
HSG niche diagnosis:		
Negative	42	(84.0%)
Positive	8	(16.0%)

**Table (7): Diagnostic performance of HSG Niche diagnosis as a regard of hysteroscopy niche diagnosis as a gold standard:**

Patient-based analysis	Modality	FN	TP	TN	FP	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	Accuracy 95% CI	P
All studies n=50	Hysteroscopy/ HSG	42	8	0	0	16% (0.07, 0.29)	0% (0.0, 1.0)	100% (0.63, 1.0)	0% (0.0, 0.08)	16% (0.07, 0.29)	<0.001*

P: p-value of Fisher’s test  
 PPV: positive predictive value

\*: statistically significant  
 NPV: negative predicative value



**Figure (5):** The Distribution of HSG niche diagnosis in all studied cases

As a regard of Hysteroscopy niche diagnosis, all patients (100%) were diagnosed as positive as shown in Table (6).

**Table (6): The Distribution of all studied cases according to Hysteroscopy niche diagnosis:**

Hysteroscopy niche diagnosis:		
Negative	0	(0.0%)
Positive	50	(100.0%)

Studying HSG behavior in the detection of niche diagnosis during patient follow up as a regard of hysteroscopy as a gold standard had an accuracy of 16%. The true positive (TP) cases were 8 patients, true negative (TN) cases were 0 patients while false positive (FP) cases were 0 patients. The diagnostic accuracy was with Sensitivity 16% and Specificity of 0%. HSG had a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 0% as shown in Table (7).

## **DISCUSSION**

**Main Study Finding:** The aim of the study is to evaluate the diagnostic role of HSG in cesarean scar niche diagnosed by hysteroscopy. And the main question to be answered is does HSG can diagnose Cesarean scar niche?

The study was conducted on 50 patients having cesarean scar niche diagnosed early by hysteroscopy to detect to what level of accuracy HCG detect niche.

After data interpretation the study shows that as regards age, the age ranged between (21-47) years with mean  $\pm$  SD ( $34.7 \pm 5.8$ ) years. The majority of patients ranged between (30-40) years and (20-30) years by 58% and 24% respectively.

As a regard of parity, the parity distribution in all cases was diagnosed as p3 in 30% (15 patients), p2 in 26% (13 patients), p1 in 18% (9 patients), p4 in 16% (8 patients), p5 in 4% (2 patients) and p8 in 4% (2 patients) with no significant difference.

HSG test has low sensitivity (16%) but high PPV (100%) for detecting this condition, while the hysteroscopy has higher sensitivity (100%) but an undefined specificity and PPV since there are no true negatives. The NPV is 0% for both tests since there are no true negatives.

**Comparison with other Literatures:** Etman et al. (12) found that regarding the relation between women Demographic data with Niches as diagnosed by Hysterosalpingography showed non-statistically significant differences (p-values  $>0.05$ ).

Van der Voet et al. (13) found that there was no statistically significant relation between niche as diagnosed by hydrosonography and women demographic data (p=0.44).

In study to Evaluate of uterine scar healing by transvaginal ultrasound in 607 nonpregnant women with a history of cesarean section,

Zhou et al. (14) showed that the average age of the two groups of patients was  $35.09 \pm 5.32$  versus  $34.00 \pm 4.83$  years old, and the median age of the two groups was 34 years old. In which there was insignificant difference between both studied groups as regards demographic data.

Bij de Vaate et al. (7) found that there was insignificant difference as regard demographic data (p =0.21).

Mohamed et al. 2021 showed that there was statistical significance between patients with and without niche observed by hysteroscopy regarding age (P value  $<0.001$ ).

Mohamed et al. (15) showed no statistical significance between patients with and without niche observed by hysteroscopy regarding parity (P value, 0.129).

Hafizi et al. (16) found that there was no significant difference between the cases who detected cesarean scar and who didn't as regard parity (p  $> 0.05$ ).

Bij de Vaate et al. (7) found that there was insignificant difference as regards obstetric history (p = 0.11).

Van der Voet et al. (13) found that there was insignificant relation between development of niche and number of cesarean section (p =0.55).

Savukyne et al. (18) found that in the patient group with CS scar niches (n = 49) for comparison with the non-niche group (n = 46), there were no statistical differences in the type of delivery. A total of 19 women had successful trials of labor in the niche group and 22 in the non-niche group (38.7% vs. 47.8%, p = 0.802). Fifteen underwent elective repeat Cesarean delivery for various clinical reasons in the niche group, in comparison with 33 women in the non-niche group (31.9% vs. 44.6% p = 0.337). Thirteen women required intrapartum emergency CS because of failed trials of labor in the niche group, versus 19 women in the non-niche group (40.6% vs. 46.3% p = 0.802).

In comparison with hystero-graphy diagnosis of cesarean scar defects, Regnard et al. (18) detected a lower rate of cesarean section scars (57.5%) via hysterosalpingography.

Anter et al. (19) found that HSG was able to detect CS scar defects in 21 cases (55.3%).

In the Indian study by Makrakis et al. 2009, a correspondence of 57.7% was obtained between the HSG and hysteroscopic findings, which are close to the rate observed in our study.

Acholonu et al. (20) found that the sensitivity of hysterosalpingography and hysteroscopy was 58.2% and 91.8%, respectively. The specificity for hysterosalpingography and hysteroscopy was 25.6% and 93.8%. The differences in sensitivity and specificity were both statistically significant.

Hysterosalpingography had a general accuracy of 50.3%, while hysteroscopy had a significantly higher accuracy of 95.5%.

One clear limitation of hysterosalpingography is the inability to precisely measure myometrial thickness and the size of the scar, both of which can be readily characterized via hystero-graphy (21).

In agreement with our results, Cepni et al. (22) revealed 75% sensitivity and 100% specificity of HSG compared to hysteroscopy in the detection of intrauterine adhesions.

Similarly, Hafizi et al. (16) found that sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of HSG in the diagnosis cesarean scar niche of women were 38.78%, 78.57%, 67.86%, 52.38%, and 57.14%, respectively, in comparison with those of hysteroscopy.

Etman et al. (23) found that using hysterosalpingography shown that it can diagnose post-CS niche as compared with hydrosomography with AUC of 0.867, level of sensitivity 83.9%, specificity 89.5%, PPV

92.9%, NPV 77.3% and accuracy 86%.

El-Mazny et al. (24) found that hystero-graphy was comparable to diagnostic hysteroscopy as shown by sensitivity, specificity, +ve predictive value, -ve predictive value and overall accuracy of 87%, 100%, 100%, 95% and 96%, respectively, in the diagnosis of scar defect; and 76%, 100%, 100%, 87% and 91%, respectively, in the diagnosis of intrauterine adhesions.

In a study performed in Babol, north of Iran by Zeinalzadeh et al. (26), sensitivity and specificity were reported as 71.4% and 92.3%, respectively. The specificity reported in the mentioned study was similar to the value obtained in the present study.

The gold standard is to look directly at the uterine cavity and scar tissue using hysteroscopy. However, HSG reveals the extent of the scar formation, while suggesting the presence of intrauterine adhesions. Furthermore, as there is a high correlation between the diagnosis by hysteroscopy and HSG, hysterosalpingography is known as one of the appropriate imaging techniques. HSG is commonly used as a first-line tool in the diagnosis of IUA because it is simple, safe, cost effective, sensitive, and minimally invasive procedure, allowing the visualization of the uterine cavity and tubal patency (26).

## **CONCLUSION**

No sufficient evidence to recommend HSG as a first-line diagnostic tool for cesarean scar niche. However, in healthcare settings without ready access to hysteroscopy HSG may serve as an acceptable alternative as it is well-tolerated, cost-effective, less invasive and doesn't require special training rather than hysteroscopy, but hysteroscopy is still the valuable gold standard for detecting high-probability patients, even asymptomatic.

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# Inpatient Versus Outpatient Management of Preterm Prelabour Rupture of Membrane. A Prospective Cohort Study

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## **Short title:**

Outpatient management of preterm prelabour rupture of membrane

## **Abstract**

**Objective:** To assess the effectiveness and safety of the outpatient management approach for patients with preterm prelabour rupture of membrane regarding the latency period, incidence of chorioamnionitis, and neonatal outcomes.

**Patients and Methods:** This prospective cohort study included 63 Patients with confirmed diagnosis of PPRM. All included patients were admitted to the inpatient ward for 48 hours where they received IV antibiotics and corticosteroids for fetal lung maturation then, 31 patients were managed as outpatient and 32 patients were managed as inpatient. The primary outcome was the latency period and gestational age at birth while the incidence of chorioamnionitis, and neonatal outcomes in terms of neonatal weight, neonatal intensive care (NICU) admission, and neonatal sepsis were secondary measures of outcome.

**Results:** The latency period (days) was significantly longer ( $29.4 \pm 15.8$  vs  $17.7 \pm 11.9$ ,  $p 0.002$ ) and the gestational age (weeks) at birth was significantly higher ( $35.0 \pm 1.8$  vs  $33.6 \pm 1.9$ ,  $p 0.004$ ) among the outpatient arm. There was no significant difference between the two arms regarding the incidence of chorioamnionitis, neonatal weight, NICU admission and neonatal sepsis.

**Conclusion:** Outpatient management of patients with PPRM is safe approach which can be adopted particularly in low risk patients.

**Key words:** Preterm prelabor rupture of membrane, outpatient management, latency period, chorioamnionitis, neonatal outcomes.

## **Introduction**

Preterm prelabour rupture of membranes (PPROM) complicates 2-3% of pregnancies and it's responsible for approximately one-third of preterm births. Half of

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the women with PPRM deliver within one week of the membrane rupture. The greatest consequence of PPRM is preterm birth which contributes to neonatal morbidity and mortality (1). Other complications that can be a consequence of PPRM include cord prolapse, cord compression, intra-amniotic infection, and placental abruption (2).

Gestational age at the time of PPRM is a key factor in deciding the management with the continuation of pregnancy seems reasonable if membrane rupture occurs between 24 and 34 weeks. Antibiotics and antenatal corticosteroids improve short term neonatal outcomes in case of expectant management (3).

According to the available guidelines, hospital based care of patients with PPRM until delivery is the standard practice (4). However, outpatient management can be implemented after 48 hours of hospital admission provided that the patient is vitally stable with no clinical or biological features suggesting chorioamnionitis. This policy of home-based care has been addressed by several retrospective studies (5)

Our study aimed to compare inpatient and outpatient care of patients with PPRM in terms of latency, gestational age at delivery, intraamniotic infection, and neonatal outcomes.

## **Patients & Methods**

This prospective observational study was conducted at Ain Shams University Maternity Hospital during the period from March 2022 to March 2023. Before the initiation of the study, approval of the Ethical Committee of the Faculty of Medicine, Ain Shams University was obtained (MS 614/2021, FWA 000017585). Using PASS 11 for sample size calculation, setting power at 99%, alpha error at 5%, and after reviewing previous results obtained by Beckman & Gardener (6), that showed that the number of days from ruptured membranes to birth among patients with PPRM who had inpatient

care versus those who had outpatient care was (12 {4.2 – 14.6} versus 32.6 {14.3-43.2} respectively); based on that, a sample size of at least 60 patients with PPRM divided into 2 groups (30 patients in each group) will be sufficient to achieve study objective. The study was registered at ClinicalTrials.gov (ID: NCT05755841)

Age of the included participants ranged from 18 to 40 years. Gestational age at recruitment ranged from 28wks+0 days to 34wks+0 days based on late first or early second trimesteric ultrasound, and date of last menstrual period. Diagnosis of membrane rupture was based on 3 features; history of gush of watery vaginal discharge, pooling of fluid at the posterior fornix or leakage of fluid through the cervix by speculum examination, and ultrasound evidence of oligohydramnios ie deep vertical pocket < 2cm. Patients who had PPRM associated with medical disorders such as diabetes mellitus, preeclampsia, systemic lupus erythematosus, and renal or hepatic impairment were excluded from the study. Moreover, patients with associated symptomatic or asymptomatic placenta previa, fetal malformations, and history of classic cesarean section were excluded as well.

Informed consent was taken from study participants before enrollment and after a thorough explanation of the purpose of the study. Patients who were diagnosed with PPRM were admitted to the hospital for 48 hours where monitoring of the patient for manifestations of intra-amniotic infection and preterm labor was ensured. All included patients received antibiotics according to the ACOG guidelines (7), and corticosteroids for fetal lung maturity. After the first 48 hours, patients who were discharged and managed as an outpatients or stayed in the hospital to be managed as an inpatients during the study period were documented and evaluated

Regarding the outpatient arm, the following criteria were ensured before managing patients as an outpatient; available transportation to the hospital throughout the day, checking

and recording temperature regularly every 4 hours, and awareness of fetal kicks so that she can feel any decrease in fetal kick count. Each patient from the outpatient arm was instructed to attend follow-up visit at the outpatient clinic during which non-stress test and complete blood count were carried out twice weekly with weekly clinical examination and ultrasound assessment. All patients were instructed about the warning features which necessitate urgent assessment at the hospital, these features included fever, constant lower abdominal pain, labor pains, vaginal bleeding, and decrease the perception of fetal kicks. As for the inpatient's arm, the same protocol was applied. In the absence of any of the warning features that necessitated delivery, delivery was planned between 36 and 37 weeks.

The primary outcome of the study was the latency period from the time of membrane rupture till delivery. Incidence of chorioamnionitis, NICU admission, neonatal sepsis, and oxygen requirements were secondary measures of outcome.

### **Statistical analysis**

Regarding the statistical analysis, quantitative variables were presented using mean and standard deviation, qualitative variables were presented using count and percentage. Student t-test was used to compare quantitative variables between two independent groups, Chi-square test was used for qualitative variables. Fisher's Exact or Monte Carlo correction was used for correction for chi-square when more than 20% of the cells have an expected count of less than 5. P value less than or equal to 0.05 was considered statistically significant.

### **Results**

This prospective study aimed to evaluate the safety and effectiveness of outpatient management of patients with PPRM with inpatient management. **Figure 1** represents a

flow chart of the study participants. **Table 1** assessed the demographic data of both arms; there was no significant difference between both approaches regarding age, BMI, parity, and hemoglobin (at PPRM and delivery). **Table 2** showed that there was no difference between the two arms regarding the mode of delivery. Gestational age when PPRM occurred, latency period, and gestational age at delivery were shown in **table 3**; the latency period was significantly longer and the gestational age at delivery was more advanced among the outpatient arm while there was no significant difference between the two arms of the study regarding the gestational age at the time of PPRM. **Figure 2** represented the rate of delivery among the study arms. **Tables 4 and 5** showed that there was no significant difference between both arms regarding hemoglobin and total leucocytic count respectively. **Table 6** showed similar rates of chorioamnionitis among the two arms of the study. **Tables 7-9** addressed the neonatal outcomes of the study participants; **table 7** showed that there was no significant difference between the two arms of the study regarding neonatal weight while **table 8** was concerned with NICU admission, oxygen requirements, and neonatal sepsis with no significant difference observed between the two arms of the study regarding these variables. **Table 9** showed no significant difference between the two arms regarding perinatal and neonatal mortality.

### **Discussion**

This prospective cohort study was conducted at Ain Shams University Maternity Hospital during the period from March 2022 to March 2023. The study aimed to compare inpatient management of patients with PPRM with outpatient management regarding the latency period, the incidence of intra-amniotic infection, neonatal weight, and neonatal complications.

Seventy-one patients with preterm prelabour

rupture of the membranes were enrolled in the study after obtaining informed consent. Out of these 71 patients, 6 patients from the outpatient cohort were lost at follow up and 2 patients from the inpatient cohort were discharged against medical advice. Out of the remaining 63 patients, 31 were managed as inpatients while 32 were managed as outpatients. There was no significant difference between the two arms of the study regarding the demographic data (Age, BMI, parity, previous cesarean section, and blood group).

The mode of delivery was assessed in our study and there was no significant difference between the two arms of the study regarding the mode of delivery. The incidence of cesarean section was 71.9 % in the inpatient arm and 77.4% in the outpatient arm. Such a high incidence of a cesarean section can be attributed to the high number of previous cesarean sections among study participants which was approximately 50% in either arm and the high number of preterm birth among study participants. Results by Guckert et al., showed similar results with no significant difference between the two arms of the study regarding the mode of delivery but the incidence of cesarean section was much lower than in our study which can be due to the high number of nulliparous women in both outpatient and inpatient groups (44.2% and 40.7% respectively), high number of cephalic presentation among both groups (66% and 68.8 %), and low number of growth restricted fetuses among both arms (8).

The gestational age when preterm prelabour rupture of membranes occurred was evaluated and there was no significant difference between the inpatient and the outpatient arm. However, the latency period was significantly longer in the outpatient arm which led to a more advanced gestational age at delivery. Our results were consistent with Mirteimouri et al., who conducted a non-randomized controlled trial to evaluate both outpatient and inpatient management of cases with

preterm prelabour rupture of membranes; the latency period was significantly longer compared with the inpatient group ( $18.7 \pm 12.9$  vs.  $7.1 \pm 5.8$  days,  $p < 0.001$ ) (9). Our results were consistent with Dussaux et al., who showed a longer latency period among patients with PPRM who received home care compared with those who received hospital care in their retrospective study which included 414 patients ( $29.9 \pm 17.6$  days vs  $11.5 \pm 10.5$  days,  $p < 0.01$ ); the outpatient arm had significantly higher gestational age at delivery ( $33.6 \{31.1-34.4\}$  vs  $32 \{29.4-33.8\}$ ,  $p < 0.01$ ), however, the home care patients had a lower gestational age at the time of membrane rupture which could be a reason for the longer latency period among them ( $28.8 \{26.6-30.5\}$  vs  $30.3 \{27.6-32.1\}$ ,  $p < 0.01$ ). Moreover, cervical length at admission was significantly shorter among the inpatient arm (3); this was not in agreement with our study which showed no significant difference between both arms of the study regarding the gestational age when rupture of the membranes occurred; this can be attributed to the nature of the included participants as our study included patients with gestational age from 28+0 weeks to 34+0 weeks which was a narrower range compared to Dussaux et al., (24 to 34 weeks). Results obtained by Guckert et al., were similar to our results as well with longer latency period and gestational age at delivery being observed in the outpatient arm (8). Catt et al., showed similar results as well with the latency period being significantly longer in the outpatient group (18 {IQR 24} vs 11 {IQR 12},  $p = < 0.001$ ) and consequently the gestational age at delivery ( $32.3 \{2.7\}$  vs  $30.6 \{3.1\}$ ,  $p = < 0.001$ ), an interesting finding in that study could be the explanation of the lower gestational age at delivery among the inpatient group that is the significantly higher incidence of chorioamnionitis on placental pathology with funisitis among the inpatient cohort (10). Rouzaire et al., had similar results as well with the latency period being significantly longer ( $38.6 \pm 23.1$  vs  $11.2 \pm$

10.2,  $p = 0.01$ ) and gestational age at delivery is significantly higher ( $36.2 \pm 2.5$  vs  $31.8 \pm 3.9$ ,  $p = < 0.001$ ) among the outpatient group (5). There are several hypotheses to explain this difference in latency periods. First, inpatient care may increase the likelihood of earlier delivery by increasing the risk of hospital-acquired infections. Second, the high stress condition associated with prolonged antenatal hospitalization may have a negative psychological impact which might indirectly decrease the latency period. Third, hospitalization may play an important role in the occurrence of more interventions (i.e., vaginal examination) (9). Our results were in disagreement with Bouchghoul et al., who showed in their multicenter retrospective study that the latency period ( $30.6\{19.0\}$  vs  $25.4\{23.2\}$ ,  $p = 0.16$ ) and the gestational age at delivery ( $32+4\{3\}$  vs  $31+5\{4\}$ ,  $p = 0.13$ ) didn't differ significantly between those who were managed as inpatient and those with effective outpatient care policy after propensity score matching; this can be attributed to the fact that tocolytic administration was significantly higher in the inpatient group (11).

Both hemoglobin and total leucocytic count were assessed in our study at the time of PPRM and at the time of delivery; there was no significant difference between the two arms of the study regarding both parameters neither at membrane rupture nor at the time of delivery. Our results were similar to Dussaux et al., who showed that the inpatient's arm had non significantly higher total leucocytic count (14.4% vs 13.4%,  $p = 0.82$ ) (3). Our results were not consistent with Guckert et al., who showed higher leucocytic count among the inpatient's arm; this could be explained by the higher incidence of infection among the inpatient arm which was obvious by the higher CRP (44.6% vs 29%,  $p = 0.002$ ) and clinical chorioamnionitis among the inpatient's arm (24% vs 15.7%,  $p = 0.039$ ) (8).

Despite the gestational age at delivery was significantly earlier among the inpatient's

arm, the incidence of clinical chorioamnionitis among the study participants was almost the same. The reason for this finding is not clear; histologic chorioamnionitis was not evaluated in our study which could be higher in the inpatient's arm. Intra-uterine infection and associated inflammation are believed to be an important cause of PTB, and histologic chorioamnionitis is associated with PTB and lower gestational age at delivery among PTBs (12). Subclinical chorioamnionitis was observed in the study conducted by Catt et al., who showed a significantly higher incidence of histologic chorioamnionitis (64% vs 47%,  $p = 0.008$ ) despite similar rates of clinical chorioamnionitis (10). Our results were consistent with Garabedian et al., who showed no difference in the incidence of chorioamnionitis between homecare and hospital-based care among patients with PPRM (13). The same finding was observed in the study conducted by Palmer et al., who showed no significant difference between both management policies regarding neither clinical nor histologic chorioamnionitis (2). Beckmann & Gardener, obtained similar results in their retrospective study that compared home-based management of patients with PPRM with hospital-based care. (6). However, the study conducted by Guckert et al., showed a significantly higher incidence of clinical chorioamnionitis in the inpatient's arm; this can be attributed to the fact that invasive procedures such as amniocentesis and chorionic villus sampling (CVS) were higher in the inpatient's arm ( $21\{3,10\}$  vs  $10\{2,5\}$ ,  $p = 0.062$ ) (8).

The neonatal weight was lower in the inpatient's arm but with no statistical significance; this finding could be attributed to the lower gestational age at delivery which was encountered in the inpatient's arm. Our results were similar to those obtained by Bouchghoul et al., who showed lower birth weight in the inpatient's arm; however, the birth weight in both arms was lower compared to our study due to lower gestational age at

delivery (11). In the previously mentioned research, patients with different risk factors for preterm delivery such as history of spontaneous preterm delivery, smoking, low-lying placenta, or placenta previa; this can explain the earlier gestational age at delivery compared to our study that excluded patients with these risk factors. Guckert et al., obtained similar results as well with a significant difference regarding neonatal birth weight in favor of the outpatient arm which was explained by earlier gestational age at delivery among the inpatient's arm taking into consideration that there was no significant difference between the two arms regarding the incidence of growth restricted babies (8).

Rates of NICU admission were similar between the two arms of the study. Among the inpatient's arm, 8 neonates were admitted to the NICU; 6 out of these 8 neonates required oxygen therapy in the form of oxygen mask (3 patients), CPAP (2 patients), and mechanical ventilator (1 patient), the remaining 2 neonates were admitted due to neonatal jaundice. As for the outpatient arm, 8 neonates were admitted to the NICU; 7 out of them were admitted for oxygen therapy which was in the form of oxygen mask (1 patient), CPAP (5 patients), and mechanical ventilator (1 patient). These findings could be explained by the fact that despite the significant difference between the two arms regarding gestational age at delivery, the mean gestational age in both arms lay in the late preterm category (34+0 - 36+6 weeks). Moreover, similar rates of chorioamnionitis were observed among the study participants. Our results were similar to those obtained by Bouchghoul et al., who showed no difference between the two management policies regarding the neonatal composite outcome (11). Our results were in disagreement with Dussaux et al., who showed higher NICU admission among the inpatient arm (209/312 {67%} vs 47/86 {54.7%},  $p=0.03$ ); these observations could be explained by several findings that were reported in the

study as lower birth weight, shorter course of antibiotic therapy, and lower gestational age at delivery (3). Guckert et al., showed a significantly higher rate of NICU admission in the inpatient's arm (49.2% versus 77.2%,  $p < 0.001$ ); a higher rate of chorioamnionitis and neonatal complications, and significantly lower birth weight among the inpatient's arm could be the explanation (8).

Neonatal sepsis was reported with no significant difference between the two arms. Beckman & Gardener, had similar results with no significant difference between the two groups regarding the incidence of neonatal infection (6). The same finding was observed in the study conducted by Palmer et al., who showed no difference regarding neonatal sepsis between home-based care and hospital care for patients with PPRM (11.5% vs 6.9%,  $p = 0.43$ ) (2). Guckert et al., showed a slightly higher incidence of neonatal infection among the inpatient's arm (22.1 % vs 13.9 %,  $p = 0.037$ ); the highly significant difference between the two arms regarding the gestational age at delivery and the birth weight put the neonates of the inpatient's arm at greater risk of infection along with the higher incidence of clinical chorioamnionitis and the longer length of stay in the NICU which was reported (8).

Perinatal mortality was evaluated in our study with no significant difference between the two arms regarding neither perinatal nor neonatal mortality. Our results were consistent with those obtained by Catt et al., who showed no difference between the two approaches regarding stillbirth or neonatal mortality (3% vs 4%,  $p > 0.999$ ) (10). Bouchghoul et al., had similar results as well with no difference between the two groups regarding either composite perinatal outcome measure or neonatal mortality (11).

## **Discussion**

**Study limitations:** Our study was not without limitations; the major limitation was

the inability to determine whether outpatient management of PPRM is associated with adverse neonatal outcome compared with inpatient management. Prospective studies with larger sample size are needed for a better assessment of the difference in neonatal outcome between home-based care and hospital care in cases of PPRM.

## **Conclusion**

The study concluded that outpatient management of patients with preterm prelabour rupture of the membranes is safe and cost-effective approach. Compared with inpatient management, it's associated with a longer latency period, higher gestational age at delivery, and higher birthweight along with similar rates of chorioamnionitis. Home-based care is suitable for patients with PPRM who are considered low-risk patients from maternal and fetal perspectives.

## **Acknowledgment**

The authors would like to express their deepest gratitude to the study participants for their cooperation throughout the study. We also would like to show our respect to our professors and colleagues at the obstetrics and gynecology department for their support.

## **Declarations of interest**

### **a) Ethical approval and informed consent:**

Informed consent was obtained from study participants. The study was registered in Clinicaltrials.gov, ID: NCT05755841 , and was approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University (MS 614/2021, FWA 000017585). All methods were carried according to the relevant guidelines and regulations in the Declaration of Helsinki

### **b) Consent for publication:**

Not applicable

### **c) Availability of data and materials:**

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

### **d) Conflicts of interest:**

The authors declare that there are neither financial nor non-financial conflicts of interest concerned with the manuscript of the study

### **e) Funding:**

The study was based on investigators' self-funding

### **f) Authors' contribution:**

Author Ahmed Mohammed Elmaraghy & Author Nermeen Rabea Kamal designed the study, and collected and analyzed the data. Author Bassem Aly Islam ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Author Adel Shafik Salah El-din revised the study for intellectual content and approved the final version of the manuscript to be published

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### **Figure legends**

**Figure 1:** Flow chart of study participants

**Figure 2:** Kaplan-Meier curve from rate of delivery among study participants

**Tables****Table 1:**

Variables		Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
Age (years)	Mean $\pm$ SD	28.6 $\pm$ 7.2	26.8 $\pm$ 4.5	$\wedge$ 0.235
	Range	18.0–45.0	18.0–35.0	
BMI (kg/m <sup>2</sup> )	Mean $\pm$ SD	27.1 $\pm$ 3.7	26.6 $\pm$ 3.3	$\wedge$ 0.600
	Range	19.2–34.2	19.7–32.1	
Parity	Nulli	11 (34.4%)	8 (25.8%)	#0.459
	Parous	21 (65.6%)	23 (74.2%)	
Previous cesarean section		16 (50.0%)	16 (51.6%)	#0.898
ABO	A	15 (46.9%)	18 (58.1%)	§0.348
	B	10 (31.3%)	6 (19.4%)	
	O	7 (21.9%)	5 (16.1%)	
	AB	0 (0.0%)	2 (6.5%)	
RH	Positive	30 (93.8%)	30 (96.8%)	§0.999
	Negative	2 (6.3%)	1 (3.2%)	

**Baseline characteristics among the study participants**

**BMI:** Body Mass Index.  $\wedge$ : Independent t-test. #: Chi square test. §: Fisher's Exact test.

**Table 2:**

Mode of delivery	Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
Cesarean	23 (71.9%)	24 (77.4%)	#0.613
Vaginal	9 (28.1%)	7 (22.6%)	

**Mode of delivery among the study participants.** #: Chi square test

**Table 3:**

Variables		Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
PPROM	Mean $\pm$ SD	31.1 $\pm$ 1.6	30.8 $\pm$ 2.2	$\wedge$ 0.558
	Range	28.1–32.9	28.0–33.9	
Delivery	Mean $\pm$ SD	33.6 $\pm$ 1.9	35.0 $\pm$ 1.8	$\wedge$ 0.004*
	Range	29.5–36.2	29.8–36.9	
Latency	Mean $\pm$ SD	17.7 $\pm$ 11.9	29.4 $\pm$ 15.8	$\wedge$ 0.002*
	Range	1.0–57.0	5.0–60.0	

**Gestational age at PPRM and delivery, and latency period among the study participant**

$\wedge$ : Independent t-test. \*: Significant

**Table 4:**

Variables		Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
PPROM	Mean $\pm$ SD	10.5 $\pm$ 1.1	10.2 $\pm$ 1.0	$\wedge$ 0.263
	Range	8.1–12.0	7.8–11.8	
Delivery	Mean $\pm$ SD	10.0 $\pm$ 1.1	9.6 $\pm$ 0.9	$\wedge$ 0.110
	Range	7.8–12.6	7.5–11.0	
#Change	Mean $\pm$ SD	-0.6 $\pm$ 0.8	-0.6 $\pm$ 0.8	$\wedge$ 0.988
	Range	-3.1–0.9	-2.5–1.7	

**Hemoglobin levels (gm/dl) at admission and delivery among the study participants:**

**Change = Delivery – Admission, negative values indicate reduction.  $\wedge$ : Independent t-test.**

**Table 5:**

Variables		Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
PPROM	Mean $\pm$ SD	10.0 $\pm$ 3.6	10.1 $\pm$ 3.6	$\wedge$ 0.846
	Range	5.1–21.9	4.6–17.4	
Delivery	Mean $\pm$ SD	10.9 $\pm$ 3.4	10.6 $\pm$ 3.1	$\wedge$ 0.772
	Range	5.5–23.0	6.0–18.9	
#Change	Mean $\pm$ SD	0.9 $\pm$ 1.5	0.5 $\pm$ 2.3	$\wedge$ 0.402
	Range	-2.3–5.8	-3.8–5.3	

**Total leucocytic count (x103/mL) at PPRM and delivery among the study groups**

**Change = Delivery – Admission, negative values indicate reduction.  $\wedge$ : Independent t-test.**

**Table 6:**

	Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
Chorioamnionitis	3 (9.4%)	3 (9.7%)	$\S$ 0.999

**Chorioamnionitis among the study participants.  $\S$ : Fisher's Exact test**

**Table 7:**

Measures	Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
Mean $\pm$ SD	2.2 $\pm$ 0.5	2.4 $\pm$ 0.6	$\wedge$ 0.095
Range	0.8–3.3	0.9–3.6	

**Neonatal weight (Kg) among the study participants.  $\wedge$ : Independent t-test**

**Table 8:**

Condition	Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
NICU admission	8 (28.1%)	8 (25.8%)	#0.836
<b>Oxygen requirements</b>			
Total	6 (18.8%)	7 (22.6%)	#0.707
CPAP	2 (6.3%)	5 (16.1%)	§0.257
Mechanical ventilator	1 (3.1%)	1 (3.2%)	§0.999
Oxygen mask	3 (9.4%)	1 (3.2%)	§0.613
<b>Neonatal sepsis</b>			
Number & %	5 (15.6%)	3 (9.7%)	§0.708

**NICU admission, oxygen requirements and neonatal sepsis among the study participants**

#: Chi square test. §: Fisher’s Exact test

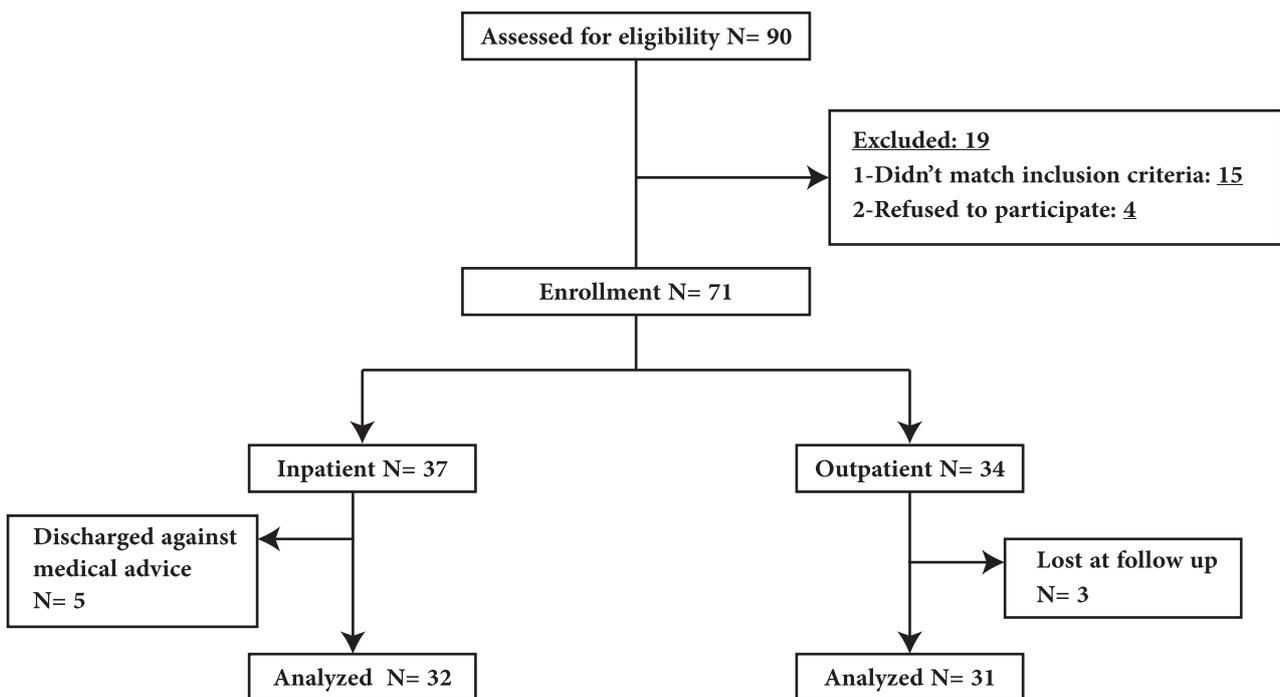
**Table 9:**

Vatiables	Inpatient care (Total=32)	Outpatient care (Total=31)	p-value
Perinatal mortality	5 (15.6%)	2 (6.5%)	§0.426
Still birth	1 (3.1%)	0 (0.0%)	§0.999
Neonatal mortality	4 (12.5%)	2 (6.5%)	§0.672

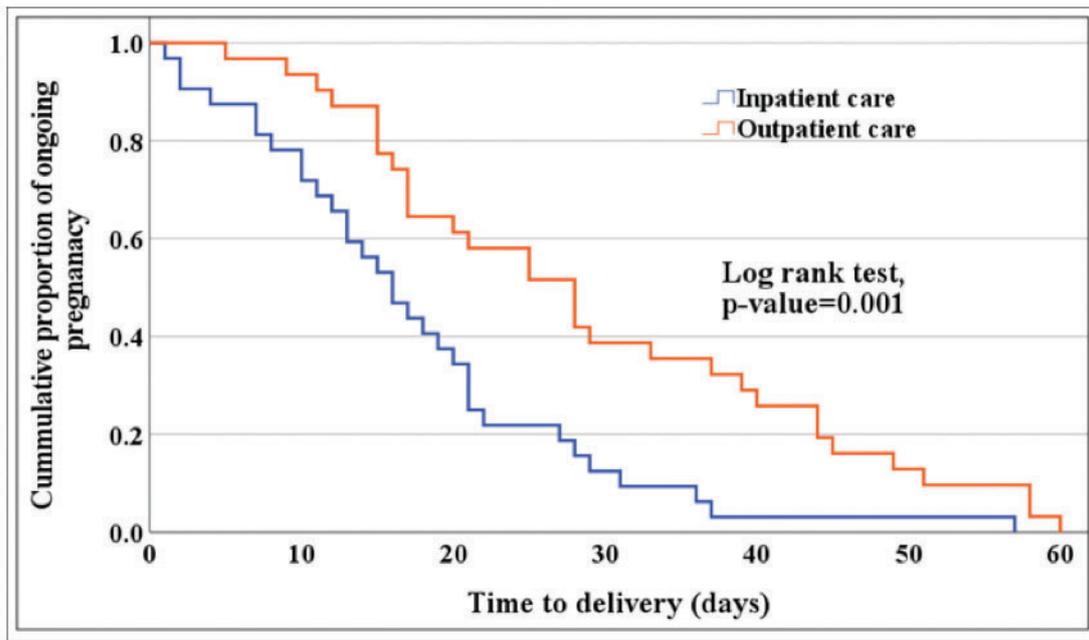
**Perinatal mortality, stillbirth, and neonatal mortality among study participants.**

§: Fisher’s Exact test

**Figures**



**Figure 1:** Flow chart of study participants



**Figure 2:** Kaplan-Meier curve from rate of delivery among study participants

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# Title: Comparison of the psychological impact of medical versus surgical management of miscarriage

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## Running Title

psychological impact of medical versus surgical management of miscarriage

## Ethical statement

- Authors declare that there is no conflict of interest
- No funding.
- Accepted by the Ethical Research Committee of the Obstetrics and Gynecology Department and institutional review board (IRB) in the Faculty of Medicine (R.23.09. 2343.R1)
- Written informed consent was taken from the participants

## Abstract

**Introduction :** psychological morbidities include anxiety, depression, and post-traumatic stress disorder occur after miscarriage. Multiple factors make the patients more vulnerable to psychiatric complications. We aimed to compare the psychological impact of medically terminated versus surgical evacuated miscarriage patients.

**Patients and Methods:** Our comparative descriptive study was conducted on patients from the Gynaecology and Obstetrics clinic of Mansoura Hospital, Egypt.

All patients were divided into two groups according to their mode of termination: group A, who had surgical evacuation, and group B, who had medical termination.

Both groups underwent psychological function assessment. The results compared to each other. The psychological function of each participant was evaluated by the Arabic version of the Hospital Anxiety and Depression Scale (HADS) within three months of miscarriage. We used the PTSD checklist for the Diagnostic Statistical Manual of Mental Disorders—5th Edition (DSM-5).

**Results :** Twenty-five patients in group A and twenty-five in group B. women in both groups have increased rates of psychiatric disorders affection regarding depression, anxiety, and PTSD. It shows that 68% in group A have

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depression compared with 68% in group B indicating no significant difference between the two groups. It shows that 72% are suffering from anxiety in group A compared with 68% having anxiety indicating no significant difference between both groups. According to PTSD, there were no significant differences between the two groups with a high rate of affection around 72% in group A versus 68% in group B.

**Conclusion:** increased rates of depression, anxiety, and PTSD in women in both groups without any significant difference between the two groups with the hypothesis of the effect mainly related to the loss of pregnancy itself regardless of the method of termination.

**Keywords:** miscarriage, depression, anxiety, and PTSD.

## **Introduction**

Higher rates of psychiatric complications are found and often prolonged in women with miscarriages compared to the general population. (1; 2). This finding should be extensively evaluated, as miscarriages are one of the obstetric complications that affects about 23 million every year all over the world. Such psychological morbidities include anxiety, depression, and post-traumatic stress disorder (PTSD) (1). Possible figures for complications after miscarriage are 32% for anxiety, 16% for depression, and 28% for PTSD (3).

Multiple factors make the patients more vulnerable to psychiatric complications such as women with previous miscarriages, a low educational level, female ostracism, and high neuroticism scores. (4). The management of miscarriage, either medical or surgical, has not previously been studied as an independent factor of psychiatric complications following miscarriage. We aimed to compare the psychological impact of medically terminated versus surgical evacuated miscarriage patients.

## **Patients and Methods**

Our comparative descriptive study was conducted on patients from the Gynaecology and Obstetrics clinic of Mansoura Hospital, Egypt. The Institution Research Board (R.23.09. 2343.R1) approved the study protocol. We got informed written consent from each participant.

**The patients will have the following eligibility criteria:**

- Having suffered a pregnancy loss in the first 13 weeks of gestation,
- Being  $\geq$  18-35 years old
- All healthy women with no medical disorder.
- The women in both groups had live children with no period of infertility.
- Having no previous psychiatric disorders

Patients with miscarriages managed expectantly, or cases presented with complete miscarriage are excluded from the study.

All patients were divided into two groups according to their mode of termination: group A, who had surgical evacuation, and group B, who had medical termination.

both methods of termination were done according to our local guidelines which are based on NICE guidelines (5). Both groups underwent psychological function assessment. The results compared to each other.

## **Psychological function assessment**

The psychological function of each participant was evaluated by the Arabic version of the Hospital Anxiety and Depression Scale (HADS) within three months of miscarriage. There are 14 items on this self-assessment scale, which includes both depression as well as anxiety dimensions: 7 items for each dimension, with a cut off of eight for anxiety and nine for depression. Since the scores for each item ranged from 0 to 3, the person

could receive a result for either anxiety or depression between zero to 21 (6).

The Arabic version of HADS is a reliable and valid tool for assessing mood states. Cronbach's  $\alpha$ s were 0.83(95%CI:0.79–0.88) for the HADS anxiety subscale and 0.77 (95% CI: 0.7–0.83) for the HADS depression subscale. The majority of patients thought that the questions of the HADS were obvious, easily understood, and covered all their concerns about their hospital anxiety and depression (6). We used the PTSD checklist for the Diagnostic Statistical Manual of Mental Disorders—5th Edition (DSM-5). (7)

### **Statistical analysis**

Data was analysed using SPSS (Statistical Package for Social Sciences) version 22. Qualitative data is introduced as number and percent, quantitative data is tested for normality by Kolmogorov-Smirnov test then described as mean and standard deviation for normally distributed data and median and range for non-normally distributed. We used Chi-Square for the categorical variable Student T-test and Mann Whitney U test.

### **Results**

Seventy-five patients with miscarriage were assessed for eligibility. Twenty patients were Excluded (Not meeting inclusion criteria) and five patients declined to participate. Twenty-five patients had surgical evacuation (group A) and twenty-five patients had medical termination (group B).

Table (1) illustrates that there were no significant differences between the two groups in the mean age, parity, residence, educational level, gestational age, number of miscarriages, and history of any chronic disease. The miscarriage in both groups occurred in the 10th week of pregnancy in most cases.

Table (2) and Figure (1) illustrate that women in both groups have increased rates

of psychiatric disorders affection regarding depression, anxiety, and PTSD

It shows that 68% (17 women out of 25) in group A have depression with a mean score of 9.44 compared with 17 in group B with a mean score of 9.80 indicating no significant difference between the two groups.

It shows that 72% (18 women out of 25) are suffering from anxiety in group A compared with 68% (17 women out of 25) having anxiety indicating no significant difference between both groups.

According to PTSD, there were no significant differences between the two groups with a high rate of affection around 72% in group A versus 68% in group B

### **Discussion**

Although multiple factors affect the risk of post-miscarriage psychiatric complications, the route of management is little discussed as an independent cause. The difference is great between surgical management and medical treatment. In the surgery route, the patient had to go to the theatre and be counselled for some complications including the anaesthesia complications. In medically treated patients, the duration is prolonged with much pain. We searched whether the psychotic complication could be related to the type of management or it is due to the event of pregnancy loss itself and if the surgery experience can aggravate the condition or the long time and pain of medical is responsible for this.

All the factors affecting the outcome such as age, parity, Residence, Educational level, Occupation Number of children, Gestational age of the pregnancy, and previous mental condition were equal between both groups to ensure the effect of the method of pregnancy termination on the outcome.

Our results showed increased rates of depression, anxiety, and PTSD in women in both groups without any significant difference between the two groups. That with

the hypothesis of the effect mainly related to the loss of pregnancy itself regardless of the method of termination. This is supported by a study that revealed that Some partners developed levels of PTS, anxiety, and depression after miscarriage to their partners. (8).

Miller et al. studied similar ideas about the mode of termination however they divided the cases as care in the emergency departments versus outpatient care and they found patients in the emergency departments were more likely to be predisposed to psychosocial aspects (9).

We cannot compare our results with this study as we compare two active methods of treatment and we excluded all patients managed expectantly or presented with complete miscarriage. We agreed that expectant management will have less impact on the psychological impact of the patients and therefore, we did not choose to compare expectant to active management.

Our limitations of the study are the small sample size and lack of long-term follow-up of the cases. We recommend further studies to discover this blind area of research and we recommend promoting psychological support for patients with miscarriage whatever the methods of management.

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**Table (1): comparison of demographic, obstetric history among studied groups.**

	<b>Group A (surgical evacuation) N=25</b>	<b>Group B (medical evacuation) N=25</b>	<b>Test of significance</b>
<b>Age (years) Mean±SD</b>	29.0±7.54	30.80±7.17	t=0.865 p=0.391
<b>Residence n(%) Urban Rural</b>	12(48.0) 13(52.0)	14(56.0) 11(44.0)	χ <sup>2</sup> =0.321 P=0.571
<b>Educational level n (%) Low Middle High</b>	3(12.0) 14(56.0) 8(32)	6(24.0) 12(48.0) 7(28.0)	χ <sup>2</sup> =1.22 P=0.543
<b>Occupation n(%) Not working Worker HCW Engineer Employee</b>	19(76.0) 2(8.0) 4(16.0) 0 0	21(84.0) 0 2(8.0) 1(4.0) 1(4.0)	χ <sup>2</sup> <sup>MC</sup> =4.77 P=0.312
<b>Parity Median (min-max)</b>	3(1-7)	4(1-8)	Z=1.42 P=0.157
<b>Number of children Median (min-max)</b>	2(0-4)	2(0-5)	Z=1.63 P=0.101
<b>Miscarriage number Median (min-max)</b>	1(1-3)	1(1-5)	Z=0.738 P=0.461
<b>Gestational age / weeks Median (min-max)</b>	10(5-25)	10(4-26)	Z=0.0 P=1.0
<b>Chronic disease n(%)</b>	3(12.0)	4(16.0)	χ <sup>2</sup> <sup>FET</sup> =1.22 P=0.543

t:Student t test , Z:Mann Whitney U test , χ<sup>2</sup>:Chi-Square test , FET :Fisher exact test , MC: Monte Carlo test

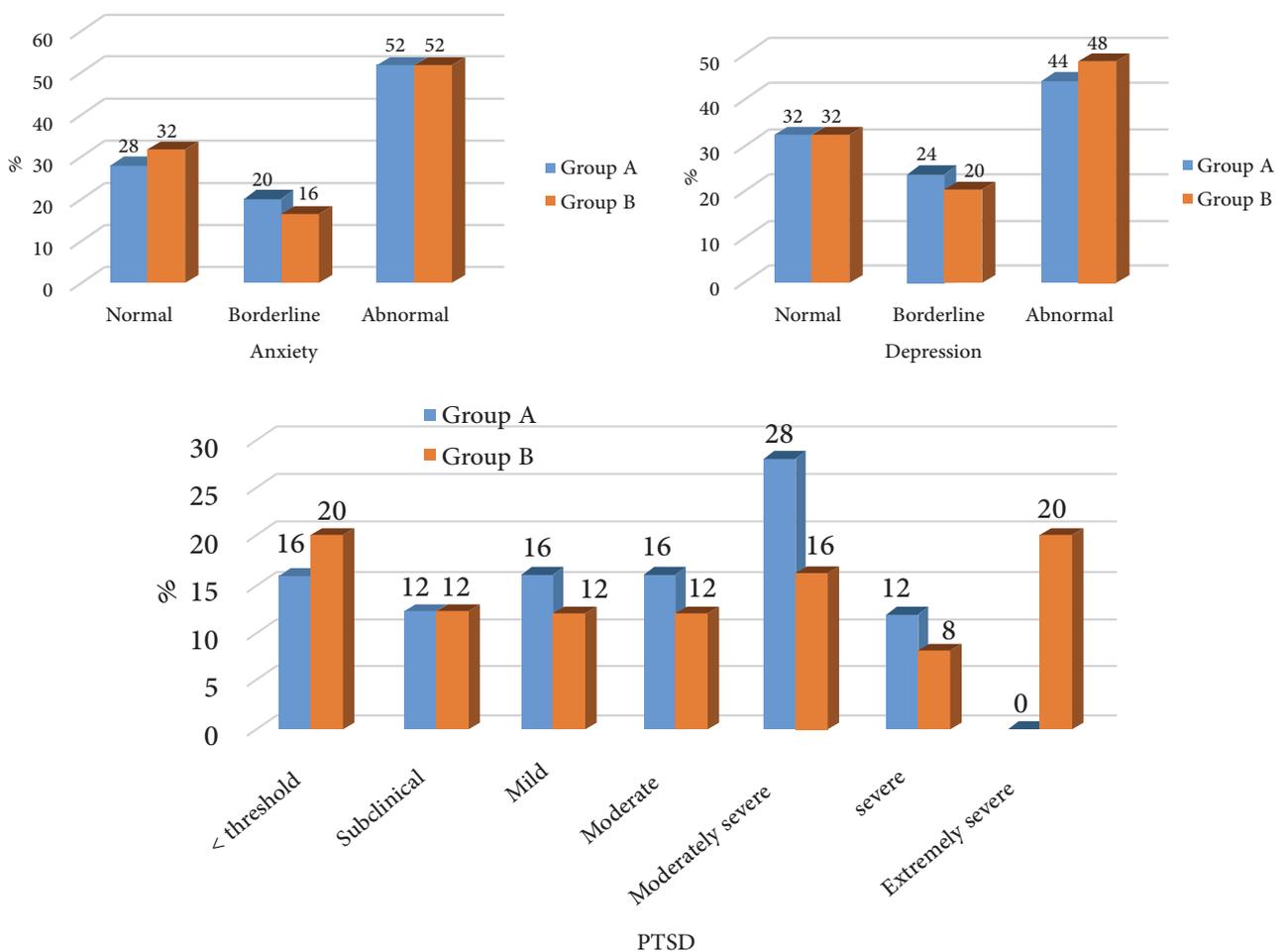
**Table (2): comparison of depression, anxiety and PTSD between studied groups**

	<b>Group A (surgical evacuation) N=25</b>	<b>Group B (medical evacuation) N=25</b>	<b>Test of significance</b>
<b>Depression Mean±SD</b>	9.44±3.37	9.80±4.59	Z=0.316 P=0.754
<b>Normal n(%) Borderline Abnormal</b>	8(32) 6(24) 11(44)	8(32) 5(20) 12(48)	Mc=0.134 P=0.935
<b>Anxiety Mean±SD</b>	9.84±4.25	10.76±5.19	Z=0.684 P=0.497
<b>Normal n(%) Borderline Abnormal</b>	7(28) 5(20) 13(52)	8(32) 4(16) 13(52.0)	χ <sup>2</sup> =0.178 P=0.915

<b>PTSD Mean±SD</b>	21.32±9.23	23.76±13.12	Z=0.761 P=0.451
<b>&lt; threshold n(%)</b>	4(16.0)	5(20.0)	Mc=6.42 P=0.492
<b>Subclinical</b>	3(12.0)	3(12.0)	
<b>Mild</b>	4(16.0)	3(12.0)	
<b>Moderate</b>	4(16.0)	3(12.0)	
<b>Moderately severe</b>	7(28.0)	4(16.0)	
<b>severe</b>	3(12.0)	2(8.0)	
<b>Extremely severe</b>	0	5(20.0)	

Z:Mann Whitney U test

**Figure (1): comparison of depression, anxiety and PTSD between studied groups**



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# Basal bolus insulin regimen with metformin versus carbohydrate insulin ratio with metformin in the management of diabetes mellitus during pregnancy

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## Running Title

Basal bolus insulin regimen versus carbohydrate insulin ratio in diabetes mellitus during pregnancy

## Ethical statement

- Authors declare that there is no conflict of interest
- No funding.
- Accepted by the Ethical Research Committee of the Obstetrics and Gynecology Department and institutional review board (IRB) in the Faculty of Medicine (MS/16.03.03).
- Written informed consent was taken from the participants.

## Abstract

**Background:** Controlling diabetes mellitus (DM) in pregnancy is important to avoid further maternal and fetal complications. This can be achieved by diet regimen, exercise, insulin and oral hypoglycemic agent like metformin. We aimed to compare between basal bolus insulin regimen with metformin and flexible basal bolus regimen according to carbohydrate insulin ratio with metformin on control of blood sugar among pregnant women with diabetes.

**Methods:** Our study is a randomized controlled trial on 60 cases of pregnant women with diabetes who are attending Obstetrics and Gynecology department at Mansoura university hospitals. Cases were randomized into two groups: Group I (basal bolus regimen group) (n = 30) including women who received oral metformin in addition to insulin by the basal bolus insulin regimen; Group II (insulin carbohydrate regimen group) (n = 30) including women who received oral metformin in addition to insulin by insulin carbohydrate regimen.

**Results:** Our result showed that there was 100% control in fasting glucose levels and 100% control in post prandial glucose level in group 1 and 70% control in group 2.

**Conclusion:** the basal bolus regimen is better than insulin carbohydrate ratio in patient with diabetes who are at mid education level with carbohydrate counting.

**Keywords:** Carbohydrate-to-insulin ratio, Diabetes, Insulin, Metformin, Pregnancy.

## **Introduction**

Egypt is listed among the world's high countries in the number of patients with Diabetes mellitus (DM). The prevalence of DM is around 15.56% among the population between 20 and 79 years of age, accordingly, diabetes that complicates pregnancies is a common problem (1).

Although Insulin is the preferred Antidiabetic treatment agent for the management of diabetes in pregnancy (2), Metformin becomes safe and more effective than insulin in lowering the 2-hour postprandial level (3). Adding metformin to the conventional insulin regimen effectively achieved good glycemic control with a lower dose of insulin (4). This combination is powerful in insulin-resistant DM with pregnancy (5).

Carbohydrate counting has been tried with success in patients with type 1 diabetes as one of the strategies used in Diabetes Control and Complications Trials (DCCT). In this protocol patients adjust their insulin dose according to the amounts of carbohydrate consumed known by frequent blood glucose measurements (6).

Using carbohydrate counting not only makes use of an insulin dose scale according to their pre-prandial blood glucose values; but they also base their dosage titration on insulin/carbohydrate ratios. These ratios allow them to vary their carbohydrate quantity within meals and from day to day, as long as there is adequate insulin to account for the carbohydrate content (7). However, little data on insulin/carbohydrate ratios to control diabetes in pregnancy is present in the literature. To our knowledge, no

previous studies compared between insulin carbohydrate ratio and basal bolus regimen after adding the metformin.

Therefore, this study was designed to compare the basal-bolus insulin regimen with metformin and flexible basal-bolus regimen according to carbohydrate insulin ratio with metformin on control of blood sugar among pregnant women with diabetes.

## **Patients and Methods**

This randomized controlled trial was conducted on 60 pregnant women between 20 and 48 years with Gestational diabetes mellitus (GDM) & type 2 DM who have uncontrolled blood sugar or poor glycemic control (Poor glycemic control is defined as fasting blood glucose > 95 mg/dl and/or 2-h postprandial blood glucose >120 mg/dl) and having a singleton pregnancy between 20 and 34 weeks who were admitted to Mansoura University Hospitals during the period between March 2016 to December 2017.

The study was started after getting signed consent from each patient and being approved by the Ethical Research Committee of the Obstetrics and Gynecology Department, and the institutional review board at Mansoura University (MS/16.03.03). A signed consent from each patient was taken.

Women with type 1 DM and those with secondary diabetes, or had other medical disorders and/or diabetes-related complications such as renal failure, heart failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic disorder, gestational hypertension, preeclampsia, fetal growth restriction and fetal macrosomia, fetal anomaly, ruptured membranes in second trimester, contraindications or hypersensitivity to metformin intake like gastrointestinal side effects and altered liver functions with or without jaundice were excluded from the study.

## **Randomization**

A computer-generated list of numbers sealed in opaque envelopes in a parallel manner was used to randomize the cases into two equal groups.

**Group 1:** The patient was given 50% of the calculated insulin dose as a basal dose of intermediate-acting insulin (where two-thirds of the dose is given AM and one-third at bedtime). The other half of the calculated dose was given as bolus short-acting insulin (where one-third of the dose is given before each meal: breakfast, lunch, dinner) (8).

**Group 2:** The patient was given 50% of the calculated dose as basal dose in group 1 and the bolus dose was given according to insulin carbohydrate ratio (every 10–15-gram carbohydrate covered by 1-unit short-acting insulin). The initial ICR was 1:15 for all participants (9).

At the first visit, all patients were educated on carbohydrate counting and on how to achieve and maintain good metabolic control.

Calculation of insulin dose: Begin with 0.7-0.8 unit/kg insulin (Humulin-R, Humulin –N) in the 1st trimester, 0.8-0.9 unit/kg in the 2nd trimester, and 0.9-1.2 unit/kg in the 3rd trimester. Insulin dose was raised at a rate of 1 IU for every 10 mg/dl higher than the target blood glucose concentration. The target blood glucose concentration was 60–95 mg/dl for fasting and less than 120 mg/dl for 2h postprandial.

Both groups added metformin (Cidophage, 500mg, CID Pharmaceuticals, Egypt) initiated at a dose of 500 mg once daily for two first days to prevent possible gastrointestinal side effects. Then dose was increased to twice daily, 1000mg /day. Metformin was stopped if maternal contraindications (such as liver or renal impairment or sepsis) or fetal growth restriction developed.

All participants were subjected to routine laboratory investigation including urine

analysis, ketone tests, urine for glycosuria or ketonuria checked twice daily, blood glucose monitoring, fasting, and three postprandial blood glucose levels 2 hours after breakfast, lunch, and dinner daily and twice weekly or every 48 h. HbA1C was done at study entry and after 1 month. All women had frequent ultrasound assessments of fetal growth and measurement of liquor.

Patients were followed up, and given Iron, calcium, vitamin B12, and folic acid supplements.

Women in group 2 who did not reach the target blood glucose concentrations for 10 days were switched to the conventional insulin metformin group. Outcomes were fasting and 2-h postprandial blood glucose.

### Statistical analysis

Data were analyzed with SPSS version 21. The normality of data was tested with a one-sample Kolmogorov-Smirnov test. Qualitative data were described using numbers and percentages. Association between categorical variables was tested using Chi-square and Fischer exact tests. Continuous variables were presented as mean  $\pm$  standard deviation (SD) for parametric data. The two groups were compared with the Student t-test (parametric data) and Mann–Whitney test (non-parametric data) while paired groups were compared by paired t-test and Wilcoxon signed rank test. P value  $<0.05$  was statistically significant.

## **Results**

The demographic data obstetric history and DM characteristics were comparable between groups. (Table 1)

There was no statistically significant difference between groups in fasting glucose levels at 3, 6, and 9 days. There was a highly significant difference in fasting glucose levels before treatment and after 9 days in both groups ( $p<0.0001$ ). (Table 2)

There was a significant difference in glycemic

control of 2-hour post-prandial glucose. Glycemic control after 3 days in group 1 was in 29 cases and group 2 11 cases only. After 6 days the glycemic control of group 1 was in 30 cases (100%), and 17 cases only in group 2. Group 1 still controlled after 9 days, and group 2 increased to 21 cases about (70%). There was no significant difference between groups regarding the hypoglycemic attacks (Table 3)

In group 2, cases were subdivided according to education level and obesity. The results showed that the mid-educated cases had significantly elevated post-prandial blood glucose levels than the high-educated cases. Moreover, the severe obesity cases had significantly elevated post-prandial blood glucose levels than the moderate obesity cases. (Table 4)

## **Discussion**

Using carbohydrate-to-insulin ratios during pregnancy is challenging because insulin requirements change so often. In the first trimester, the body is more sensitive to insulin, and insulin requirements drop. During the second half of the pregnancy, insulin resistance causes an increase in the insulin requirement so weekly insulin adjustments are needed (10).

The addition of metformin benefits the patients in group 1 to achieve rapid control

These results are in agreement with the results of Feig et al. showed that adding metformin is associated with proper glycemic control in 76.1 % without increasing the dose of insulin compared with insulin alone (11). The same results were confirmed by another study comparing two groups of pregnant women with type 2 DM, one used insulin alone and the other was insulin with metformin (12).

Only 70% of the second group (21 cases) were controlled for their post-prandial blood glucose and it was a depressing result that was most properly due to low compliance of

patients, lack of experience with food, diet control, and self-management, because most of these women were newly diagnosed as GDM the duration of diabetes, was between 12- 84 month.

To our knowledge, no study added metformin to insulin carbohydrate ratio in type 2 DM with pregnancy.

In our study, we add the metformin to insulin carbohydrate ratio by 10-15 gm carbohydrate needed without using sensitivity factor and in type 2 DM and GDM.

A study by Bongiovanni, et al. assessed carbohydrate-to-insulin ratio values in pregnant women with type 1 diabetes. Their result was that the ratio decreased on average from 9.6 to 5.4 at breakfast, from 10 to 8.4 at lunch, and from 12.5 to 6.1 at dinner (13).

In a study, Zagury et al. studied the changes in carbohydrate ratio during the day in diabetic pregnant women with type 1 DM and the result was a progressive reduction at every meal (mean of 8.2 g/IU for breakfast, 7.7 g/IU for lunch and 7 g/IU for dinner) (9).

Both studies tried to adjust of insulin dose during pregnancy and their result was 100% control. These studies are not in agreement with ours, because all of them are dealing with DM type 1, using different rout in the calculation of insulin carbohydrate ratio, and with no addition of metformin.

On the other hand, in carbohydrate counting regimen, weighing foods and initially recording food intake is an extra work that can be burdensome, and most people do not enjoy it. Blood glucose level testing before and after meals can also be difficult, but it is necessary to determine the appropriate dose of treatment (usually insulin) needed to restore normal glucose levels.

The Increasing flexibility in the types and timing of foods provided by carbohydrate counting can make weight management a challenge. Patients may be tempted to take more liberties with their eating. Given

the increased flexibility, this management approach provides in controlling blood glucose. This is an issue that needs to be raised with patients before they start using the carbohydrate calculation method (14).

In our study, we found that the level of education and orientation can affect the control of blood glucose by insulin carbohydrate ratio as patients with primary education only achieved control in 50% of them but in highly educated patients the control was in 92% of the cases. Also, we found that the degree of obesity can have effect, as patients with moderate degree of obesity showed control in 94% of cases, but in those with severe degree of obesity the control was only in 33% and they needed to increase the insulin dose. There were only 3 cases of hypoglycemic bouts during our journey and they were due to missed meals

### **Conclusions**

The basal bolus regimen is better than the insulin carbohydrate ratio in patients with diabetes who are not educated well with carbohydrate counting. Also, metformin has a beneficial effect on glycemic control without the need to increase the insulin dose more than the calculated dose according to the patient's weight and without increasing the risk of hypoglycemia. It is necessary to teach the patients and their families about carbohydrate counting in their diet.

### **Financial support and sponsorship**

Nil.

### **Conflict of Interest**

Nil.

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**Table (1): Demographic data, obstetric history and DM characters of the studied groups**

Variables	Group1 (n=30)	Group2 (n=30)	$\chi^2$	P value
Age/years (Mean $\pm$ SD)	30.73 $\pm$ 4.60	32.73 $\pm$ 4.27	t=1.91	0.06
Gestational age/ weeks (Mean $\pm$ SD)	29.03 $\pm$ 2.83	28.86 $\pm$ 2.27	t=0.251	0.802
Gravidity Median (Min-Max)	3.00 (1.00- 6.00)	3.00 (1.00- 7.00)	Z=1.363	0.173
Parity Median (Min-Max)	2.00 (0.00- 4.00)	2.00 (0.00- 5.00)	Z=1.826	0.068
BMI (Mean $\pm$ SD)	34.44 $\pm$ 3.7	34.38 $\pm$ 4.84	0.051	0.960
Non-obese No (%)	2 (6.7 %)	1 (3.3 %)	0.351	0.554
Obese No (%)	28 (93.3 %)	29 (96.7 %)		
<b>Education No (%)</b>				
Primary	9 (30.0 %)	14 (46.7%)	1.76	0.184
Higher	21 (70.0 %)	16 (53.3 %)		
<b>Type of DM No (%)</b>				
Gestational DM	16 (53.3 %)	10 (33.3 %)	2.443	0.118
Type 2 DM	14 (46.7 %)	20 (66.7 %)		
Duration of DM (month) Median (Min-Max)	36.00 (12- 60)	36.00 (12- 84)	0.143	0.886
HbA1c (Mean $\pm$ SD)	6.48 $\pm$ 0.70	6.45 $\pm$ 0.67	0.129	0.898

Data are presented as mean  $\pm$  SD, frequency (%), or median (IQR). BMI: Body mass index, DM: diabetes mellites, HbA1c: Hemoglobin A1C. t: student t-test,  $\chi^2$ : chi square test.

**Table (2): Difference between groups regarding fasting blood glucose**

Variables	Group1 (n=30)	Group2 (n=30)	t-test	P value
FBG day3	28 (93.3 %)	27 (90.0%)	0.001	0.972
FBS day6	30 (100.0%)	30 (100.0%)	0	1
FBS day9	30 (100.0%)	30 (100.0%)	0	1
Paired t-test P <sub>before-day9</sub>	t=7.27 P<0.001**	t=10.4 P<0.001**	-	-

Data are presented as frequency (%). FBG: fasting blood glucose. \*\* P<0.001 is statistically highly significant.

**Table (3): Difference between two groups in post-prandial blood glucose levels and hypoglycemic attacks**

Variables	Group1 (n=30)	Group2 (n=30)	t-test	P value
2h PP day3	28 (93.33%)	11 (36.7%)	5.624	<0.001**
2h PP day6	29 (96.6%)	17 (56.7%)	4.087	<0.001**
2h PP day9	30 (100.0%)	21 (70.0%)	10.59	0.002*
Paired t-test P <sub>before-day9</sub>	t=9.59 P=<0.001**	t=8.34 P=<0.001**	-	-
<b>Hypoglycemia</b>			$\chi^2$	<b>p-value</b>
Yes	1 (3.3%)	2 (6.7%)	2.06	0.561
No	29 (96.7%)	28 (93.3%)		

Data are presented as frequency (%). 2h PP: 2-hour post-prandial glucose.  $\chi^2$ : chi square test. \* Significant p <0.05, \*\*highly significant p <0.001.

**Table (4): Difference between post-prandial blood glucose control in (Group 2) according to the level of education and obesity**

Variables	Mid educated (n=16)	High educated (n=14)	t-test	P value
2h PP day 9	126.87±12.93	118±7.1	2.2	0.030*
Control	8 (50%)	13 (92%)	2.79	0.009*
	Moderate obesity (n=17)	Severe obesity (n=12)		
2h PP day 9	117.70±5.1	130±13.88	-3.50	0.002*
Control	16 (94.11%)	4 (33.33%)	4.4	<0.001**

Data are presented as mean ± SD. 2h PP: 2-hour post-prandial glucose. frequency (%). \* Significant p <0.05, \*\*highly significant p <0.001.

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# Angiogenic and Placental factors as Predictors for Gestational Hypertensive Disorders: Which is appropriate?

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## Short title

Angiogenic and Placental factors as Predictors for Gestational Hypertensive Disorders.

## Abstract

**Objectives:** To assess the value of sequential estimation of biomarkers for prediction of gestation hypertension (GHTN) and preeclampsia (PE) and to stratify PE according to time of development and severity.

**Patients & Methods:** 80 normotensive (NT) newly pregnant women who continued pregnancy and were free of hypertensive manifestation (NT group), and the GHTN group included 80 newly pregnant NT women who developed high blood pressure (BP) measures without proteinuria after the 20th gestational week (GW). Early-onset PE (EO-PE) was diagnosed if a GHTN woman developed proteinuria before the 34th GW, but after the 34th GW, it is Late-onset PE (LO-PE). PE was diagnosed as mild if BP was <160/110 with +1 proteinuria on the dipstick, otherwise it is severe PE. Blood samples were obtained at the 12th, 24th, 32nd, and 36th GW for ELISA estimation of serum levels of placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1), pregnancy protein 13 (PP13), and pregnancy-associated plasma protein-A (PAPP-A) levels. The outcome is the ability of the estimated biomarkers' levels to distinguish women liable to develop GHTN or PE among NT pregnant women.

**Results:** 9 women developed EO-PE and 25 had LO-PE. 20 women had mild and 14 women had severe PE. Statistical analyses defined a high sFlt-1/PLGF ratio as specific, and low PAPP-A level as a screening predictor for GHTN at the 12th GW, and at the 24th GW low serum levels of PP13 were defined as the highly significant screening, and high sFlt-1/PLGF as a highly significant specific predictor for EO-PE. In the 32nd GW sample, low PP13 levels were defined as the most significant screening predictor, and high sFlt-1/PLGF ratio was the specific predictor for LO-PE.

**Conclusion:** Sequential estimation of multiple serum

biomarkers for screening of pregnant women to distinguish women vulnerable to developing HPD is required for early detection of these women, especially the high-risk women. The best policy is an estimation of serum PP13 at the 12th GW and an estimation of PP13, sFlt-1, and PLGF to calculate the sFlt-1/PLGF ratio at the 24th and 32nd GW to define women vulnerable to develop PE and to stratify them according to time and severity of PE.

**Keywords:** Gestational hypertension, Preeclampsia, Early prediction, Serum Biomarkers.

## **Introduction**

Hypertensive pregnancy disorders (HPD) are associated with negative pregnancy outcomes and may be the leading cause of maternal and perinatal deaths worldwide. During pregnancy, uterine vasculature undergoes significant remodeling in the form of vascular growth both in length and circumference to accommodate for the increased blood volume to the fetoplacental unit <sup>(1)</sup>.

Preeclampsia (PE) is a multifactorial pathology that makes clinical diagnosis a challenge <sup>(2)</sup>. PE has no cure and is associated with a compromised uterine vascular adaptation to pregnancy sufficient to induce fetal mal-development <sup>(1)</sup>.

There is accumulating evidence demonstrating the importance of placental proteins and anti-angiogenic factors for the prediction of PE <sup>(2)</sup>. Galectin 13 (Placental Protein-13; PP13) is a pregnancy-specific galectin protein, which is localized on the syncytiotrophoblast surface and released as placental-associated extracellular vesicles to the maternal uterine vein <sup>(3)</sup>. PP13 is a regulatory protein that has bidirectional action because it has a role in extending the immune tolerance of the mother to the growing fetus <sup>(4)</sup> and because it is involved in pregnancy-induced uterine vascular system remodeling <sup>(3)</sup>.

Pregnancy-associated plasma protein-A (PAPP-A) is a metalloprotease secreted by mesenchymal stromal cells and increases the availability of insulin-like growth factor by cleaving it from its binding protein <sup>(5)</sup>. PAPP-A has proven to be a reliable prenatal screening marker and reduced PAPP-A levels have a strong positive predictive value for small gestational age and intrauterine growth restriction <sup>(6)</sup>.

The placental growth factor (PLGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) are altered in complicated pregnancies and are associated with PE mostly through induction of endothelial dysfunction which is an important component of PE <sup>(7)</sup>.

## **Objectives**

This study tried to assess the value of sequential estimation of an array of biomarkers for prediction of the possibility of getting gestation hypertension (GHTN) and progress of GHTN to PE and to stratify the risky women according to the possible time of developing PE and its probable severity.

## **Design**

Prospective comparative selective clinical trial.

## **Setting**

Departments of Obstetrics & Gynecology and Clinical Pathology, Faculty of Medicine, Benha University.

## **Ethical Consideration**

The detailed study protocol was introduced for approval by the departmental committee before committing to case collection. Thereafter, the protocol was freely discussed with all the attendants of the Obstetrics outpatient clinic, and those accepted to participate in the study signed a fully informed written patients' consent. After the

completion of case collection and the end of the estimation of the assigned biomarkers, the final approval of the study protocol by the Local Ethical Committee, Benha University was obtained and registered by the code: RC:3-11-23.

### **Study participants**

All newly pregnant women who attended the Obstetrics outpatient clinic for assurance of being pregnant were evaluated for determination of demographic data including age, weight, and height for calculation of body mass index (BMI) as the result of dividing weight in kg by height in meter square with BMI of  $<25$  kg/m<sup>2</sup> is the cutoff point for defining average weight women. History taking included the number of previous pregnancies and its outcome, as regards the development of HPD, diabetes mellitus (DM), or anemia, mode of previous delivery, neonatal data and the number of living offspring. Medical history was also inquired to ensure the absence of essential hypertension, manifest DM, kidney, cardiac or hepatic diseases, and blood diathesis and coagulopathies.

### **Exclusion criteria**

The presence of a history of adverse pregnancy outcomes, especially PE, the presence of essential hypertension, manifest DM, kidney diseases, hemoglobinopathies, autoimmune disorders, or maintenance of immunosuppressive therapy are the exclusion criteria. Women who had multiple gestational sacs on US diagnosis of pregnancy, and women who attended after the end of the 1st trimester, refused to participate in the study or to sign the written consent or lost during follow-up were also excluded from the study.

### **Inclusion criteria**

Newly pregnant women who attended the clinic early in pregnancy had singleton gestational sacs and were free of exclusion

criteria were enrolled in the study.

### **Diagnosis and categorization of GHTN**

Gestational hypertension was defined as the development of high systolic and diastolic blood pressure (SBP & DBP) measures reaching up to  $\geq 140$  and  $\geq 90$  mmHg, respectively, on two separate measurements at least 4–6 hours apart without detection of protein in the urine after the 20<sup>th</sup> GW in a previously normotensive (NT) woman at the time of pregnancy diagnosis<sup>(8)</sup>. PE was defined as the development of GHTN in association with proteinuria quantified as 1+ on the dipstick<sup>(9)</sup>. Concerning PE severity, PE was considered mild (MPE) if SBP and DBP were  $<160$  and  $<110$  mmHg, respectively, with proteinuria of 1+ and absence of systemic manifestations, while Severe PE (SPE) was diagnosed if SBP and DBP measures were  $\geq 160$  and  $\geq 110$  mmHg, respectively, with proteinuria  $\geq 2+$  on a voided random urine<sup>(10)</sup>. As regards the timing of PE development, PE was categorized as early-onset (EO-PE) and late-onset (LO-PE) if PE, irrespective of severity, was diagnosed before or after the 34<sup>th</sup> GW, respectively<sup>(11, 12)</sup>.

### **Sample size calculation**

The null hypothesis of the current study is the detection of significant differences in levels of serum biomarkers between women who completed their pregnancy and were free of gestational hypertensive manifestations (NT women), and women who developed GHTN or PE, irrespective of its timing and/or severity. Atakul (13) detected a significant difference between control (n=24), mild (n=32) and severe PE (n=32) women in serum levels of PAPP-A, and Nikuei et al. (14) reported a significant difference in sFlt-1/PLGF between PE and control women in a study included 23 women developed mild, 15 women developed severe PE, and 20 normal term pregnant. Using the G\*Power

(Version 3.1.9.2) (15), the sample size was calculated to be 80 GHTN and 80 NT women. Considering the effect size of 0.20 by the F test model, the calculated sample size of 80 women per group was found to provide a study power of 80% using  $\alpha$ -error 5 and ensure the certainty of the null hypothesis.

### **Study rationale**

This selective-based case-control study aimed to collect 80 women who had developed GHTN during their pregnancy course, irrespective of being associated or not with proteinuria. The only condition for selection is that these women must be normotensive at time of diagnosis of pregnancy at the 6th gestational week (GW). On the other side, 80 women who were NT at the 6th GW and continued NT till the 36th GW were also collected.

Both SBP and DBP were measured and registered at the 12th GW (Baseline measure), at the 24th GW to distinguish GHTN women, at the 32nd GW with evaluation of the level of proteinuria to detect women who developed EO-PE among the women had GHTN and to assure that control women were still NT, and at the 36th GW to detect women who developed LO-PE among GHTN women and to assure normality of BP of NT women.

Blood samples were obtained aseptically at the 12th GW for estimation of baseline levels of the studied biomarkers and to evaluate its predictability for the development of GHTN. Other blood samples were withdrawn at the 24th and the 32nd GW to estimate the biomarkers' levels and to determine their distinguishing ability for women vulnerable to develop EO-PE and LO-PE, respectively among GHTN women. The last blood samples were collected at the 36th GW to estimate the biomarkers' levels and ensure the differences between NT and GHTN women and between EO-PE and LO-PE.

### **Blindness**

One author, El Sayed LK, was responsible for case collection and clinical stratification of women according to blood pressure measurements and was blinded about the estimated biomarkers' levels. Another author, Rachwan MT, was responsible for blood sample collection and conduction of investigations and was blinded about which sample was obtained from case or control women and about the timing of sampling concerning gestation weeks. The 3rd author, Mohamed SA, was responsible for the interpretation of clinical and lab data to evaluate the study outcome.

### **Blood sample processing and storage**

Blood samples were collected in plain tubes and were allowed to clot and centrifuged at 3000 rpm for 10 minutes to separate serum. The obtained serum was collected in a sterile numbered Eppendorf tube and stored at -20°C till it was assayed using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and was read using a 96-well microplate ELISA reader (Dynatech. MR 7000).

### **Laboratory investigations**

1. Human placental growth factor (PLGF) was measured with an Abcam ELISA kit (Cat. No. ab260056 Abcam Inc., Cambridge, USA) <sup>(16)</sup>.
2. Serum levels of human soluble fms-like tyrosine kinase-1 (sFlt-1) were estimated using an Abcam ELISA kit (Cat. No. ab289705, Abcam Inc., Cambridge, USA) <sup>(17)</sup>.
3. Serum human pregnancy protein 13 was assayed using an Abcam ELISA kit (Cat. No. ab100553, Abcam Inc., Cambridge, USA) <sup>(18)</sup>.

4. Serum pregnancy-associated plasma protein-A levels were measured using an Abcam ELISA kit (Cat. No. ab235647, Abcam Inc., Cambridge, USA) <sup>(19)</sup>.

**Study outcomes**

The outcome of the current study is the ability of the estimated biomarkers' levels for:

1. Distinguishing women liable to develop GHTN among NT pregnant women.
2. Identification of women vulnerable to progress to PE among GHTN women.
3. Differentiation between PE women according to timing and severity of PE.

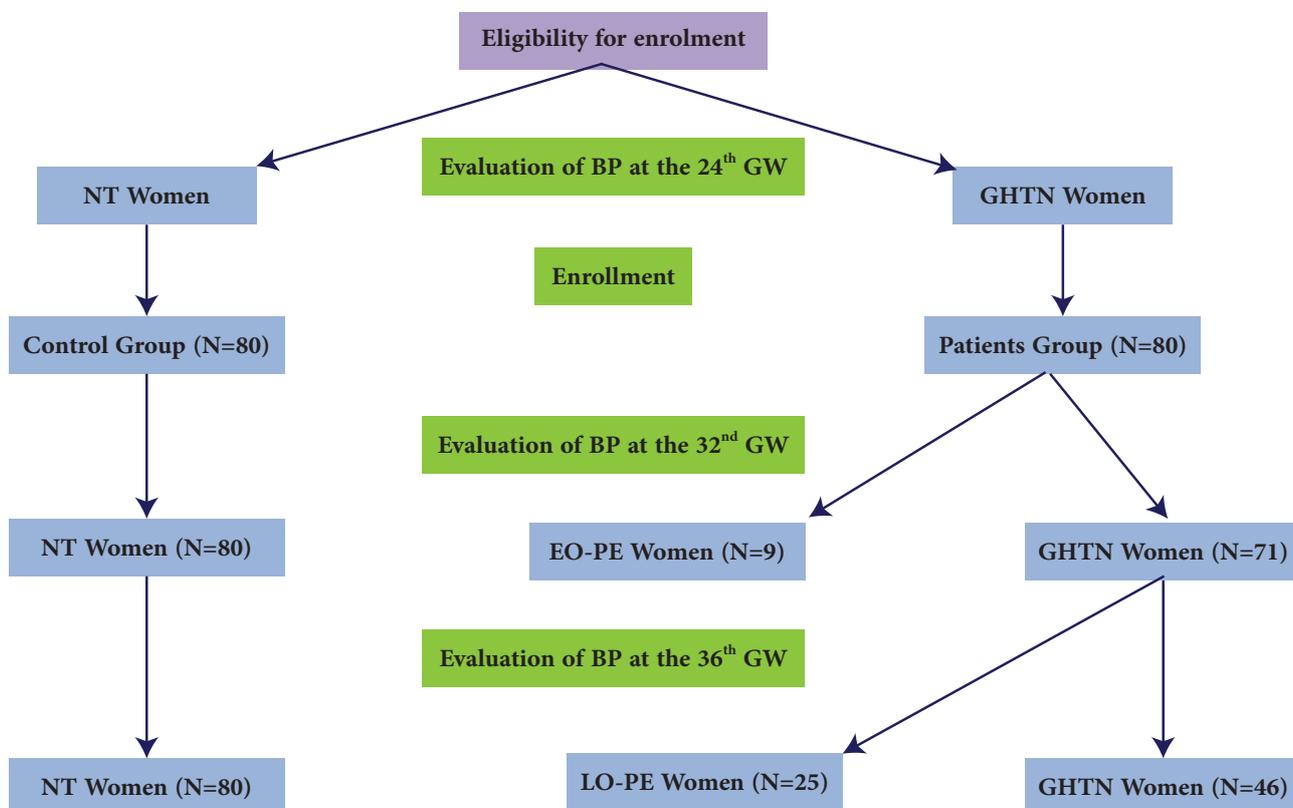
**Statistical analysis**

One-way ANOVA test and Chi-square test (X2 test) were used to assess the significance of the intragroup comparisons. Evaluation of predictability was conducted using

the Receiver characteristic curve. The significance of the area under the ROC curve (AUC) was assessed concerning the area under the reference curve. The significance of the predictors was assured using the Regression Analysis. Statistical analyses were conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). The significance of the results was determined using a P-value at a cutoff point of 0.05.

**Results**

Throughout the study duration and considering the selective basis of the study, 80 pregnant women were selected from those who continued their pregnancy free of GHTN (NT group). Also, 80 women who developed GHTN and were diagnosed at the 24th GW were collected as the GHTN group. The diagnostic flowchart is shown in Figure 1, and the enrolment data of women of both groups are shown in Table 1.



**Figure 1: Study Flow Chart**

**Table 1: Women's enrolment data**

Data	Group	NT (n=80)	GHTN (n=80)	P-value
Age (years)	Average (SD)	27.8 (3.7)	28.5 (3.6)	0.226
BMI (kg/m <sup>2</sup> )	Overweight	43 (53.75%)	35 (43.75%)	0.206
	Obesity	37 (46.25%)	45 (56.25%)	
	Average (SD)	29.3 (2.9)	29.6 (2.6)	0.488
Gravidity	Primigravida	47 (58.75%)	54 (67.5%)	0.251
	Multigravida	33 (41.25%)	45 (32.5%)	
Parity among multigravida	Para-1	14 (42.4%)	18 (69.2%)	0.077
	Para-2	13 (39.4%)	7 (26.9%)	
	Para-3	6 (18.2%)	1 (3.9%)	
Number of living offspring	No	2 (10.5%)	1 (12.5%)	0.648
	One	8 (42.2%)	5 (62.5%)	
	Two	7 (36.8%)	1 (12.5%)	
	Three	2 (10.5%)	1 (12.5%)	

P indicates the significance of intergroup differences at a cutoff point of 0.05

Blood pressure measures estimated at the time of enrolment and the 12th GW of women of both groups showed insignificant differences. At the 24th GW, BP measures were significantly ( $P<0.001$ ) higher in GHTN than in NT women. Throughout the duration from the 24th to the 32nd GW, 9 GHTN women showed significantly higher BP measures than the remaining 71 GHTN women, developed proteinuria, and were grouped as EO-PE. Moreover, the BP measures of the remaining 71 GHTN women were significantly ( $P<0.001$ ) higher in comparison to the BP measures of NT women. During follow-up between the 32nd and 36th GW, 25 GHTN women showed flared-up BP measures that were significantly ( $P=0.0005$  &  $<0.001$  for SBP & DBP, respectively) higher in comparison to the corresponding measures of GHTN women ( $n=46$ ) as shown in table 2. Further, these 25 women developed proteinuria and regarding the development of PE after the 34th GW, these 25 women were grouped as LO-PE (Fig. 1, Table 2).

Collectively, there were 34 PE women; 9 had early and 25 had late PE, and women who had EO-PE showed significantly higher SBP ( $P=0.02$ ) and DBP ( $P=0.0061$ ) than women who had LO-PE. As regards the severity of PE; 20 women had mild and 14 women had severe PE, irrespective of the timing of PE development. Women who had severe PE showed significantly ( $P<0.001$ ) higher BP measures than women who had mild PE as shown in Table 2, figure 2.

**Table 2: Time-course blood pressure measures of the studied women categorized according to the detected blood pressure disorders**

Variate	Group Parameter	SBP (mmHg)	P-value	DBP (mmHg)	P-value
Enrolment	NT group (N=80)	116.3 (6.3)	0.267	75.6 (4.5)	0.306
	GHTN group (n=80)	115.1 (7.3)		74.9 (4.1)	
12 <sup>th</sup> GW	NT group (N=80)	118.4 (7.3)	0.110	79.9 (5.5)	0.086
	GHTN group (n=80)	119.9 (4)		81.5 (6.2)	
24 <sup>th</sup> GW	NT group (N=80)	120 (8.4)	<0.001	81.5 (6)	<0.001
	GHTN group (n=80)	140.2 (7.9)		94.4 (4.9)	
32 <sup>nd</sup> GW	NT group (N=80)	120.9 (8.2)	<0.001	82 (5.3)	<0.001
	GHTN group (n=71)	144 (4.9)		95 (2.2)	
36 <sup>th</sup> GW	NT group (N=80)	122.1 (6.8)	<0.001	82.7 (5.2)	<0.001
	GHTN group (n=46)	146 (5.5)		94.5 (2.8)	
32 <sup>nd</sup> GW	GHTN group (N=71)	144.8 (5.2)	<0.001	95 (1.8)	<0.001
	EO-PE group (n=9)	162 (11.8)		108 (8.5)	
36 <sup>th</sup> GW	GHTN group (N=46)	147 (3.6)	0.0005	95.5 (1.4)	<0.001
	LO-PE group (n=25)	153 (8.5)		100.8 (5.4)	
Timing of PE	EO-PE (n=9)	162 (11.8)	0.020	108 (8.5)	0.0061
	LO-PE (n=25)	153 (8.5)		100.8 (5.4)	
Severity of PE	Mild PE (n=20)	147.9 (2.4)	<0.001	98.5 (4.2)	<0.001
	Severe PE (n=14)	166.1 (6.7)		108.8 (5.5)	

The P-value indicates the significance of the difference in BP measures at a cutoff point of 0.05

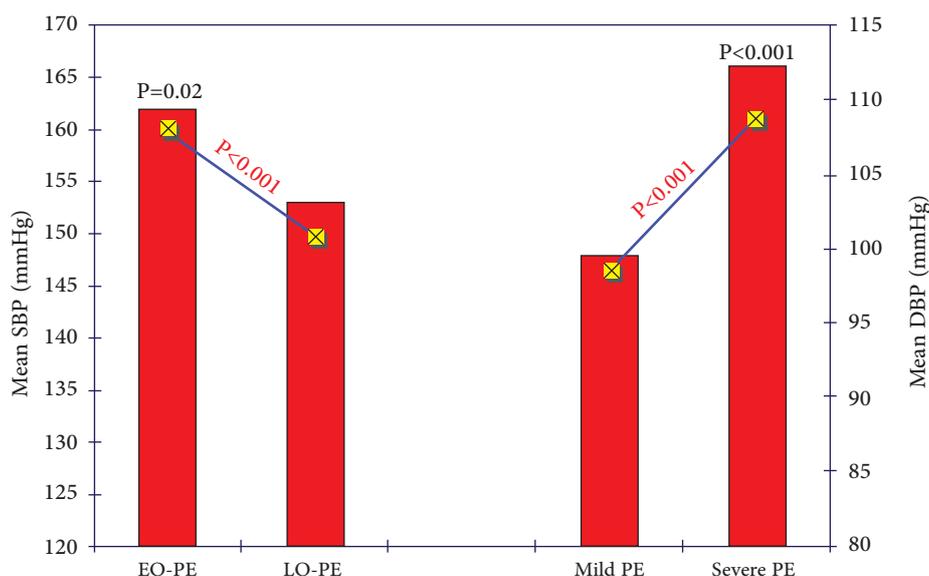


Fig. (2) Mean SBP & DBP measures in PE women categorized according timing and severity

Estimated serum levels of the studied biomarkers in samples obtained at enrolment showed insignificant differences between the enrolled women. Serum levels of PP-13 and PAPP-A estimated in women's samples were significantly ( $P < 0.001$ ) lower in GHTN women than NT women throughout the pregnancy course. Moreover, serum PP-13 and PAPP-A levels were significantly lower in samples of EO-PE and severe PE women than levels estimated in samples of LO-PE and mild PE women, respectively (Table 3).

**Table 3: Time-course serum levels of PP-13 and PAPP-A estimated in samples of the studied women categorized according to the detected blood pressure disorders**

Variate	Group Biomarker	PP-13 (ng/ml)	P-value	PAPP-A (mIU/ml)	P-value
Enrolment	NT (N=80)	135 (13.8)	0.158	1194 (217.3)	0.204
	GHTN (N=80)	132 (13)		1145 (265.9)	
12 <sup>th</sup> GW	NT (N=80)	157.5 (15.8)	<0.001	1857 (339.6)	<0.001
	GHTN (N=80)	137.3 (9.8)		1042 (252.4)	
24 <sup>th</sup> GW	NT (N=80)	216.4 (31.4)	<0.001	2014 (341.9)	<0.001
	GHTN (N=80)	161.2 (13.9)		955.5 (266.4)	
32 <sup>nd</sup> GW	NT (N=80)	240 (35.2)	<0.001	2056 (464.4)	<0.001
	GHTN (N=71)	196 (20.7)		822.6 (241)	
36 <sup>th</sup> GW	NT (N=80)	298 (27.2)	<0.001	2200 (490.6)	<0.001
	GHTN (N=46)	236 (21.6)		788 (248.3)	
Timing of PE	EO-PE (N=9)	97.8 (4.1)	0.0127	529 (112.4)	0.0084
	LO-PE (N=25)	112.9 (16.8)		670.2 (134.5)	
Severity of PE	Mild PE (N=20)	115.8 (17.4)	0.0014	744.5 (86)	<0.001
	Severe PE (N=14)	99 (5.1)		510 (108.1)	

The P-value indicates the significance of differences in BP measures at a cutoff point of 0.05

Throughout the pregnancy course, serum levels of sFlt-1 progressively increased and serum PLGF progressively decreased with progressive increase of sFlt-1/PLGF ratio in samples of GHTN than NT women. The difference between serum levels of sFlt-1 and PLGF, and the in-between ratio between PE women differentiated according to time of development of PE were insignificant, while the differences according to the severity of PE were significant (Table 4).

**Table 4: Time-course serum levels of sFlt-1 and PLGF with the sFlt-1/PLGF ratio estimated in samples of the studied women categorized according to the detected blood pressure disorders**

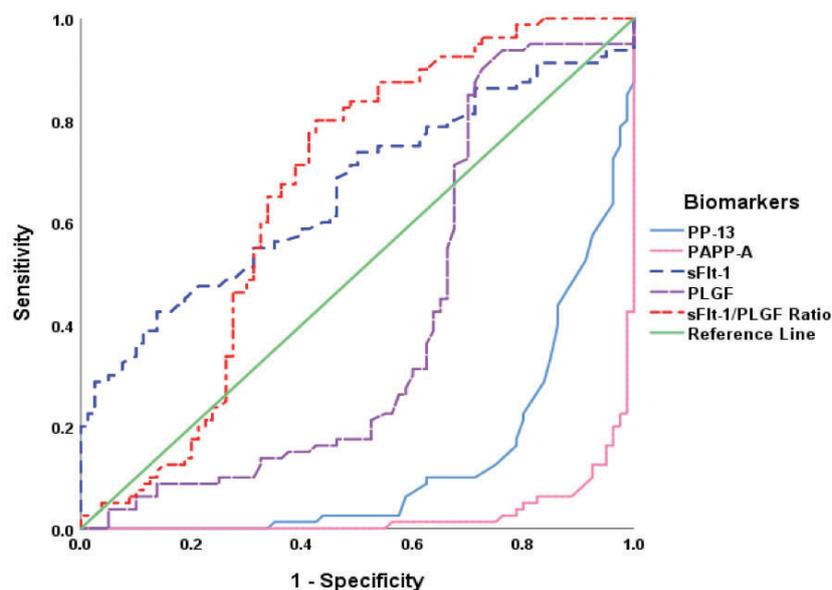
Variate	Biomarker Group	sFlt-1	P	PLGF	P	sFlt-1/PLGF	P
Enrolment	NT (N=80)	145.1 (19.4)	0.188	33 (7.7)	0.461	4.63 (1.2)	0.614
	GHTN (N=80)	149 (17.9)		34.1 (10.9)		4.73 (1.4)	
12 <sup>th</sup> GW	NT (N=80)	555 (127.5)	0.0003	156 (52.6)	0.015	4.2 (2.3)	0.027
	GHTN (N=80)	645.4 (175.6)		138.1 (38.9)		5 (2.15)	
24 <sup>th</sup> GW	NT (N=80)	658.1 (187.9)	<0.001	280.8 (71.8)	<0.001	2.58 (1.25)	<0.001
	GHTN (N=80)	1022.2 (391.1)		179.7 (46)		6.2 (3.6)	
32 <sup>nd</sup> GW	NT (N=80)	1000.2 (219.3)	<0.001	505 (128.5)	<0.001	2.2 (1.14)	<0.001
	GHTN (N=71)	2417.8 (558.8)		98 (20.7)		25.25 (6)	
36 <sup>th</sup> GW	NT (N=80)	1426 (443.2)	<0.001	600.4 (129.2)	<0.001	2.5 (0.85)	<0.001
	GHTN (n=46)	2001.4 (561.3)		83 (20.6)		24.8 (7.4)	
Timing of PE	EO (n=9)	3055.7 (415.8)	0.299	73.8 (8.8)	0.062	42 (7.7)	0.061
	LO (n=25)	2815.7 (630.4)		82 (11.6)		35.2 (9.4)	
Severity of PE	Mild (n=20)	2694 (588)	0.045	83.4 (11.6)	0.016	33.1 (8.6)	0.0031
	Severe (n=14)	3090 (476)		74 (9)		42.3 (7.6)	

The P-value indicates the significance of differences in BP measures at a cutoff point of 0.05

Statistical analysis of the estimated biomarkers' levels in the 12th GW samples using ROC analysis defined high serum sFlt-1 and high sFlt-1/PLGF ratio as specific predictors for oncoming GHTN, but despite the equal AUC, its significance concerning the area under the reference line was higher for sFlt-1/PLGF ratio. Also, ROC curve analysis stratified other biomarkers as screening parameters for oncoming GHTN according to the AUC as follows: low serum levels of PAPP-A, PP13, and PLGF (Table 5, Fig.3). Regression analysis defined low PAPP-A as the predictor with persistently significant standardized coefficient, followed by low serum levels of PP13 (Table 5). To verify the predictability of low serum levels of PP13 and PAPP-A, the paired-sample area difference under the ROC curves showed a significant (P<0.001) difference between AUCs of PP13 and PAPP-A (AUC difference= 0.103; Std. Error difference=0.196; 95% CI: 0.049-0.157) in favor of PAPP-A.

**Table 5: Statistical analyses for the serum levels of the studied biomarkers estimated in the 12<sup>th</sup> GW samples as predictors for oncoming GHTN**

	Receiver Operating Characteristic Curve				Regression analysis	
	AUC	Std.	P	95% CI	$\beta$	P
PP13	0.131	0.028	<0.001	0.075-0.186	-0.247	<0.001
PAPP-A	0.028	0.010	<0.001	0.007-0.048	-0.674	<0.001
sFlt-1	0.659	0.043	0.001	0.574-0.744	0.083	0.068
PLGF	0.401	0.048	0.031	0.308-0.495	-0.128	0.003
sFlt-1/PLGF	0.659	0.045	<0.001	0.571-0.747	0.088	0.057

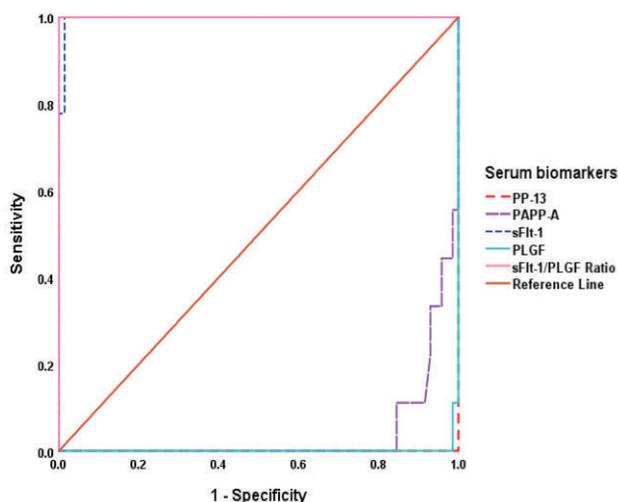
**Fig. 3:** ROC curve analysis of biomarkers' levels estimated in the 12th GW samples for prediction of oncoming GHTN

ROC curve analysis differentiated the estimated biomarkers' levels in the 24th GW samples for prediction of EO-PE as screening biomarkers with highly significant AUC; PP13, PLGF, and PAPP-A in decreasing order of significance and sFlt-1/PLGF ratio and serum sFlt-1 levels as specific predictors for EO-PE (Table 6, Fig. 4a). Regression analysis assured that low serum levels of PP13 is highly significant screening biomarker for EO-PE and excluded both of PLGF and PAPP-A, while defined high sFlt-1/PLGF as highly significant specific predictor for EO-PE and excluded high serum sFlt-1 (Table 6).

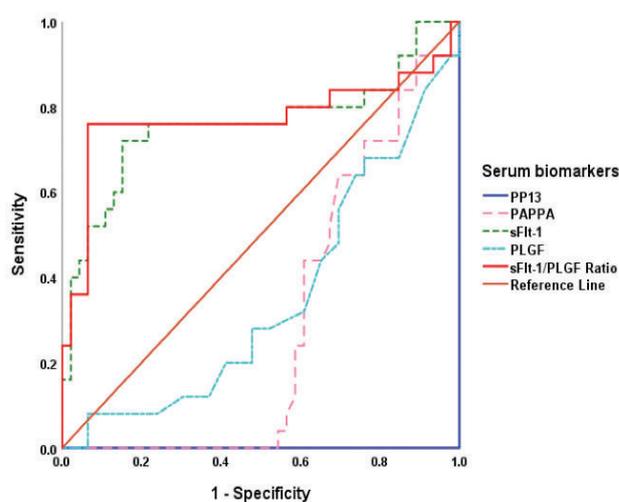
Evaluation of the ability of estimated biomarkers' levels in the 32nd GW sample for predicting the development of LO-PE using the ROC curve defined low PP13 as the most significant screening predictor, while low serum levels of PAPP-A and PLGF could predict LO-PE but with low significant AUC. On the other side, high serum sFlt-1 and high sFlt-1/PLGF ratio could define patients liable to develop LO-PE with nearly equal AUC (Table 6, Fig. 4b). Verification of these biomarkers using Regression Analysis defined low PP13 as the only significant screening predictor and high sFlt-1/PLGF ratio as the specific predictor (Table 6)

**Table 6: Statistical analyses for the serum biomarkers' levels estimated in the 24<sup>th</sup> & the 32<sup>nd</sup> GW samples as predictors for oncoming PE**

Sample time	Biomarkers	Receiver Operating Characteristic Curve				Regression analysis	
		AUC	Std.	P	95% CI	$\beta$	P
The 24 <sup>th</sup> GW (for prediction of EO-PE)	PP13	0.000	0.000	<0.001	0.000	-0.230	<0.001
	PAPP-A	0.040	0.022	<0.001	0.000-0.084	-0.093	0.419
	sFlt-1	0.997	0.004	<0.001	0.989-1.000	-0.054	0.641
	PLGF	0.002	0.003	<0.001	0.000-0.007	0.231	0.052
	sFlt-1/PLGF	1.000	0.000	<0.001	1.000-1.000	0.758	<0.001
The 32 <sup>nd</sup> GW (for prediction of LO-PE)	PP-13	0.000	0.000	<0.001	0.000	-0.857	<0.001
	PAPP-A	0.291	0.060	0.004	0.172-0.409	-0.135	0.846
	sFlt-1	0.759	0.069	<0.001	0.623-0.895	0.055	0.255
	PLGF	0.349	0.068	0.037	0.217-0.482	0.078	0.727
	sFlt-1/PLGF	0.772	0.073	<0.001	0.630-0.914	0.126	0.020



**Fig. 4a:** ROC curve analysis of biomarkers' levels estimated in the 24<sup>th</sup> GW samples for prediction of oncoming EO-PE

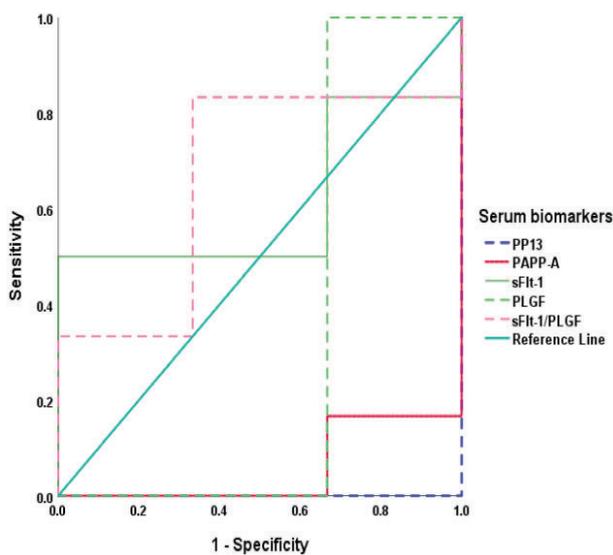


**Fig. 4b:** ROC curve analysis of biomarkers' levels estimated in the 24<sup>th</sup> GW samples for prediction of oncoming LO-PE

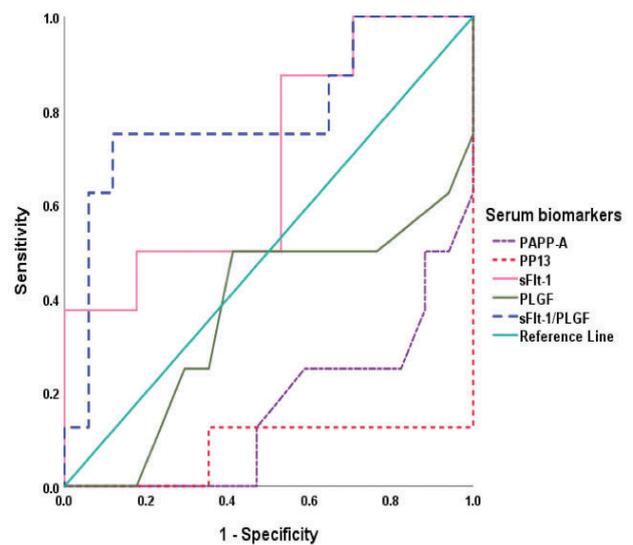
Using the ROC curve analysis for serum biomarkers' levels estimated in the 24<sup>th</sup> GW samples, low serum levels of PP13 and PAPP-A were found to be significant screening predictors for severe EO-PE (Fig. 5a), but Regression Analysis excluded PAPP-A and assured the utility of PP13 as a screening biomarker for severe EO-PE. According to the estimated serum biomarkers' levels in the 32<sup>nd</sup> GW samples, ROC curve analysis defined low serum PP13 and PPAP-A as the significant screening and high sFlt-1/PLGF ratio as the significant specific predictor for severe LO-PE (Fig. 5b). However, Regression Analysis defined low PP13 serum levels in the 32<sup>nd</sup> GW sample as the significant screening predictor for severe LO-PE (Table 7).

**Table 7: Statistical analyses for the serum levels of the studied biomarkers estimated in the 24<sup>th</sup> & the 32<sup>nd</sup> GW samples as predictors for severity of oncoming PE**

Sample time	Biomarkers	Receiver Operating Characteristic Curve				Regression analysis	
		AUC	Std.	P	95% CI	$\beta$	P
The 24 <sup>th</sup> GW (for prediction of severe PE among women who had EO-PE)	PP13	0.000	0.000	<0.001	0.000	-0.230	<0.001
	PAPP-A	0.040	0.022	<0.001	0.000-0.084	-0.093	0.419
	sFlt-1	0.997	0.004	<0.001	0.989-1.000	-0.054	0.641
	PLGF	0.002	0.003	<0.001	0.000-0.007	0.231	0.052
	sFlt-1/PLGF	1.000	0.000	<0.001	1.000-1.000	0.758	<0.001
The 32 <sup>nd</sup> GW (for prediction of severe PE among women who had LO-PE)	PP13	0.000	0.000	<0.001	0.000	-0.857	<0.001
	PAPP-A	0.291	0.060	0.004	0.172-0.409	-0.135	0.846
	sFlt-1	0.759	0.069	<0.001	0.623-0.895	0.055	0.255
	PLGF	0.349	0.068	0.037	0.217-0.482	0.078	0.727
	sFlt-1/PLGF	0.772	0.073	<0.001	0.630-0.914	0.126	0.020



**Fig. 5a:** ROC curve analysis of biomarkers' levels estimated in the 32<sup>nd</sup> GW samples for prediction of oncoming severe EO-PE



**Fig. 5b:** ROC curve analysis of biomarkers' levels estimated in the 32<sup>nd</sup> GW samples for prediction of oncoming severe LO-PE

## **Discussion**

The results of the current study shed light on two important points; first, no single serum biomarker could predict the oncoming GHTN, the possibility of progress of GHTN to PE or stratify patients according to timing and severity of PE. Second, a single sample for estimation of serum biomarkers' levels could falsely exclude the possibility of committing GHTN or define women as vulnerable to developing PE. In support of these findings, serum biomarkers' levels estimated throughout the pregnancy course showed significant differences between NT and GHTN women, thus just estimation of any biomarker in a single sample can give fake results, if not interpreted with levels of other biomarkers and clinical findings.

Moreover, ROC curve analysis for serum biomarkers' levels estimated in the 12th GW samples showed its ability to be used as early predictors for GHTN with varied AUC, but Regression Analysis defined low serum levels of PAPP-A and PP13 in the 12th GW samples as the biomarkers that might distinguish women vulnerable to develop GHTN at or after the 24th GW and any of them could be used as early screening test for hypertensive pregnancy disorders (HPD).

In line with this finding, multiple previous studies assured the applicability of estimated serum PAPP-A levels early in pregnancy as a predictor for oncoming pregnancy adverse events, where Luewan et al. (19) documented that pregnant women with low 1st-trimester PAPP-A levels must be managed as PE high-risk women, and Ramezani et al. (20) found the risk for developing gestational diabetes mellitus (GDM) was 3.98-fold higher in women had low PAPP-A during the 11-14 GW than women had normal serum PAPP-A levels, and concluded that low PAPP-A level is a risk factor that might be used for early prediction of GDM. Also, Genc et al. (21) documented that the 1st-trimester screening PAPP-A test could be used for

early prediction of pregnancy complications, and Gupta et al. (22) detected a significant difference between serum levels of PAPP-A and PLGF in samples obtained during the 1st-trimester from normotensive and PE women. Thereafter, Melamed et al. (23) found the adjusted relative risk using low PAPP-A serum level estimated during the 1st trimester as a predictor for oncoming placenta-mediated complications including PE was 2.48 versus 2.28 for low PLGF.

Despite the ability of estimated serum PAPP-A levels at the 12th GW to early predict GHTN, its levels estimated at the 24th and 32nd GW failed to predict PE or to stratify it according to timing. Similarly, Jie et al., (2023) (24) detected an increased risk for PE in women who had normal PAPP-A levels during the 2nd trimester as judged by abnormal uterine artery Doppler findings.

Contrary to PAPP-A, low serum levels of PP13 in the 12th GW sample could be used for screening pregnant women for the possibility of development of GHTN and the 24th and the 32nd GW samples could be used as screening tests with high sensitivity for distinguishing women liable to develop EO and LO-PE, respectively among GHTN women and to define women who will develop severe PE, irrespective of time of having PE among women vulnerable to develop PE.

In line with the usefulness of low serum PP13 as a biomarker for the predictive screening for HPD, Wu et al. (25) in a meta-analysis documented that decreased expression levels of PP13 expression is one of the earliest signs of PE development with high predictive performance. Also, Piskun et al. (26) using immunohistochemistry detected lower expression of PP13 in syncytiotrophoblast of chorionic villi of placentae of PE women than in placenta of normal pregnancies and concluded that the lowest production of PP13 is accompanied by placental dysfunction and PE. Recently, Palalioglu & Erbiyik (27) documented the relation between endothelial

dysfunction parameters; PP13, P-selectin, and E-selectin and the development of PE.

Experimentally using an animal model, PP13 was found to have a dilatory action on uterine and placental vasculature in late pregnancy through a pathway consisting of small conductance  $Ca^{2+}$ -activated  $K^{+}$  channels- Nitric Oxide- big conductance  $Ca^{2+}$ -activated  $K^{+}$  channels. So the reduced PP13 levels lead to a diminution of this dilatory action with the subsequent release of vasoactive substances and induction of hypertensive disorders (1).

The calculated sFlt-1/PLGF ratio, according to levels estimated in the 24th and the 32nd GW samples, could be used as a specific predictor for the development of EO and LO-PE, irrespective of the severity of PE. These findings go in hand with the previous retrospective studies that documented the ability of high sFlt-1/PLGF ratio to identify women who were liable to develop PE among GHTN women and to predict PE development within the oncoming 4 weeks (28, 29). Moreover, Rowson et al (30) detected significantly lower serum PLGF and higher sFlt-1 with a high ratio in pregnant women who gave samples during the 2nd trimester and developed PE in comparison to women who did not develop PE and gave samples at the same time.

In support of the high diagnostic yield of high sFlt-1/PLGF ratio and its specificity for PE women among GHTN women, Miller et al (31) documented the superior clinical performance of sFlt-1/PLGF over hypertension and proteinuria alone to predict PE. Also, Kluivers et al. (32) detected significantly increased serum levels of sFlt-1 with high levels of sFlt-1/PLGF ratio in PE than non-PE women, and attributed these increased levels to upregulation of the expression levels of sFlt-1 that occurs synergistically with the progress of pregnancy and increases of blood pressure measures. In another study, Kurlak et al. (33) detected low levels of PLGF, and high sFlt-1 levels with a

high in-between ratio in the maternal serum of PE women and found estimated levels of selenium, zinc and manganese were all lower, while copper levels were high in PE women and suggested a possible role for deregulated levels of these antioxidant micronutrients for the development of the antiangiogenic state in PE women.

The reported diagnostic value of each biomarker at a certain time during pregnancy indicated the need for more than one biomarker to verify the pregnant women according to the possibility of PE development, and to necessitate the sequential estimation of these biomarkers using multiple samples obtained during pregnancy. The only obstacle to applying a similar protocol as routine screening protocol is the cost of the ELISA estimation of these biomarkers. However, from the cost-benefit point of view, the cost of screening for early prediction and management of pregnancy-associated complications to provide safe pregnancy outcomes concerning the mother and the fetus is surely lower than the management of complications or confronting the risk of maternal and fetal morbidities and mortalities. In line with this suggestion, Garay et al. (34) also suggested the possibility of cost-saving with the implementation of biomarkers-based screening for PE through the reduction of unnecessary hospitalizations.

## **Conclusion**

Sequential estimation of multiple serum biomarkers for screening of pregnant women to distinguish women vulnerable to developing HPD is required for early detection of these women, especially high-risk women. The best policy is an estimation of serum PP13 at the 12th GW and an estimation of PP13, sFlt-1, and PLGF to calculate the sFlt-1/PLGF ratio at the 24th and 32nd GW to define women vulnerable to developing PE and to stratify them according to time and severity of PE.

## **Limitation**

The inclusion of women free of risk of hypertensive disorders is a limitation of the outcomes of this study, thus a similar study protocol was recommended to be tried for women with a high risk for HPD.

## **Recommendation**

The inclusion of similar protocols for the prediction of other pregnancy-associated complications, especially small for gestational age, intrauterine growth restriction, GDM, gestational anemia, and postpartum PE is mandatory to accomplish a complementary screening protocol. Also, screening campaigns funded by great companies and hospitals are required to establish screening protocols using large sample-sized populations.

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# Maternal and perinatal Outcomes of Cases with Severe Preeclampsia before 34 Weeks of Gestation

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## **Abstract**

**Background:** Pre-eclampsia is a pregnancy complication that affects approximately 5% of pregnancies worldwide. It is characterized by the onset of high blood pressure and protein in the urine after 20 weeks of pregnancy or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive patient. Severe pre-eclampsia before term is associated with higher risks for both the mother and the fetus.

**Aim of the Work:** To evaluate the maternal and perinatal outcomes of cases with severe preeclampsia before 34 weeks and to evaluate the benefits and risks of a policy of early delivery by induction of labor or by caesarean section, and policy of delaying delivery (expectant management) for women with severe pre-eclampsia between 26 and 34 weeks gestation.

**Patients and Methods:** This study is a prospective Observational study. This study start from 6 to 12 months after protocol approval of the ethical committee. This study conducted at Ain Shams University Maternity Hospital. Study Population: The study will be conducted on records of pregnant women attending Ain Shams University Maternity Hospital.

**Results:** The study assessed severe preeclampsia cases before 34 weeks, with a cohort of 90 participants (mean age: 29.58 years). Most were aged 18-30 years (81.1%), with diverse gravidity and parity. Prior cesarean sections and abortions were common. Symptoms included headache (57.8%) and vomiting (40.0%). Maternal outcomes showed complication-free courses in 71.1%, but 32.2% required ICU admission. Neonatal challenges included respiratory distress syndrome (75.6%) and NICU admission (56.7%). Cesarean section rate was 97.8%, this underscores the multifaceted nature of severe preeclampsia before 34 weeks, affecting both maternal and perinatal outcomes.

**Conclusion:** This study comprehensively investigated severe preeclampsia cases before 34 weeks of gestation, revealing demographic characteristics, clinical features, and outcomes. Maternal complications, including ICU

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admission, were observed in a substantial proportion, emphasizing the critical nature of severe preeclampsia. Neonatal outcomes were marked by challenges such as respiratory distress syndrome and low birth weight, with notable neonatal mortality. Gestational age, blood pressure parameters, and interventions like steroid use and immediate delivery played significant roles in influencing outcomes.

**Keywords:** Preeclampsia, 34 Weeks of Gestation.

## **INTRODUCTION**

Pre-eclampsia is a pregnancy complication that affects approximately 5% of pregnancies worldwide. It is characterized by the onset of high blood pressure and protein in the urine after 20 weeks of pregnancy or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive patient. Severe pre-eclampsia before term is associated with higher risks for both the mother and the fetus <sup>1</sup>.

Maternal complications of severe pre-eclampsia can include organ damage, stroke, and even death <sup>2</sup>.

Perinatal complications of severe pre-eclampsia can include premature birth, low birth weight, and intrauterine growth restriction, and infants born to mothers with severe pre-eclampsia are at increased risk for neonatal morbidity and mortality <sup>3</sup>.

The management of severe pre-eclampsia often involves delivery of the baby, as this is the only way to cure the condition. However, the timing of delivery depends on the gestational age of the fetus and the severity of the mother's condition. If the fetus is not yet mature enough to survive outside the womb, delivery may be delayed until the fetus is more developed <sup>2</sup>.

Close monitoring of maternal and fetal well-being is important in the management

of severe pre-eclampsia before term. This may involve regular blood pressure checks, proteinuria testing, and fetal monitoring to assess the fetal heart rate and well-being. Based on the results of these tests, healthcare providers can make informed decisions about the timing of delivery <sup>4</sup>.

Maternal and perinatal outcomes can be improved by early identification and management of severe pre-eclampsia. It is important for pregnant women to be aware of the signs and symptoms of the condition and to seek medical attention if they suspect they may have it. This can help ensure that appropriate care is provided in a timely manner <sup>5</sup>.

Materno-perinatal outcomes of cases with severe pre-eclampsia before term are important considerations in the management of this condition. Prolonging the pregnancy carries the risk of further maternal and fetal complications, while delivering the baby too prematurely can also have negative consequences. It is important to carefully weigh the risks and benefits of both options and make an informed decision based on the gestational age of the fetus and the severity of the mother's condition. Close monitoring of maternal and fetal well-being can help optimize the care of pregnant women with severe pre-eclampsia before 34 weeks <sup>6</sup>.

## **AIM OF THE WORK**

To evaluate the maternal and perinatal outcomes of cases with severe preeclampsia before 34 weeks and to evaluate the benefits and risks of a policy of early delivery by induction of labor or by caesarean section, and policy of delaying delivery (expectant management) for women with severe pre-eclampsia between 26 and 34 weeks gestation.

**Research Hypothesis:** Women with severe pre-eclampsia who deliver before 34 week are more likely to have adverse maternal and

perinatal outcomes compared to those who deliver at term. So it is important to carefully weigh the risks and benefits of a policy of early delivery by induction of labor or by caesarean section, and a policy of delaying delivery (expectant management).

**Research Question:** In case of severe preeclampsia before term what is the association between gestational age at delivery and materno-perinatal outcomes? And what are the materno-perinatal outcomes in both policies of management (immediate delivery and expectant management).

## **PATIENTS AND METHODS**

**Type of Study:** Prospective Observational study.

**Time of study:** 6 to 12 months after protocol approval of the ethical committee.

**Study Setting:** Ain Shams University Maternity Hospital.

**Study Population:** The study will be conducted on records of pregnant women attending Ain Shams University Maternity Hospital with the following criteria:

**Inclusion criteria:** Single living fetus and gestational age between 26 and 34 weeks.

**Preeclamptic women with one or more of the following:** blood pressure greater than or equal to 160/110 mm Hg measured twice at least 4 hours apart while the patient is on bed rest, renal abnormalities: Serum creatinine >1.1 mg/dl or doubling of the serum creatinine in the absence of other renal disease, impaired liver function that not account for by alternative diagnosis and as indicated by elevated liver enzymes to (double the normal concentration), or severe persistent upper quadrant or right epigastric pain, visual disturbance such as photophobia or scotomata and cerebral disturbance as severe Headache not accounted for by alternative diagnosis.

**Exclusion criteria:** Multifetal gestation,

congenital fetal malformations by 1st or 2nd trimesteric anomaly scan, women with true labor pain and women with other known systemic diseases or endocrine disorders.

**Sample Size:** The study will be conducted on 90 records.

**Sample size justification:** By using power analysis and sample size software PASS 15 version (15.0.10) program for sample size calculation, setting confidence level at 90 % margin of error +/-10%, and after reviewing previous study results 7. showed that the percentage of perinatal death among women with severe preeclampsia before term who had either interventional or expectant management were (49.5 % ), based on that and after considering 10 % drop out rate, a sample size of at least 90 patients with preeclampsia including interventional and expectant management will be sufficient to achieve study objective.

**Ethical Consideration:** This study will be done after approval of the ethical committee of the department of obstetrics and gynecology, faculty of medicine, Ain Shams University. Informed consent will be taken from all participants before recruitment in the study, and after explaining the purpose and procedures of the study. The investigator will obtain the written, signed informed consent of each subject prior to performing any study specific procedures on the subject.

**Study observations:** gestational age at time of diagnosis, admission and at time of delivery, magnesium sulphate and steroid administration, antihypertensive drugs used, maternal monitoring data as vitals, input output chart, CBC count, liver function test, LDH, serum creatinine level, fetal monitoring data as fetal movement count, cardiotocography (non-stress test), Ultrasonographic findings, indications for delivery, the mode of delivery and maternal and fetal condition with continued intensive intrapartum and postpartum care (till time of discharge)

**Duration of observation is from time of diagnosis to time of discharge.**

**Outcomes: Primary outcome:** Neonatal Intensive Care Unit admission. **Secondary outcomes: Obstetric outcomes:** uncontrolled blood pressure, abruption, HELLP, Eclampsia, Kidney affection through Increase in SCr by  $>$  or  $= 0.3$  mg/dl within 48 hours; or Increase in SCr to  $>$  or  $= 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume  $< 0.5$  ml/kg/h for 6 hours or initiation of renal replacement therapy and maternal death. **Perinatal outcomes:** intraventricular hemorrhage diagnosed by cranial ultrasound, respiratory distress, need for mechanical ventilation and perinatal death.

**Statistical analysis: Statistical analysis of the data:** Data were fed to the computer and analyzed using IBM SPSS software package version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used

to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. Friedman's test (Fr test): was used for continuous data to test for significant difference between more than two dependent non- parametric data along different time points For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (P-value): P value of  $>0.05$  indicates non-significant results, P value of  $<0.05$  indicates significant results & P value of  $<0.01$  indicates highly significant results.

## **RESULTS**

This prospective observational study was conducted on 90 pregnant women with severe preeclampsia attending Ain Shams University Maternity Hospital.

**Table (1): Demographic characteristics among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Age (years)	Mean $\pm$ SD	29.58 $\pm$ 6.10	
	Median	28.0	
	Range	19.0- 44.0	
Age groups	18-30 years	73	81.1%
	> 35 years	17	18.9%

The mean age of our studied cases was 29.58 $\pm$  6.10 years and ranged from 19 to 44 years. The age group between 18- 30 years was the most represented age group (81.1%) followed by age group  $>35$  years (18.9%) [Table 5, Figure 1].

**Table (2): Obstetric history among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Gravidity	G1	34	37.8%
	G2	15	16.7%
	G3	15	16.7%
	G4	12	13.3%
	G5	8	8.9%
	G6	2	2.2%
	G7	2	2.2%
	G8	2	2.2%
	Mean± SD	2.66± 1.78	
Parity	P0	41	45.6%
	P1	14	15.6%
	P2	20	22.2%
	P3	8	8.9%
	P4	5	5.6%
	P5	1	1.1%
	P6	1	1.1%
	Mean± SD	1.21± 1.4	
History of previous CS	No	54	60.0%
	Yes	36	40.0%
History of abortion	No	63	70.0%
	Yes	27	30.0%

*No.= number, %= percentage*

The mean parity and gravidity was 2.66± 1.78 and 1.21± 1.4 respectively with 37.8% cases were primigravida, 40% cases had history of previous CS and 30% of them had history of abortion [Table 6, Figures 2-5].

**Table (3): Clinical history among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Medical history	Free	26	28.9%
	GHTN	61	67.8%
	Chronic HTN	3	3.3%
	Free	51	56.7%
	Appendectomy	9	10.0%
	Tonsillectomy	16	17.8%
	D&C	8	8.9%
Surgical history	Others: as breast abscess, cystectomy, hernioplasty, myomectomy	6	6.7%
History of SPET in previous pregnancy	No	80	88.9%
	Yes	10	11.1%

**SPET: Severe preeclampsia, GHTN: Gestational hypertension, GDM: Gestational Diabetes Mellitus**

Regarding medical history, 61 cases (67.8%) had gestational hypertension, and 3.3% of them had chronic hypertension. Surgical history of studied women revealed that 17.8% of them reported tonsillectomy, 8.9% had D&C and 10% had appendectomy. Ten (11.1%) women had history of severe preeclampsia in previous pregnancy [Table 7, Figure 6].

**Table (4): Clinical presentation among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Clinical presentation	Headache	52	57.8%
	Vomiting	36	40.0%
	Epigastric pain	28	31.1%
	Blurred vision	23	25.6%
	Abdominal pain	16	17.8%
	Vaginal bleeding	13	14.4%
	Passage of liquor	12	13.3%
	Valvular edema	11	12.2%
	Decreased fetal kicks	8	8.9%

As regard clinical presentation of severe preeclampsia, headache was the most common presentation (57.8%), followed by vomiting (40%), then epigastric pain (31.1%), blurring of vision (25.6%), and abdominal pain (17.8%). The least presented manifestations was valvular edema (12.2%) and decreased fetal kicks (8.9%) [Table 8, Figure 7].

**Table (3): Clinical history among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
General appearance	GGC	75	83.3%
	Fair GC	14	15.6%
	Poor GC	1	1.1%
Obstetric examination	FL<GA	7	7.8%
	FL=GA	83	92.2%
Abdominal examination	Lax	86	95.6%
	Rigid	4	4.4%

**GGC: Good general condition, GC: General condition, FL: Femur length, GA: Gestational age**  
Clinical examination of the studied women revealed that most cases (83.3%) had good general condition, most of them (92.2%) had fetuses whose FL=GA and most of them (95.6%) had lax abdomen [Table 9].

**Table (6): Vital signs among the studied cases.**

	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
Systolic BP (mm/Hg)	164.47	±18.14	160.0	160.0	180.0	90.0	200.0
Diastolic BP (mm/Hg)	101.66	±11.33	100.0	100.0	110.0	60.0	140.0
Heart rate (beats/min)	84.41	±6.07	80.0	80.0	90.0	70.0	110.0
Temperature (oC)	Normal (≈37oC)						

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, -Friedman Test

The mean systolic and diastolic blood pressure in the studied patients were 164.47±18.14 mm/Hg and 101.66± 11.33 mm/Hg respectively. While the mean heart rate was 84.41±6.07 beats/min. Almost all cases had normal temperature [Table 10, Figure 8].

**Table (7): Distribution of cases as regard CBC.**

	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
Hb (g/dl)	11.24	±1.30	11.2	10.6	12.1	7.3	13.9
Platelets count (×10 <sup>3</sup> /μL)	230.28	±136.0	210.0	165.0	260.0	83.0	1290.0

**SD= standard deviation, IQR: Inter-quartile range**

The mean hemoglobin was 11.24±1.30 g/dl. The mean platelets count was 230.28±136.0 x10<sup>3</sup>/ μL [Table 11].

**Table (8): Distribution of patients as regard liver function tests.**

	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
ALT (IU/L)	42.67	±80.38	16.0	10.0	40.0	3.0	645.0
AST (IU/L)	60.87	±89.58	29.5	21.00	58.65	13.0	518.0
INR	0.98	±0.08	1.0	0.93	1.0	0.8	1.2

*SD= standard deviation, IQR: Inter-quartile range*

**This table shows:**

The mean ALT was 42.67±80.38 IU/L and ranged from 3 IU/L to 645 IU/L. The mean AST was 60.87±89.58 IU/L and ranged from 13 IU/L to 518 IU/L. The mean INR was 0.98±0.08 [Table 12].

**Table (9): Kidney function test & Urine analysis among the studied cases.**

Parameters		Studied cases (No. = 90)						
		Mean	± SD	Median	IQR		Range	
Albumin in urine (g/day)		1.78	±0.97	2.0	1.0	2.0	0.0	3.0
Serum creatinine (mg/dl)		0.89	±0.37	0.8	0.7	1.0	0.3	3.2
eGFR (mL/min/1.73m <sup>2</sup> )		84.92	±25.69	79.5	67.0	103.0	16.7	153.0
UOP	Normal	89 (98.9%)						
	Oliguria	1 (1.1%)						

*SD: standard deviation, IQR: Interquartile range, n: number, %: percentage, UOP: Urine output*

Albumin in urine was positive in 78 (86.7%) patients with mean of 1.7±0.97. The mean serum creatinine was 0.89±0.37 mg/dl while the mean eGFR was 84.92±25.69 mL/min/1.73m<sup>2</sup>. Assessment of urine output revealed that one case reported oliguria while the majority were normal [Table 13].

**Table (10): Ultrasound findings among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Ultrasound findings	Normal	47	52.2%
	Abnormal	43	47.8%

*No.= number, %= percentage*

This table shows that abnormal ultrasound findings was reported in 47.8 % cases [Table 14].

**Table (11): Systolic blood pressure among the studied cases at different periods.**

Systolic BP (mm/Hg)	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
At admission SBP	164.67	±16.23	160.0	160.0	170.0	90.0	200.0
Intraoperative SBP	142.52	±26.71	140.0	120.0	160.0	10.0	200.0
Post-delivery SBP	122.83	±13.37	120.0	110.0	130.0	100.0	180.0
Test value	126.4						
P-value	<0.001						

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant,

**-Friedman Test**

Systolic blood pressure was measured at admission, intraoperative and post-delivery. The results showed significant steadily decline in systolic blood pressure 164.67±16.23 mm/Hg at admission then 142.52±26.71 mm/Hg intraoperatively to 122.83± 13.37 mm/Hg after delivery (*p*<0.001) [Table 15, Figure 9].

**Table (12): Diastolic blood pressure among the studied cases at different periods.**

Diastolic BP (mm/Hg)	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
<b>At admission DBP</b>	102.89	±9.97	100.0	100.0	110.0	60.0	140.0
<b>Intraoperative DBP</b>	88.10	±13.52	90.0	80.0	100.0	60.0	120.0
<b>Post-delivery DBP</b>	77.36	±9.17	80.0	70.0	80.0	60.0	110.0
<b>Test value</b>	120						
<b>P-value</b>	<0.001						

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, **-Friedman Test**

Diastolic blood pressure was measured at admission, intraoperative and post-delivery. The results showed significant steadily decline in systolic blood pressure 102.89± 9.97 mm/Hg at admission then 88.10± 13.52 mm/Hg intraoperatively to 77.36± 9.17 mm/Hg after delivery (*p*<0.001) [Table 16, Figure 10].

**Table (13): Management among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
<b>MgSo4</b>	<b>loading 10gm, maintenance 5g\4hr</b>	89	98.9%
	<b>loading 30gm,maintainence 5g\4hr</b>	1	1.1%
<b>Steroid</b>	<b>Not taken</b>	60	66.7%
	<b>Taken</b>	22	24.4%
	<b>Taken at hospital</b>	2	2.2%
	<b>Took rescue dose on admission</b>	6	6.7%
<b>Anti-hypertensives</b>	<b>Labipress</b>	90	100.0%
	<b>Epilat</b>	73	81.1%

According to management, all studied cases was treated by MgSo4 and antihypertensive drugs. Most cases (98.9%) were on MgSo4 loading 30gm, maintenance 5g\4hr. Lapipress was taken in all cases. Steroid was used in 24.4% cases, at hospital in 2.2% of cases and taken as rescue dose on admission in 6.7% cases [Table 17].

**Table (14): Maternal outcome among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Maternal outcome	Free	64	71.1%
	ICU admission	29	32.2%
	Uncontrolled BP	10	11.1%
	HELLP syndrome	8	8.9%
	Placental abruption	5	5.6%
	Renal insufficiency	2	2.2%
	Retinal detachment	1	1.1%
	Eclampsia	1	1.1%
	Convulsions	1	1.1%

**HELLP: Hemolysis, Elevated Liver enzymes and Low Platelets**

The studied women were followed up until delivery to detect maternal and fetal complications. Regarding maternal outcome, ICU admission was reported in 32.2% cases, uncontrolled hypertension in 11.1% cases, HELLP syndrome was found in 8.9% cases and placental abruption in 5.6% cases. Renal insufficiency, retinal detachment, eclampsia and convulsions were found in 2.2%, 1.1%, 1.1%, \ and 1.1% respectively [Table 18, Figure 11].

**Table (15): Perinatal outcome among the studied cases.**

		Studied cases (No. = 90)	
		No.	%
Perinatal outcomes	Free	8	8.9%
	RDS	68	75.6%
	LBW	60	66.7%
	PT	12	13.3%
	Grower	6	6.7%
	IUGR	3	3.3%
	Still birth	3	3.3%
	Hepatosplenomegaly	1	1.1%
NICU admission	No	39	43.3%
	Yes	51	56.7%
Neonatal death	No	66	73.3%
	Yes	24	26.7%
EFW (gm)	Mean± SD	1463.67± 608.44	
	Median	1400	
	Range	200- 3000	

**RDS: Respiratory distress syndrome, LBW: Low birth weight, IUGR: Intrauterine growth restriction, PT: preterm, EFW: estimated fetal weight**

Regarding perinatal outcome, respiratory distress syndrome was found in 75.6% cases, 66.7% reported low birth weight, and 13.3% of live born babies were delivered preterm. NICU admission was reported in 56.7% cases while neonatal death was reported in 26.7% cases, The mean estimated fetal weight (EFW) was 1463.67± 608.44 grams [Table 19, Figure 12].

**Table (16): Gestational age among the studied cases at different periods.**

Gestational age (weeks)	Studied cases (No. = 90)						
	Mean	± SD	Median	IQR		Range	
At admission	31.43	±2.58	32.07	30.29	33.43	17.0	34.0
At diagnosis	31.50	±2.25	32.07	30.29	33.43	23.43	34.0
At delivery	31.66	±2.11	32.21	30.29	33.43	26.00	36.0

Gestational age was assessed at admission, diagnosis and post-delivery. The mean gestational age was 31.43± 2.58 weeks at admission, 31.50± 2.25 weeks at diagnosis and 31.66± 2.11 weeks after delivery [Table 20].

**Table (17): Distribution of the studied cases as per delivery and neonatal outcome.**

		Studied cases (No. = 90)	
		No.	%
Delivery	NVD	2	2.2%
	C.S	88	97.8%

This table shows that most cases (97.8 %) cases were delivered by CS.

**Table (18): Analysis of factors affecting neonatal death.**

	No neonatal death (N=66)		Neonatal death (N=24)		Test value (ZMWU)	P-value
	Mean	SD	Mean	SD		
Age	29.14	6.32	30.87	5.35	1.263	0.207
Gravidity	2.12	1.91	3.21	2.25	2.084	<b>0.037</b>
Parity	0.98	1.18	1.83	1.76	2.108	<b>0.035</b>
eGFR	86.65	26.57	81.29	23.97	0.463	0.644
Hb	11.18	1.33	11.39	1.24	1.167	0.243
At admission SBP	165.15	15.32	163.33	18.80	0.251	0.802
Intraoperative SBP	141.92	28.24	144.17	22.39	1.691	0.091
Post-delivery SBP	122.88	14.12	122.71	11.32	0.322	0.747
At admission DBP	103.94	9.59	100.00	10.63	0.458	0.647
Intraoperative DBP	88.55	13.38	86.87	14.13	0.282	0.778
post-delivery DBP	77.31	8.97	77.50	9.89	0.272	0.786
Gestational age (weeks)	32.13	1.94	29.79	2.19	4.42	<b>&lt;0.001</b>

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \*Mann-Whitney U test

Gravidity, parity and gestational age were significant factors to affect incidence of neonatal death (*P*<0.05) [Table 21, Figure 13].

**Table (19): Relation between steroid administration and neonatal death.**

		No neonatal death (N=66)		Neonatal death (N=24)		Chi-Square test	
		N	%	N	%	Test value	P-value
Steroid	Not taken	45	68.2%	15	62.5%	6.361	0.105 <sup>MC</sup>
	Taken	18	27.3%	4	16.7%		
	Taken at hospital	1	1.5%	1	4.2%		
	Took rescue dose on admission	2	3.0%	4	16.7%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between steroid administration and neonatal death (*p*>0.05).

**Table (20): Relation between US findings and neonatal death.**

		No neonatal death (N=66)		Neonatal death (N=24)		Chi-Square test	
		N	%	N	%	Test value	P-value
US findings	Normal	38	57.6%	10	41.7%	1.790	0.181
	Abnormal	28	42.4%	14	58.3%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between US findings and neonatal death (*p*>0.05)

**Table (21): Analysis of factors affecting NICU admission**

	No NICU admission (N=39)		NICU admission (N=51)		Mann-Whitney U test	
	Mean	SD	Mean	SD	Test value	P-value
Age	29.66	5.42	29.53	6.62	0.179	0.858
Gravidity	2.74	2.02	2.16	2.05	1.413	0.158
Parity	1.49	1.62	1.00	1.18	1.282	0.200
eGFR	87.05	26.31	82.79	25.31	1.038	0.299
Hb	11.16	1.14	11.30	1.42	0.268	0.789
At admission SBP	162.82	17.76	166.08	14.98	0.969	0.332
Intraoperative SBP	138.08	21.11	145.92	30.06	1.355	0.175
Post-delivery SBP	121.41	10.19	123.92	15.37	1.989	<b>0.047</b>
At admission DBP	101.28	10.56	104.12	9.42	1.583	0.113
Intraoperative DBP	85.26	13.23	90.27	13.47	0.511	0.609
post-delivery DBP	76.92	8.00	77.70	10.06	0.194	0.846
Gestational age (weeks)	30.99	2.53	31.90	1.95	1.549	0.121

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \*Mann-Whitney U test

Post-delivery systolic blood pressure was the only significant factor to affect incidence of NICU admission (*P*=0.047) [Table 25, Figure 14].

**Table (19): Relation between steroid administration and neonatal death.**

		No neonatal death (N=66)		Neonatal death (N=24)		Chi-Square test	
		N	%	N	%	Test value	P-value
Steroid	Not taken	45	68.2%	15	62.5%	6.361	0.105 <sup>MC</sup>
	Taken	18	27.3%	4	16.7%		
	Taken at hospital	1	1.5%	1	4.2%		
	Took rescue dose on admission	2	3.0%	4	16.7%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between steroid administration and neonatal death (*p*>0.05).

**Table (20): Relation between US findings and neonatal death.**

		No neonatal death (N=66)		Neonatal death (N=24)		Chi-Square test	
		N	%	N	%	Test value	P-value
US findings	Normal	38	57.6%	10	41.7%	1.790	0.181
	Abnormal	28	42.4%	14	58.3%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between US findings and neonatal death (*p*>0.05)

**Table (21): Analysis of factors affecting NICU admission**

	No NICU admission (N=39)		NICU admission (N=51)		Mann-Whitney U test	
	Mean	SD	Mean	SD	Test value	P-value
Age	29.66	5.42	29.53	6.62	0.179	0.858
Gravidity	2.74	2.02	2.16	2.05	1.413	0.158
Parity	1.49	1.62	1.00	1.18	1.282	0.200
eGFR	87.05	26.31	82.79	25.31	1.038	0.299
Hb	11.16	1.14	11.30	1.42	0.268	0.789
At admission SBP	162.82	17.76	166.08	14.98	0.969	0.332
Intraoperative SBP	138.08	21.11	145.92	30.06	1.355	0.175
Post-delivery SBP	121.41	10.19	123.92	15.37	1.989	<b>0.047</b>
At admission DBP	101.28	10.56	104.12	9.42	1.583	0.113
Intraoperative DBP	85.26	13.23	90.27	13.47	0.511	0.609
post-delivery DBP	76.92	8.00	77.70	10.06	0.194	0.846
Gestational age (weeks)	30.99	2.53	31.90	1.95	1.549	0.121

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \*Mann-Whitney U test

Post-delivery systolic blood pressure was the only significant factor to affect incidence of NICU admission (*P*=0.047) [Table 25, Figure 14].

**Table (22): Relation between steroid administration and NICU admission.**

		No NICU admission (N=39)		NICU admission (N=51)		Chi-Square test	
		N	%	N	%	Test value	P-value
Steroid	Not taken	25	64.1%	35	68.6%	0.179	<b>0.036<sup>MC</sup></b>
	Taken	7	17.9%	15	29.4%		
	Taken at hospital	2	5.1%	0	0.0%		
	Took rescue dose on admission	5	12.8%	1	2.0%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was significant relation between steroid administration and NICU admission (*p*=0.036).

**Table (23): Relation between US findings and NICU admission.**

		No NICU admission (N=39)		NICU admission (N=51)		Chi-Square test	
		N	%	N	%	Test value	P-value
US findings	Normal	20	51.3%	28	54.9%	0.116	0.733
	Abnormal	19	48.7%	23	45.1%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between US findings and NICU admission (*p*>0.05).

**Table (24): ICU admission Comparison between the two groups regarding maternal outcome.**

	No ICU admission (N=61)		ICU admission (N=29)		Test value	P-value
	Mean	SD	Mean	SD		
Age	29.77	6.01	29.21	6.38	0.438	0.661
Gravidity	2.28	2.15	2.69	1.81	1.306	0.192
Parity	1.15	1.42	1.34	1.37	0.769	0.442
eGFR	85.36	23.13	83.85	31.82	1.074	0.283
Hb	11.17	1.27	11.38	1.38	0.38	0.704
At admission SBP	163.61	15.28	166.90	18.15	1.75	0.080
Intraoperative SBP	135.97	25.24	156.31	24.72	1.6	0.110
Post-delivery SBP	121.80	12.32	125.00	15.35	3.311	<b>0.001</b>
At admission DBP	102.30	8.64	104.14	12.40	3.428	<b>0.001</b>
Intraoperative DBP	84.51	11.54	95.66	14.45	0.718	0.473
post-delivery DBP	76.56	7.72	79.11	11.71	0.568	0.57
Gestational age (weeks)	31.71	2.19	31.07	2.36	1.366	0.172

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant, \*Mann-Whitney U test

Post-delivery systolic blood pressure and diastolic blood pressure at admission were significant factors affecting incidence of ICU admission (*P*=0.001) [Table 28, Figure 15].

**Table (25): Relation between steroid administration and RDS.**

		No RDS (N=22)		RDS (N=68)		Chi-Square test	
		N	%	N	%	Test value	P-value
Steroid	Not taken	14	63.6%	46	67.6%	1.039	0.883 <sup>MC</sup>
	Taken	6	27.3%	16	23.5%		
	Taken at hospital	1	4.5%	1	1.5%		
	Took rescue dose on admission	1	4.5%	5	7.4%		

*p*≤0.05 is considered statistically significant, *p*≤0.01 is considered high statistically significant,

\* Chi-Square test, MC: Monte-Carlo correction

There was no significant relation between steroid administration and RDS (*p*>0.05).

## **DISCUSSION**

Severe preeclampsia, characterized by hypertension and significant organ dysfunction, poses substantial risks to both maternal and perinatal health, particularly when it occurs before 34 weeks of gestation. This critical period in pregnancy necessitates urgent medical attention and close monitoring due to the heightened potential for adverse outcomes. Maternal complications associated with severe preeclampsia include eclampsia, stroke, renal failure, and HELLP syndrome, while perinatal risks encompass preterm birth, intrauterine growth restriction, and neonatal morbidity and mortality. Understanding the specific maternal and perinatal outcomes in cases of severe preeclampsia before 34 weeks of gestation is paramount for optimizing clinical management strategies and improving both maternal and neonatal well-being <sup>8</sup>.

The current study aimed to evaluate the maternal and perinatal outcomes of cases with severe preeclampsia before 34 weeks and to evaluate the benefits and risks of a policy of early delivery by induction of labor or by caesarean section, and policy of delaying delivery (expectant management) for women with severe pre-eclampsia between 26 and 34 weeks gestation.

In the current study involving 90 cases of severe preeclampsia before 34 weeks of

gestation, the mean age of the participants was 29.58 years (SD ± 6.10), with a median age of 28 years, and an age range of 19 to 44 years. The majority of the cases, representing 81.1%, were within the 18-30 year age group, while 18.9% were above 35 years.

These findings align with those of a study by **Lamminpää et al.** <sup>9</sup> published in BMC Pregnancy and Childbirth, which reported a higher incidence of preeclampsia in women of advanced maternal age (≥35 years old) at 9.4%, compared to 6.4% in younger women. Their research emphasized the increased risk associated with advanced maternal age, suggesting a significant impact on preeclampsia outcomes.

The current study results showed that most cases had gravidity of 1 to 5, with primigravida being common. Women with higher gravidity (G6-G8) were also noted. Parity ranged from nulliparous to grand multiparous, with a mean of 1.21, indicating many were experiencing their first or second delivery.

In the same line with our study **Conde-Agudelo and Belizan** <sup>10</sup>, found that nulliparity, was associated with an increased risk of preeclampsia, similarly in **Jyothsna Rani** <sup>11</sup>. They found that severe preeclampsia was seen more commonly in primigravida (54.4%).

In consistent with current study results

**Hernandez-Diaz et al.**<sup>12</sup> founded in The BMJ that while the overall risk of preeclampsia decreases in subsequent pregnancies, it significantly rises for women with a history of preeclampsia in their first pregnancy, highlighting the impact of previous episodes on future risks.

The current study resulted in 67.8% had gestational hypertension, 3.3% had chronic hypertension.

In contrast, **Moodley et al.**<sup>13</sup> reported that a past history of hypertensive disease was present in 46% of their patients.

The study done by **Bromfield et al.**<sup>14</sup> a retrospective examination of claims data published in BMC Pregnancy and Childbirth explores the link between hypertensive disorders in pregnancy and outcomes for both mothers and newborns. The analysis encompasses chronic hypertension, superimposed preeclampsia, and preeclampsia, revealing elevated risks of stillbirth, preterm birth, and low birth weight among mothers affected by these conditions.

The current study results revealed symptoms included headache, noted in 57.8% of cases, followed by vomiting (40.0%), epigastric pain (31.1%), blurred vision (25.6%), and abdominal pain (17.8%). Additionally, vaginal bleeding, passage of liquor, and valvular edema were reported in 14.4%, 13.3%, and 12.2% of cases, respectively. Decreased fetal kicks were reported in 8.9% of cases.

In the same line **Kuchake et al.**<sup>15</sup> revealed that occurrence of headache and vision disturbances between a normal group and a preeclampsia group. In the preeclampsia group, 14.25% reported headaches, significantly higher than the 0.5% in the normal group. Similarly, vision disturbances were reported in 79.48% of the preeclampsia group compared to 58.60% in the normal group.

The current study results showed the

distribution of complete blood count (CBC) parameters was as follows: the mean hemoglobin (Hb) level was 11.24 g/dl with a standard deviation of  $\pm 1.30$ , and the median was 11.2 g/dl with an interquartile range (IQR) of 10.6 to 12.1 g/dl, ranging from 7.3 to 13.9 g/dl. The mean platelet count was  $230.28 \times 10^3/\mu\text{L}$  with a standard deviation of  $\pm 136.0$ , and the median was  $210.0 \times 10^3/\mu\text{L}$  with an IQR of 165.0 to  $260.0 \times 10^3/\mu\text{L}$ , ranging from 83.0 to  $1290.0 \times 10^3/\mu\text{L}$ .

In a study done by **Kuchake et al.**<sup>15</sup> revealed significant differences in hemoglobin levels (Hb), platelet count, between the two groups ( $p < 0.0124$ ,  $p < 0.0001$ , respectively), with the preeclampsia group showing lower Hb levels, lower platelet counts levels.

The current study results showed that ultrasound findings varied: 52.2% of cases showed normal results, while 47.8% exhibited abnormal findings. This indicates a significant portion of cases with abnormal findings as oligohydrominous, abnormal umbilical artery doppler detected via ultrasound, highlighting the importance of this imaging modality in the assessment and management of severe preeclampsia, as it can provide valuable insights into maternal and fetal health status.

In the same line **Geerts & Odendaal**<sup>16</sup> highlighted the importance of ultrasound findings, particularly fetal weight estimation and Doppler waveform analysis of fetal vessels, in predicting fetal outcomes and morbidity.

The current study results showed that systolic blood pressure (SBP) measurements showed distinct patterns across different stages of care. At admission, the mean SBP was 164.67 mm/Hg with a standard deviation of  $\pm 16.23$ , and the median was 160.0 mm/Hg with an interquartile range (IQR) of 160.0 to 170.0 mm/Hg, ranging from 90.0 to 200.0 mm/Hg. Intraoperatively, the mean SBP was 142.52 mm/Hg with a standard deviation of  $\pm 26.71$ , and the median was 140.0 mm/Hg with an IQR of 120.0 to 160.0 mm/Hg, ranging

from 10.0 to 200.0 mm/Hg. Post-delivery, the mean SBP decreased to 122.83 mm/Hg with a standard deviation of  $\pm 13.37$ , and the median was 120.0 mm/Hg with an IQR of 110.0 to 130.0 mm/Hg, ranging from 100.0 to 180.0 mm/Hg. The test value of 126.4 with a p-value of  $<0.001$  indicates significant differences in SBP across these stages of care.

In the same line **Gunderson et al.**<sup>17</sup> revealed that that systolic blood pressure trajectories during early pregnancy, along with standard clinical risk factors, can provide valuable information for predicting the risk of developing preeclampsia and gestational hypertension later in pregnancy.

The current study results showed that diastolic blood pressure (DBP) measurements showed distinct patterns across different stages of care. At admission, the mean DBP was 102.89 mm/Hg with a standard deviation of  $\pm 9.97$ , and the median was 100.0 mm/Hg with an interquartile range (IQR) of 100.0 to 110.0 mm/Hg, ranging from 60.0 to 140.0 mm/Hg. Intraoperatively, the mean DBP decreased to 88.10 mm/Hg with a standard deviation of  $\pm 13.52$ , and the median was 90.0 mm/Hg with an IQR of 80.0 to 100.0 mm/Hg, ranging from 60.0 to 120.0 mm/Hg. Post-delivery, the mean DBP further decreased to 77.36 mm/Hg with a standard deviation of  $\pm 9.17$ , and the median was 80.0 mm/Hg with an IQR of 70.0 to 80.0 mm/Hg, ranging from 60.0 to 110.0 mm/Hg. The test value of 120 with a p-value of  $<0.001$  indicates significant differences in DBP across these stages of care.

In consistent with our study results **Gunnarsdóttir et al.**<sup>18</sup> demonstrated that Elevated diastolic BP from early to mid-gestation was associated with increased risks of preeclampsia and SGA, especially for women also delivering preterm.

Also **Kuchake et al.**<sup>15</sup> showed that In terms of blood pressure diagnosis, both systolic and diastolic blood pressures were significantly

higher in the preeclampsia group compared to the normal group ( $p < 0.0001$ ).

The current study results showed that maternal outcomes varied, with 71.1% experiencing a complication-free course. However, 32.2% required ICU admission, indicating the severity of the condition. Uncontrolled blood pressure (11.1%) was a significant concern, potentially leading to adverse maternal outcomes such as HELLP syndrome (8.9%), placental abruption (5.6%), and renal insufficiency (2.2%). Rare but critical complications included retinal detachment, eclampsia, and convulsions, each occurring in less than 2% of cases.

In a study done by **Grimes et al.**<sup>19</sup> they identified that among 100 cases of severe preeclampsia, 32% required intensive care unit (ICU) admission, highlighting the severity of the condition. Complications observed in this study included HELLP syndrome (11%), placental abruption (5%), and renal insufficiency (2%)

The current study results showed that perinatal outcomes were marked by significant challenges. The majority of infants experienced respiratory distress syndrome (RDS) at 75.6%, with a high incidence of low birth weight (66.7%). Preterm birth occurred in 13.3% of cases, while a smaller proportion exhibited growth restriction (6.7%) and intrauterine growth restriction (IUGR) (3.3%). Neonatal intensive care unit (NICU) admission was necessary for 56.7% of infants, underscoring the critical care required for these neonates. Unfortunately, neonatal death occurred in 26.7% of cases, highlighting the severity of perinatal complications associated with severe preeclampsia. The mean estimated fetal weight (EFW) was 1463.67 grams, with a wide range from 200 to 3000 grams, further reflecting the variability in fetal outcomes in this population.

In the same line the study by **Sibai**,<sup>20</sup> discussed the complications associated

with severe preeclampsia, including a high incidence of respiratory distress syndrome (RDS) at 75.6% and a high proportion of low birth weight (66.7%) and preterm birth (13.3%).

Also **McKenzie & Trotman**<sup>21</sup> showed that neonates born to women with preeclampsia exhibited neonatal admission (59% vs. 13%), and neonatal deaths (28% vs. 0%) compared to controls, highlighting the significant impact of preeclampsia on neonatal outcomes.

The current study results showed that gestational age at various stages showed consistent patterns. Mean gestational age at admission was 31.43 weeks ( $\pm 2.58$ ), with a median of 32.07 weeks and an interquartile range (IQR) of 30.29 to 33.43 weeks. Similarly, mean gestational age at diagnosis was 31.50 weeks ( $\pm 2.25$ ), with a median of 32.07 weeks and an IQR of 30.29 to 33.43 weeks. At delivery, the mean gestational age was slightly higher at 31.66 weeks ( $\pm 2.11$ ), with a median of 32.21 weeks and an IQR of 30.29 to 33.43 weeks. The range of gestational age varied from 17.0 to 34.0 weeks at admission, 23.43 to 34.0 weeks at diagnosis, and 26.00 to 36.0 weeks at delivery, indicating the broad spectrum of gestational ages represented in the study population.

In alignment with our study results **McKenzie & Trotman**<sup>21</sup> revealed that neonates born to women with preeclampsia exhibited significantly higher rates of prematurity (47% vs. 4%), low birth weight (58% vs. 6%), very low birth weight (25% vs. 1%), small for gestational age (31% vs. 2%).

The current study results showed that the mode of delivery was predominantly cesarean section (C.S), with 88 cases (97.8%) undergoing this procedure. Natural vaginal delivery (NVD) was relatively rare, occurring in only 2 cases (2.2%). This high rate of cesarean delivery aligns with the often urgent need for delivery in cases of severe preeclampsia to mitigate maternal and fetal risks.

In the same line **McKenzie & Trotman**<sup>21</sup> revealed that Women with preeclampsia (68%) were significantly more prone to cesarean section delivery compared to those without (27%) (OR=2.6; 95% CI: 1.9–3.7;  $p < 0.001$ ). Among preeclamptic women, 47% of cesarean deliveries were urgent, while 44% were emergency, contrasting with 29% for each category in non-preeclamptic deliveries.

Also **Kuchake et al.**<sup>15</sup> showed that Cesarean delivery rates were notably higher in the preeclampsia group (65.75%) compared to the normal group (10.13%), indicating a higher incidence of obstetric interventions due to complications associated with preeclampsia.

In contrast, **Patanik et al.**<sup>22</sup> and **Saxena et al.**<sup>23</sup> showed that vaginal route of delivery was more common than CS.

The analysis compares factors between cases with no neonatal death (N=66) and those with neonatal death (N=24). Among the variables examined, gravidity ( $p=0.037$ ) and parity ( $p=0.035$ ) show statistically significant differences, indicating higher gravidity and parity in cases with neonatal death. Gestational age at delivery also significantly differs between the groups ( $p<0.001$ ), with neonatal death cases having a lower mean gestational age (29.79 weeks) compared to those without neonatal death (32.13 weeks). Other factors such as maternal age, estimated glomerular filtration rate (eGFR), hemoglobin (Hb) levels, and blood pressure measurements did not show statistically significant differences between the two groups. However, intraoperative systolic blood pressure (SBP) showed a borderline significance ( $p=0.091$ ). This analysis highlights the importance of gravidity, parity, and gestational age as significant factors affecting neonatal death in cases of severe preeclampsia.

In consistent with current study results **McKenzie & Trotman**<sup>21</sup> indicated a

significant association between neonatal death and gestational age. Among neonatal deaths, a notable proportion were premature (47%), low birth weight (58%), very low birth weight (25%), and small for gestational age (31%). This suggests that premature and growth-restricted neonates are at higher risk of mortality.

The relationship between steroid administration and neonatal death was analyzed in the study. Among cases with no neonatal death (N=66), 68.2% did not receive steroids, 27.3% received steroids, and 3.0% received a rescue dose on admission. In contrast, among cases with neonatal death (N=24), 62.5% did not receive steroids, 16.7% received steroids, 4.2% received steroids at the hospital, and 16.7% received a rescue dose on admission. The Chi-Square test indicates no statistically significant association between steroid administration and neonatal death ( $\chi^2=6.361$ ,  $p=0.105$ ). While there appears to be a higher proportion of neonatal deaths among cases receiving a rescue dose on admission.

In the same line **Mwita et al.**<sup>24</sup> investigated the effect of antenatal corticosteroid (ACS) use on perinatal mortality among preterm births in rural and semi-urban areas across six low- and middle-income countries. Surprisingly, despite a rise in ACS utilization among low-birth-weight infants, neonatal mortality rates didn't decline in this subgroup, and mortality rates actually increased across the population.

The relationship between steroid administration and NICU admission was examined in the study. Among cases not admitted to the NICU (N=39), 64.1% did not receive steroids, 17.9% received steroids, 5.1% received steroids at the hospital, and 12.8% received a rescue dose on admission. In contrast, among cases admitted to the NICU (N=51), 68.6% did not receive steroids, 29.4% received steroids, and 2.0% received a rescue dose on admission. The Chi-Square test revealed a statistically significant

association between steroid administration and NICU admission ( $\chi^2=0.179$ ,  $p=0.036$ ). Specifically, a higher proportion of cases admitted to the NICU received steroids compared to those not admitted, indicating a potential relationship between steroid use and the need for neonatal intensive care.

In the same line **Mwansa-Kambafwile et al.**<sup>25</sup> showed that antenatal steroid therapy is very effective in preventing neonatal mortality and morbidity

The comparison between maternal outcomes in cases with and without ICU admission was conducted. Among cases without ICU admission (N=61), mean maternal age was 29.77 years, with a gravidity mean of 2.28 and parity mean of 1.15. In comparison, among cases with ICU admission (N=29), the mean maternal age was slightly lower at 29.21 years, with a slightly higher gravidity mean of 2.69 and parity mean of 1.34. However, none of these differences were statistically significant ( $p>0.05$ ). Similarly, there were no significant differences between the two groups regarding estimated glomerular filtration rate (eGFR), hemoglobin (Hb) levels, intraoperative and post-delivery systolic and diastolic blood pressure (SBP, DBP), and gestational age ( $p>0.05$ ). The only significant differences were observed in post-delivery SBP ( $p=0.001$ ) and post-delivery DBP ( $p=0.001$ ), with higher mean values in cases admitted to the ICU. These findings suggest that while there are some differences in blood pressure parameters between the groups, maternal outcomes did not significantly differ between cases with and without ICU admission in severe preeclampsia.

In consistent with our study results **Desalegn & Haile**<sup>26</sup> revealed that Women with higher blood pressure levels (170/110 mmHg or higher) had lower improvement rates compared to those with lower levels (140/90 - 169/109 mmHg) ( $p = 0.0282$ ) indicated to ICU admission.

## **CONCLUSION**

This study comprehensively investigated severe preeclampsia cases before 34 weeks of gestation, revealing demographic characteristics, clinical features, and outcomes. Maternal complications, including ICU admission, were observed in a substantial proportion, emphasizing the critical nature of severe preeclampsia. Neonatal outcomes were marked by challenges such as respiratory distress syndrome and low birth weight, with notable neonatal mortality. Gestational age, blood pressure parameters, and interventions like steroid use played significant roles in influencing outcomes.

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# Reducing surgical site infection rate in gynecologic oncologic cases: effect of a gynecology specific bundle

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**Ethical approval:** Study had been approved by institutional board of ethics, and written informed consents were obtained from all subjects included in the study.(Code Number: MS.20.03.1067).

**Conflict of interest:** No conflict of interest.

**Financial support:** No financial support.

## **Abstract**

**Objective:** To evaluate the effect of a preventive bundle on surgical site infection rates in Gynecologic Oncology surgery in Mansoura University Hospital.

**Subjects and methods:** Prospective Randomized Controlled Trial that was conducted over a period of 24 months during 2020 and 2022 on 80 patients admitted to Obstetrics and Gynecology department at Mansoura University Hospital. General, abdominal, and pelvic examinations and lab investigations were performed. Randomization of patients into 2 groups: group I (bundle implementation), group II (without bundle).

**Results:** SSI was more common in group (2) after first week and one month of follow up, and no statistically significant variation in 2ry interventions among SSI cases of the studied groups. There is significant association between BMI and cases of SSI. SSI was more common in cases with BMI more than 25, diabetic cases and cases who received radiotherapy. There is no significant statistical association between SSI and suspected primary pathology of the studied groups, but there is statistically significant association with operative time.

**Conclusion:** This study showed that implementation of a perioperative surgical site infection prevention bundle was associated with a marked reduction in surgical site infection rate in patients undergoing gynaecological oncology surgeries.

**Keywords:** surgical site infection, gynecologic oncology, preventive bundle.

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## **INTRODUCTION**

Surgical site infection (SSI) is any infection occurs within 30 days after an operation in any part of the body where the surgery was performed, that classified into superficial incisional, deep incisional or in other organs or spaces manipulated or opened during an operation(1).In gynecologic surgery, surgical site infections include superficial incisional cellulitis, deep incisional abscesses, and vaginal cuff or pelvic cellulitis or formation of abscess. (2)

The Gynecologic Oncology field has an elevated risk of SSIs due to high-complexity surgeries, patient co-morbidities, and liability for contamination from endogenous vaginal, cervical and gastrointestinal microorganisms to the operative area. (3)

SSIs remain the most common complication of gynaecological surgeries, nearly 10 to 35% of gynecologic oncology surgeries. SSIs are associated with delayed initiation of adjuvant therapy and worse overall survival(4,5).

Infections of the surgical wound commonly occur either late in the hospital course or soon after discharge. Wound infection symptoms can include fever and increased pain at the incision site. Clinical features may reveal skin erythema, or induration, purulent discharge from the incision, and possible fascial dehiscence on probing the deeper layers. (6)

The risk factors for SSI can be divided into patient and procedure related risk, modifiable or non modifiable. SSIs are usually the result of many non modifiable risk factors. Procedure related risks are considered to be modifiable (2).

Patients undergoing gynaecological oncology surgery are considered immuno-compromised, so it is vital to minimize the risk of SSI by the use of surgical site infection reduction bundles. Best practices to lower SSIs include preoperative, intraoperative, and postoperative activities.(7)

SSI is managed through antibiotic therapy, wound drainage, and wound debridement as appropriate. Specific management of the wound depends on the nature and location of infection. Whenever feasible, and if systemic signs of infection are absent, microbiological culture data should be obtained before starting broad-spectrum antibiotics, so that culture findings can guide changes in antibiotic therapy.(8)

## **Patients and methods**

Prospective Randomized Controlled Trial that was conducted over a period of 24 months during 2020 and 2022 on 80 patients admitted to Obstetrics and Gynecology department at Mansoura University Hospital after obtaining acceptance from institutional research board faculty of medicine, Mansura university.

All gynecologic Oncology elective cases had been included in the study except:

Women who had received antimicrobial therapy within 7 days before entrance into study, had history of hypersensitivity to study drug, with un-controlled diabetes, had infection at time of screening for enrolment of study, undergoing emergency operations, who are using corticosteroids, or other immunosuppressive drugs.

## **Study design**

A detailed history of each patient was taken with an explanation of the study protocol, and then informed consent was obtained. General, abdominal, and pelvic examinations and lab investigations were performed. Randomization of patients into **2groups: groupI** (bundle implementation), **groupII**(without bundle implementation). Group I was subjected to specific bundle used to prevent surgical site infections based on ACOG practice bulletin 2018.(4).

## **Gynecology Specific Bundle included**

**Preoperative measures:** Advise patient showering at night before operation using chlorhexidine gluconate shower soap, Maintain euglycemic (RBS<200mg/dl), any necessary hair removal should be done immediately preoperative by electric clippers, prophylactic antibiotics administration, all patients without any allergy received Cefazolin (1stgen cephalosporins) the recommended does is 2g for patients weighing <120kg and 3g for patients >120kg, administered up to 30 minutes before incision, while metronidazole & clindamycin used for patients with allergies.

**Intraoperative measures:** Preoperative skin preparation at surgical site with Betadine surgical scrub, maintain adequate aseptic technique, minimize operating room traffic.

**Postoperative measures:** Maintain euglycemia, Patient education about symptoms and signs of SSI, Sterile dressing removal after 48 H.

**Group II:** patients without bundle implementation: Included

**Preoperative measures:** Prophylactic antibiotics administration, all non-allergic patients received Cefazolin (1stgen cephalosporins) the recommended does is 2g for patients weighing <120kg and 3g for patients >120kg, given up to 30 minutes prior to incision, while metronidazole & clindamycin used for patients with allergies.

**Intraoperative measures:** Preparing the incisional area with povidone iodine (Betadine surgical scrub).

**Postoperative measures:** Sterile dressing removal after 48 h.

Follow up

Cases of the two groups were followed up in hospital then at gynecology outpatient clinic after one week and after one month to detect any sign of surgical site infection, Wounds were assessed using ASEPSIS score for surgical site infections (9) as follows:

**(ASEPSIS Score):**

Additional treatment	<ul style="list-style-type: none"> <li>• Antibiotics 10</li> <li>• Drainage of pus under local anaesthesia 5</li> <li>• Debridement of wound general anaesthesia 10</li> </ul>
Serous Discharge	Daily 0 – 5
Erythema	Daily 0 – 5
Purulent exudates	Daily 0 – 10
Separation of deep tissues	Daily 0 – 10
Isolation of Bacteria	10
Stay as inpatient prolonged over 14 days	5
Total Score	

Category of infection	
0-10	Satisfactory healing
11- 20	Disturbance of healing
21-30	Minor wound infection
31-40	Moderate wound infection
<40	Severe wound infection

## **Sample size**

was based on infection rate among cases with Full Bundle Implementation pre and post intervention (4.51% and 1.87, respectively) retrieved from previous research (Andiman et al et al., 2018). Using G\*power version 3.0.10 using McNemar test, 2-tailed, with  $\alpha$  error = 0.05 and power = 80.0% and effect size = 2.48. The calculated sample size will be 48 patients and by adding 10% to avoid drop out then the total calculated sample size will be 50 patients at least.

## **Ethical consideration**

A written informed consent was taken from each participant after being informed about the objectives of the study. During the study, confidentiality and privacy were maintained.

## **Statistical analysis**

Statistical Package of Social Science (SPSS) program for Windows (Standard version 26) was used to analyze data. The normality of data was tested first with one-sample Kolmogorov-Smirnov test. Qualitative data were clarified using number and percent. Association between categorical variables had been tested using Chi-square test. Continuous variables were described as mean  $\pm$  SD (standard deviation) for normally distributed data. The threshold of significance is fixed at 5% level. The result had been considered significant when  $p \leq 0.05$ . The smaller p-value obtained, the more significant were the results.

## **Results**

The current study showed that mean age was 59.42 years, mean BMI was 30.52, 55% were rural residents, 70 % were married, and 70 % were housewives and 42.5% had primary education. In regard to the control group mean age was 58.67, mean BMI was 29.25, 62.5% were rural residents, 75% were married, 65 % were housewives, and 47.5%

had primary education. There was non-statistically significant difference between the 2 groups ( $P > 0.05$ ). As shown in table (1).

The current study showed that in regard to study group multigravida were 87.5%, 55% were diabetic, 75% had positive surgical history, 90% had negative past history of SSI, 7.5% had history of radiotherapy, while in regard to control group multigravida were 77.5 %, 50% were diabetic, 67.5% had positive surgical history, 82.5% had negative past history of SSI and 5% had history of radiotherapy. There was non-statistically significant difference between the 2 groups ( $P > 0.05$ ). As shown in table (2).

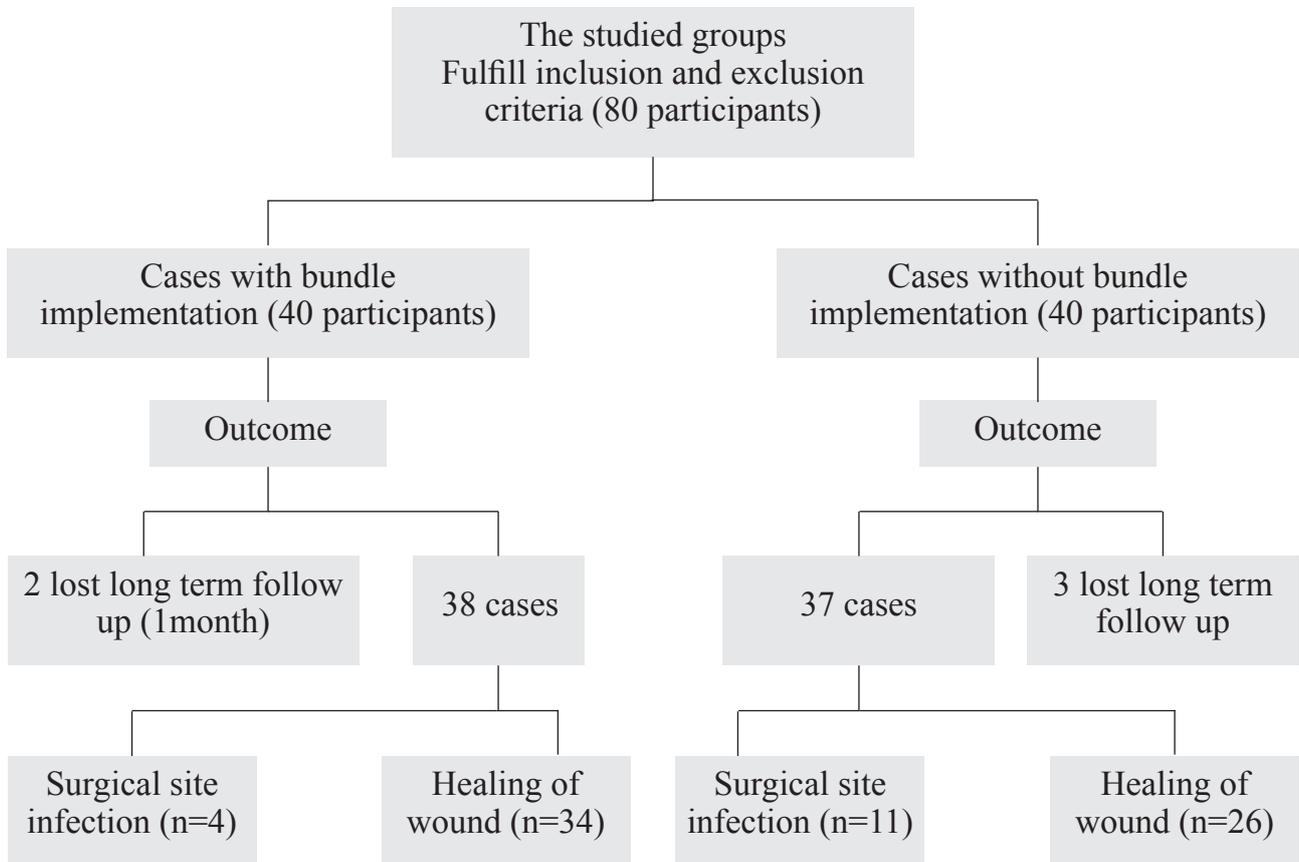
As regard pre-operative suspected primary pathology among studied groups, table (3). showed no significant variation among studied groups.

The wound was assessed after one week of surgery by ASEPSIS score for all cases then after one month but few cases missed long term follow-up, results showed after one month of following up of the cases that only 10.5% of the cases of group (1) showed signs of SSI, 30% of group (2) showed signs of SSI. There was statistical significant association between type of the study and SSI. Table (4) showed that SSI is more common in group (2) after first week and one month of follow up. Table (5) showed no statistically significant variation in 2ry interventions among SSI cases of the studied groups.

Table (6) showed that there is significant association between BMI and cases of SSI. SSI was more common in cases with BMI more than 25, while no significant association between SSI and other socio-demographic data (age, residence, marital status, occupation and educational level).

Table (7) showed that there is significant association between SSI cases and Diabetes and past history of radiotherapy. SSI was more common in diabetic cases and cases who received radiotherapy. Table (8) showed that there is no statistical significant association

between SSI and suspected primary pathology of the studied groups. Table (9) showed that there is statistically significant association among SSI and operative time. SSI were more common in staging laparotomy operations and in lengthy operation.



**Figure (1):** Flow chart of the studied groups

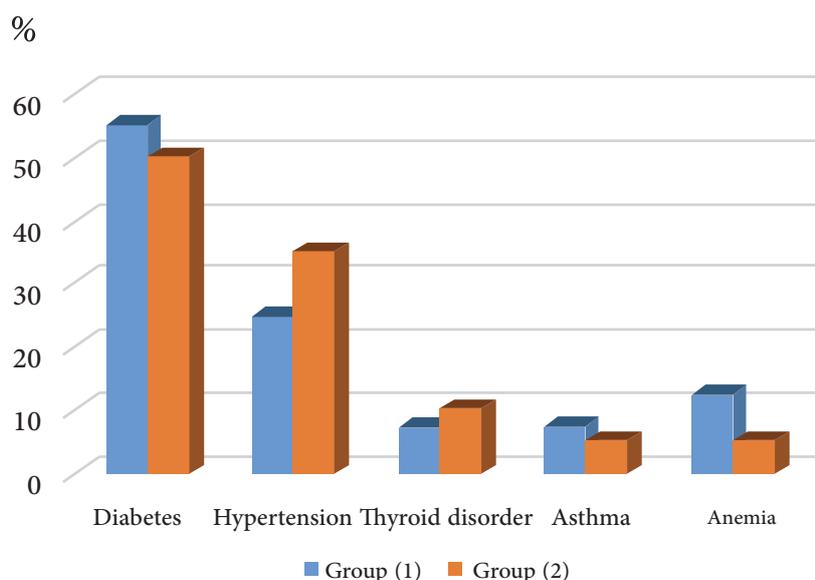
**Table (1):** Sociodemographic data among the studied groups.

Sociodemographic data	Group (1) (n=40)	Group (2) (n=40)	Test of significance	P value
Age (Years) Mean ± SD Min-Max	59.42±13.66 34-76	58.67±14.12 32-71	t=0.241	0.810
BMI Mean ± SD	30.52±2.82	29.25±3.27	t=1.86	0.066
Residence Urban Rural	18 (45.0%) 22 (55.0%)	15 (37.5%) 25 (62.5%)	χ <sup>2</sup> =0.464	0.496
Marital status Married Single Divorced Widowed	28 (70.0%) 2 (5.0%) 3 (7.5%) 7 (17.5%)	30 (75.0%) 1 (2.5%) 4 (1.0%) 5 (12.5%)	MC	0.847

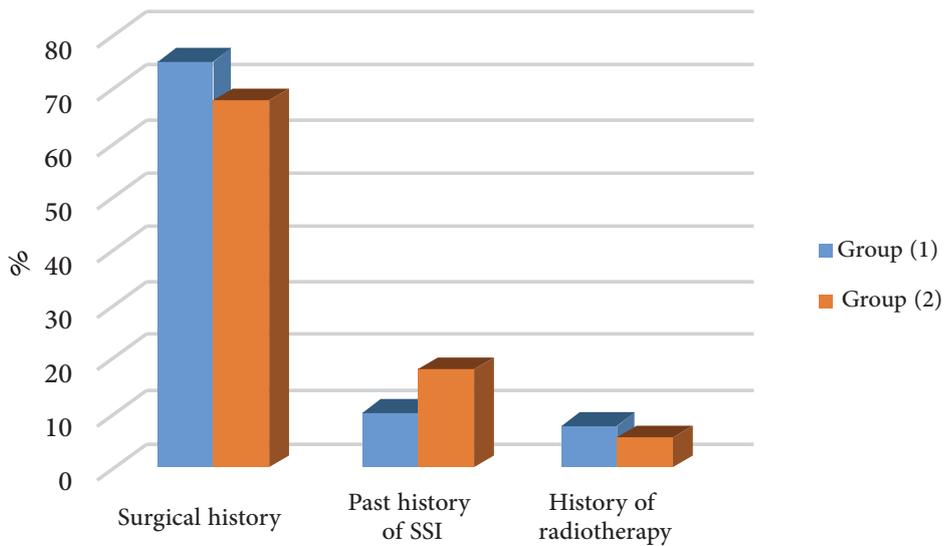
Occupation Worker House wife	12 (30.0%) 28 (70.0%)	14 (35.0%) 26 (65.0%)	$\chi^2 = 0.228$	0.633
Education level Illiterate Primary Secondary High	2 (5.0%) 17 (42.5%) 14 (35.0%) 7 (17.5%)	1 (2.5%) 19 (47.5%) 15 (37.5%) 5 (12.5%)	$\chi^2 = 0.521$	0.914
t: Independent t test, $\chi^2$ : Chi square test, MC: Monte carlo test				

**Table (2): Obstetric, medical, surgical and past history among the studied groups**

Items	Group (1) (n=40)	Group (2) (n=40)	Test of significance	P value
Gravidity Multigravida Null gravida	35 (87.5%) 5 (12.5%)	31 (77.5%) 9 (22.5%)	$\chi^2 = 1.38$	0.239
Comorbidities Diabetes Hypertension Thyroid disorder Asthma Anemia	22 (55.0%) 10 (25.0%) 3 (7.5%) 3 (7.5%) 5 (12.5%)	20 (50.0%) 14 (35.0%) 4 (10.0%) 2 (5.0%) 2 (5.0%)	$\chi^2 = 0.201$ $\chi^2 = 0.952$ FET FET FET	0.654 0.329 1.0 1.0 0.432
Surgical history Positive Negative	30 (75.0%) 10 (25.0%)	27 (67.5%) 13 (32.5%)	$\chi^2 = 0.167$	0.683
Past history of SSI Positive Negative	4 (10.0%) 36 (90.0%)	7 (17.5%) 33 (82.5%)	$\chi^2 = 0.949$	0.330
History of radiotherapy	3 (7.5%)	2 (5%)	FET	1.0
t: Independent t test, $\chi^2$ : Chi square test, FET: Fisher exact test, SSI: surgical site infection				



**Figure (4): Co-morbidities among the studied groups**



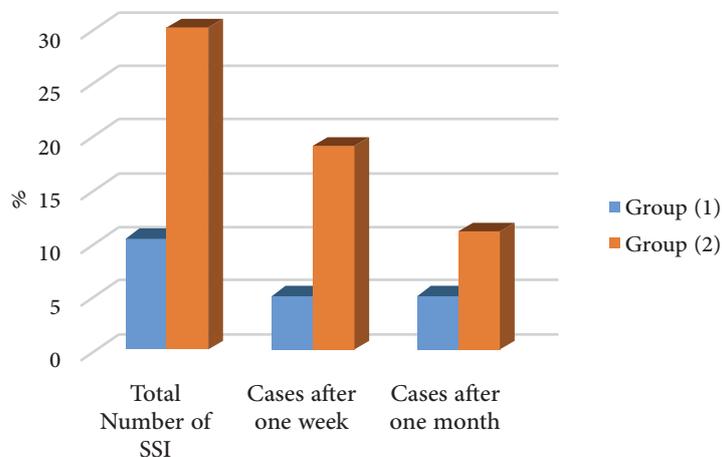
**Figure (5):**Previous surgical, SSI and radiotherapy history among the studied groups

**Table (3) Pre-operative suspected primary pathology among studied groups:**

Suspected lesion	Group (1) (n=40)	Group (2) (n=40)	Test of significance	P value
Ovarian	21 (52.5%)	25 (62.5%)	$\chi^2 = 1.41$	0.494
Uterine	17 (42.5%)	12 (30.0%)		
Cervical	2 (5.0%)	3 (7.5%)		

**Table (4): Assessment of wound healing and SSI cases among the studied groups**

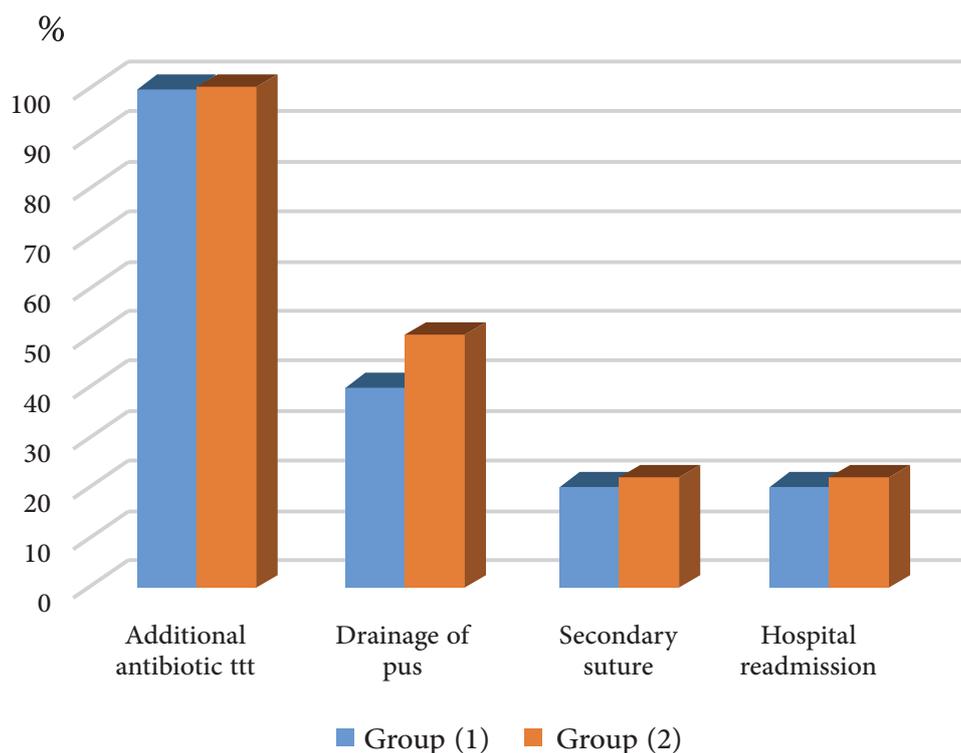
	Group (1) (n=38)	Group (2) (n=37)	Test of significance	P value
Total Number of SSI	4 (10.5%)	11 (30%)	$\chi^2 = 4.32$	0.037*
Cases after one week	2 (5.25%)	7 (19%)	FET	0.086
Cases after one month	2 (5.25%)	4 (11%)	FET	0.430



**Figure (6):** SSI cases among the studied groups

**Table (5): Secondary outcome in cases with SSI among studied groups**

SSI cases	Group (1) n=4	Group (2) n=11	P value
Additional antibiotic treatment	4 (100%)	11 (100%)	1.0
Drainage of pus	2 (50.0%)	7 (63.6%)	1.0
Secondary suture	1 (25.0%)	3 (27.2%)	1.0
Hospital readmission	1 (25.0%)	3 (27.2%)	1.0



**Figure (7): Secondary outcome in cases with SSI among studied groups**

**Table (6): Association between surgical site infection and sociodemographic data among the studied groups**

Sociodemographic data	Group (1) (n=4)	Group (2) (n=11)	Test of significance	P value
Age (Years) Mean ± SD Min-Max	59.42±13.66 34-76	58.67±14.12 32-71	t=0.091	0.928
BMI Mean ± SD	31.52±2.82	27.25±3.27	t=2.31	0.038*
Residence Urban Rural	1 (25%) 3 (75%)	4 (36.3%) 7 (63.7%)	FET	0.450

<b>Marital status</b>				
<b>Married</b>	2 (50%)	9 (81.8%)	MC	0.740
<b>Single</b>	1 (25%)	0 (0%)		
<b>Divorced</b>	0 (0%)	0 (0%)		
<b>Widowed</b>	1 (25%)	2 (18.2%)		
<b>Occupation</b>				
<b>Worker</b>	1 (25%)	2 (18.2%)	FET	0.789
<b>House wife</b>	3 (75%)	9 (81.8%)		
<b>Education level</b>				
<b>Illiterate</b>	0 (0%)	0 (0%)	MC	0.730
<b>Primary</b>	1 (25%)	5 (45.5%)		
<b>Secondary</b>	3 (75%)	4 (36.3%)		
<b>High</b>	0 (0%)	2 (18.2%)		
<b>t: Independent t test, FET: Fisher exact test, MC: Monte carlo test</b>				

**Table (7): Association between surgical site infection and obstetrical, medical, surgical and past history among the studied groups**

Items	Group (1) (n=4)	Group (2) (n=11)	P value
<b>Gravidity</b>			
<b>Multigravida</b>	3 (75.0%)	8 (72.7%)	1.0
<b>Null gravida</b>	1 (25.0%)	3 (27.3%)	
<b>Comorbidities</b>			
<b>Diabetes</b>	3 (75%)	6(54.5%)	0.064*
<b>Hypertension</b>	2 (50%)	5 (45.5%)	1.0
<b>Thyroid disorder</b>	0 (0%)	1 (9.1%)	1.0
<b>Asthma</b>	1 (25%)	2 (18.2%)	0.154
<b>Anemia</b>	2 (50%)	1 (9.1%)	
<b>Surgical history</b>			
<b>Positive</b>	3 (75%)	9 (81.8%)	1.0
<b>Negative</b>	1 (25%)	2 (18.2%)	
<b>Past history of SSI</b>			
<b>Positive</b>	3 (75%)	5 (45.5%)	0.569
<b>Negative</b>	1 (25%)	6 (54.5%)	
<b>History of radiotherapy</b>	3 (75%)	1 (9.1%)	0.033*

**Table (8): Association between SSI and pre-operative suspected primary pathology among studied groups**

Suspected lesion	Group (1) (n=4)	Group (2) (n=11)	Test of significance	P value
<b>Ovarian</b>	3 (75%)	7 (63.6%)	MC	1.0
<b>Uterine</b>	1 (25%)	2 (18.2%)		
<b>Cervical</b>	0 (0%)	2 (18.2%)		

**Table (9): Association between SSI and operative data among the studied groups**

Items	Group (1) (n=4)	Group (2) (n=11)	Test of significance	P value
<b>Type of incision</b> Midline Low transverse abdominal	3(75.0%) 1(25.0%)	8 (72.7%) 3 (27.3%)	FET	1.0
<b>Type of surgery</b> Staging laparotomy TAH+BSO Wertheim operation	3 (75%) 1 (25.0%) 0 (0%)	7 (63.6%) 2 (18.2%) 2 (18.2%)	MC	1.0
<b>Operative time</b> Less than 2h More than 2h	1 (25.0%) 3 (75.0%)	4 (36.4%) 7 (63.6%)	FET	0.001*
<b>Blood loss during surgery</b> Less than 500ml 500-1000 ml	2 (50%) 2 (50%)	6 (54.6%) 5 (45.4%)	FET	1.0
<b>Blood transfusion</b> Yes No	1 (25%) 3 (75%)	4 (36.4%) 7 (63.6%)	FET	1.0
<b>FET: Fisher exact test, MC: Monte carlo test</b>				

## **Discussion**

Surgical site infections had been reported to be the most common hospital acquired infections by the American College of Surgeons (ACS), nearly 20%. SSIs are linked to significant morbidity as increased length of hospital stay by approximately 10 days, hospitalization costs by approximately \$20, 000 per admission, readmission rates, significant reduction in the quality of life, and increased mortality <sup>(10)</sup>.

In the field of gynecologic oncology, in spite of the reported SSI rate of 3–36% for main procedures and about 30% hospital readmission rate owing to postoperative SSIs; the studies on the use of preventive bundle to reduce SSI are scant. <sup>(11)</sup>

The current study included 80 gynecologic Oncology elective cases, divided into 2 groups: study group (40Cases with bundle implementation, 2 lost follow up after month) and control group (40Cases without bundle implementation, 3 lost follow up).

The current study showed there was non-significant statistical difference between the 2 groups in socio-demographic characteristics ( $P>0.05$ ), also in obstetrical, medical, surgical and past history of the studied groups. ( $P>0.05$ ).

In concordance with our findings, Van Nguyen et al, 2019 evaluated gynecologic oncology patients, 339 patients (control) underwent surgery without using the bundle, and 224 patients following it (study group) at a large academic tertiary centre in Toronto, Canada, there was insignificant difference in demographics as their age, BMI, diabetes and hypertension. <sup>(12)</sup>

Similarly, Van Nguyen et al, 2019 showed non-statistically significant difference among the 2 groups in primary malignancy ( $P=0.14$ ), coping with our study <sup>(12)</sup>

In disagreement with that, Johnson et al, 2016 compared the preintervention and intervention groups as regard primary malignancy distribution, procedure of

surgery and Operative time (min), and there was significant statistical difference between them ( $P \leq 0.001$ ).<sup>(13)</sup>

The majority of published bundles in gynecologic oncology were successful to reduce the rate of SSIs in many. Johnson et al, 2016 concluded a significant reduction in the risk of SSI after carrying out a bundle before laparotomy in gynecologic oncology cases (6% to 1.1%, relative risk reduction of 82.4%,  $p = 0.01$ ), which included sterile closing tray and changing staff glove for fascial and skin closure, removal of dressing at 24 to 48 hour postoperatively, chlorhexidine soap on discharge and follow-up nursing phone call.<sup>(13)</sup>

Agarwal et al, 2019 showed significant reduction in overall surgical site infection and readmission rate after investigating the incidence of 30-day SSI before and after the introduction of evidence-based "bundled interventions" in gynaecologic malignancy.<sup>(14)</sup>

Interestingly, the current study illustrated association between SSI rate and different parameters. There was statistically significant association between SSI and socio-demographic data, SSI was associated with BMI, SSI was more common in obese patients ( $P=0.038$ ).

Moreover, the current study found statistically significant association between SSI and obstetric, medical, surgical and past history, SSI was associated with diabetes and history of radiotherapy. There was statistically significant association between SSI and operative details, SSI were associated with type of surgery and operative time, as SSI were more common in staging laparotomy operations than TAH+BSO and Wertheim operations, also SSI were more common in operations lasted more than 2 hours than operations lasted less.

In harmony with our findings, Van Nguyen et al, 2019 demonstrated independent predictive factors associated with an increased risk for overall SSIs in gynecological surgery as surgery prior to carrying out of the bundle,

BMI  $> 30$  kg/m<sup>2</sup> and operative duration  $>180$ min, also Diabetes has been identified as a risk factor.<sup>(12,15)</sup>

Prolonged surgical procedure ( $>180$  min) in both abdominal and laparoscopic approaches has been demonstrated to be a risk factor for SSI, also, an incision length  $\geq 20$  cm could serve a role in SSI development.<sup>(16)</sup>

The rates of SSI in gynaecological procedures appear to be low in vaginal and laparoscopic hysterectomy techniques (50% reduction in SSI incidence) in comparison to laparotomy (3.9% rate of SSI for open hysterectomies and 1.4% for minimally invasive procedures). Robotic interventions in some reviews may be associated with a higher risk due to prolonged surgical procedure.<sup>(17)</sup>

## **Conclusion**

This study showed that implementation of a gynecologic perioperative surgical site infection prevention bundle was associated with a significant reduction in surgical site infection rate in patients undergoing gynaecological oncology surgeries.

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### **Legends to tables**

Table (1): Sociodemographic data among the studied groups.

Table (2): Obstetric, medical, surgical and past history among the studied groups.

Table (3) Pre-operative suspected primary pathology among studied groups.

Table (4): Assessment of wound healing and SSI cases among the studied groups.

Table (5): Secondary outcome in cases with SSI among studied groups.

Table (6): Association between surgical site infection and sociodemographic data among the studied groups.

Table (7): Association between surgical site infection and obstetrical, medical, surgical and past history among the studied groups.

Table (8): Association between SSI and pre-operative suspected primary pathology among studied groups:

Table (9): Association between SSI and operative data among the studied groups.

### **Legends to figures**

Figure (1): Flow chart of the studied groups

Figure (2): Age distribution among the studied groups

Figure (3): Educational level among the studied groups

Figure (4): Comorbidities among the studied groups

Figure (5): Previous surgical Hx, past hx of SSI and radiotherapy history among the studied groups.

Figure (6): SSI cases among the studied groups.

Figure (7): Secondary outcome in cases with SSI among studied groups

### **List of abbreviation**

(SSIs): Surgical site infections

(ACOG): American College of obstetrics and gynaecology

(RBS): Random blood sugar

(TAH+BSO): Total abdominal hysterectomy and bilateral salpingo-oophorectomy

(ACS): American College of Surgeons

(BMI): Body mass index

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# Intraoperative Placement of the Non-Hormonal Copper Intrauterine Devices in Women Undergoing Cesarean Delivery

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## **Short title:**

Copper IUD Placement During Cesarean Delivery

## **Conflict of interest:**

MNA, AAHA and MAASh conceived and supervised the study; MAE was responsible for data collection, analyzed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

## **Sponsors and funding sources:**

There are none to be declared.

## **Abstract**

**Background:** Intrauterine devices (IUDs) are a popular contraceptive option for women worldwide. While traditionally inserted postpartum, there is growing interest in intraoperative placement during cesarean delivery as a convenient and effective strategy. This study aimed to evaluate the efficacy and safety of non-hormonal copper IUD insertion during cesarean sections and compare outcomes with postpartum insertion.

**Methods:** This prospective case-control study enrolled women aged 18-45 years undergoing cesarean section at Benha University's Obstetrics & Gynecology department from June 2021 to June 2023. Participants were divided into two groups: Group 1 (intrapartum) received IUD insertion during cesarean section, and Group 2 (postpartum) received insertion six weeks after discharge.

**Results:** Of the 130 women assessed, 104 met inclusion criteria and were included in the study (Group 1: n=50, Group 2: n=54). There were no failed insertions in either group. Hemoglobin levels were significantly lower in Group 1 compared to Group 2 after one week (9.3 vs. 10 g/dl, P=0.000) and six weeks (9.75 vs. 10.35 g/dl, P=0.0001). At six weeks, bleeding and IUD removal rates were 4% in Group 1 and 7.41% in Group 2 (P=0.457). Rates of expulsion were 2% in Group 1 and 3.7% in Group 2 (P=0.604). Displacement and removal rates were similar between groups (4% vs. 3.7%, P=0.937).

**Conclusions:** Intraoperative placement of non-hormonal copper IUDs during cesarean delivery is a safe and effective contraceptive option with comparable complication rates to postpartum insertion. While hemoglobin levels were lower in the intrapartum group, overall outcomes support the feasibility and utility of this approach in clinical practice.

**Keywords:** Intrauterine device, cesarean delivery, contraception, copper IUD, expulsion, complication rates.

## **Introduction**

In recent years, intrauterine devices (IUDs) have gained considerable popularity as a highly favoured method of long-term reversible contraception. These devices, small in size, are inserted into the uterus by a healthcare professional through the vaginal canal. There exist two primary categories of IUDs – hormonal variants, which discharge progestin, and non-hormonal copper IUDs. Functionally, IUDs chiefly operate by impeding fertilization, boasting a remarkable efficacy rate of over 99% in preventing pregnancy<sup>[1]</sup>. Depending on the specific type, they offer continuous contraception for a span ranging from 3 to 10 years. The appeal of IUDs lies in their manifold benefits, including exceptional effectiveness, prolonged duration of action, prompt reversibility, freedom from adherence constraints, and minimal incidence of side effects<sup>[2]</sup>.

Although IUDs offer notable advantages, their utilization rates persist below those of alternative contraceptive options in specific geographical areas. Several obstacles hinder broader acceptance, including initial out-of-pocket expenses, healthcare provider prejudice against women who have not given birth, and apprehensions regarding potential side effects. Nevertheless, initiatives are actively being pursued to encourage the use of IUDs, particularly among young and nulliparous individuals, through extensive counselling services and enhanced availability<sup>[3]</sup>.

The practice of inserting intrauterine contraceptive devices during cesarean deliveries is increasingly being recognized as a viable means of offering efficient long-term contraception. Both hormonal and copper IUDs can be securely implanted during cesarean procedures. Immediate insertion addresses the barriers that many women encounter when scheduling a separate appointment for insertion at a later date, enabling them to depart from the hospital with their chosen contraceptive method already in place. This approach holds potential benefits, particularly for women undergoing planned cesarean sections. Nonetheless, uncertainties persist regarding the optimal timing for IUD insertion during the cesarean procedure. Furthermore, concerns linger regarding potential risks such as uterine perforation, expulsion, and bleeding<sup>[4]</sup>.

We aimed to determine the efficacy of non-hormonal Copper IUD insertion during a cesarean section, as well as the rate of expulsion and complication.

## **Patients and Methods**

This prospective case-control study was conducted to determine the efficacy of non-hormonal Cu-IUD implantation during cesarean sections, as well as to assess the rates of expulsion and complications at the Obstetrics & Gynecology department of Faculty of Medicine of Benha University during the period from June 2021 to June 2023.

An informed written consent was obtained from the patient or relatives of the patients. The study was done after approval from the Ethical Committee Benha University Hospitals Inclusion criteria were age 18-45 years, absence of infectious diseases, no intranatal bleeding, hemoglobin (Hb) level  $\geq$  9 g/dl, full-term pregnancy without medical disorders, and singleton uncomplicated pregnancy.

Exclusion criteria were known copper allergy, history of pelvic infection, prenatal outflow of

amniotic fluid, uterine abnormalities, history of HIV, previous failed IUD, uterine fibroid, history of post-operative complications, hemorrhagic disorder, history of ectopic pregnancy. The participants were categorized into two groups:

Group 1 (intrapartum group): Comprising 50 cases, this group underwent cesarean sections with simultaneous non-hormonal Cu-IUD insertion.

Group 2 (postpartum group): Consisting of 54 participants, this group received postpartum IUD insertion during a postpartum visit 6 weeks after hospital discharge.

All participants were subjected to full history taking (During prenatal visits, detailed medical histories were obtained from each participant. This involved discussions about the participant's obstetric and gynecological history, including the number of previous pregnancies, history of cesarean sections, any medical conditions, and contraceptive preferences postpartum. This comprehensive history-taking process aimed to ensure that participants met the medical criteria for cesarean section and were suitable candidates for non-hormonal Cu-IUD insertion.

### **Clinical examination**

Comprehensive clinical examinations were conducted during prenatal visits to assess the participants' overall health and ascertain their eligibility for cesarean section and subsequent IUD insertion. The clinical examination involved vital sign assessments, abdominal palpation, and pelvic examinations. Any potential contraindications, such as uterine anomalies or infections, were carefully identified and taken into consideration for patient selection.

### **IUD insertion**

Cesarean section procedures were performed according to established protocols. Following the safe delivery of the baby and within 10 minutes

of placental removal, a non-hormonal Cu-IUD was implanted in the uterine fundus in the study group. Implantation was done by experienced obstetricians using ring forceps through the hysterotomy incision, with IUD strings threaded into the cervix.

### **IUD insertion assessment**

Before patients were discharged from the hospital, a thorough assessment of the inserted IUD was conducted. A speculum examination was performed to visually confirm the presence of the IUD strings, thus verifying that the device was in place within the uterine cavity. This step aimed to ensure proper IUD positioning and exclude any initial signs of IUD expulsion.

### **Follow-up visits**

Participants were scheduled for follow-up visits at one week and six weeks postpartum. During these visits, participants were questioned about any symptoms, concerns, or complications. Physical and pelvic examinations were conducted to confirm IUD presence and assess symptoms like infection or heavy bleeding.

### **Clinical and ultrasonographic examinations**

At the follow-up visits, thorough clinical and pelvic examinations were conducted by trained healthcare professionals. These examinations were designed to confirm the presence and positioning of the IUD, assess symptoms like pain or discomfort, and identify potential signs of infection or heavy bleeding. To enhance accuracy, transvaginal ultrasonography was employed to visualize the IUD and its location within the uterine cavity.

### **Expulsion confirmation**

The occurrence of IUD expulsion was confirmed both clinically and through transvaginal

ultrasonography. Any cases of expulsion were documented and further investigated.

### **Patient management**

Participants reporting pelvic discomfort, fever, heavy bleeding, unusual vaginal discharge, or other concerns were advised to seek medical attention at any time. In cases of bleeding, discomfort, expulsion, pregnancy, or patient requests, IUD removal was carried out according to hospital policy. Antibiotics were administered in alignment with the Maternity Hospital's Caesarean section policy.

### **Primary outcome**

The primary outcome measure of this study was the efficacy of non-hormonal Cu-IUD implantation during cesarean section. Successful insertion of the IUD within the uterine cavity during the cesarean procedure was the key parameter to assess. The determination of successful insertion was based on postoperative imaging or direct observation during follow-up visits.

### **Secondary outcome**

Rate of Expulsion

### **Statistical analysis**

The data collected underwent analysis using Stata version 17 software. Continuous variables were depicted as mean  $\pm$  standard deviation and median with interquartile ranges. Normality of the data was assessed through Skewness

and Kurtosis tests. Categorical variables were presented as frequencies and percentages. Mean comparisons were conducted using independent samples t-tests, while median comparisons utilized the Mann–Whitney test (Wilcoxon rank sum test). Proportions were analyzed using the chi-square test or Fisher's exact test. Additionally, multiple logistic regression analysis was employed to evaluate the association between intrapartum IUCD insertion and the incidence of complications post-insertion, with adjustments made for potential confounding factors.

### **Results**

A total of 130 women who were seeking IUD insertion were enrolled in the study and were assessed for the inclusion criteria. Among the 130 women enrolled, only 104 (80%) women met the inclusion criteria and were included in this study and divided into two cohorts; 50 patients (48.08%) in group 1 (intrapartum group) and 54 patients (51.92%) in group 2 (postpartum group), the 104 women were followed for up to 6 weeks after insertion of IUCD.

Upon analysis, there was no significant difference between the women in the two groups regarding most of the basic characteristics and obstetric history. The mean age of the women in group 1 (intrapartum) and group 2 (postpartum group) were 28.72 ( $\pm 4.67$ ) and 28.72 ( $\pm 3.98$ ) respectively with no significant difference (P value= 0.998), median hemoglobin level before insertion of the IUCD in group 1 (intrapartum) and group 2 (postpartum group) were 10 g/dl (9.8-11), 10 g/dl (9.7-10.6) respectively with no significant difference ( P value= 0.209). Table 1

**Table 1: Comparison between the two groups regarding patients' basic characteristics and obstetric history**

Characteristics	Group 1 Intrapartum group (n=50)	Group 2 Postpartum group (n= 54)	Significance P value	Test value
Maternal age, mean (SD), (years)	28.72 ( $\pm 4.67$ )	28.72 ( $\pm 3.98$ )	0.998	t= 0.0026
Gravidity (median)	2 (1-3)	2 (1-3)	0.6918	z= -0.400
Parity (median)	1 (0-2)	1 (0-2)	0.8182	z = -0.240

<b>Blood group</b>				
A <sup>+</sup>	13 (26%)	9 (16.67%)	0.9320	z = 0.087
B <sup>+</sup>	6 (12%)	11 (20.37%)		
O <sup>+</sup>	16 (32%)	22 (40.74%)		
AB <sup>+</sup>	4 (8%)	1 (1.85%)		
A <sup>-</sup>	4 (8%)	5 (9.26%)		
B <sup>-</sup>	5 (10%)	1 (1.85%)		
O <sup>-</sup>	2 (4%)	3 (5.55%)		
AB <sup>-</sup>	0 (0%)	2 (3.70%)		
<b>Hemoglobin level before insertion (median) (g/dl)</b>	10 (9.8-11)	10 (9.7-10.6)	0.209	z = -1.260

### Primary analysis:

The complications after insertion of the IUCD as failed insertion, hemoglobin level, post insertion pain, bleeding & IUCD removal, displacement & IUCD removal, expulsion and perforation in the two groups were followed for up to 6 weeks and were compared as shown in Table 2.

**Table 2: Comparison between groups regarding patients' complications**

Complications	Group 1 Intrapartum group (n=50)	Group 2 Postpartum group (n= 54)	Significance P value	
Failed insertion	0 (0%)	0 (0%)	----	----
Hemoglobin level after 1 week of insertion	9.3 (9-9.9)	10 (9.6-10.5)	0.000	z = 4.488
Hemoglobin level after 6 weeks of insertion	9.75 (9.2 -10.2)	10.35 (9.9-10.8)	0.0001	z = 3.836
Post insertion pain 1 week	0 (0%)	0 (0%)	----	----
Post insertion pain 6 week	2 (4%)	3 (5.56 %)	0.711	0.1373
Bleeding & Removed 1 week	1 (2%)	0 (0%)	0.296	1.0905
Bleeding & Removed 6 week	2 (4%)	4 (7.41%)	0.457	0.5545
Displaced & Removed 1 week	0 (0%)	0 (0%)	----	----
Displaced & Removed 6 week	2 (4%)	2 (3.7%)	0.937	0.0062
Expulsion 1 week	1 (2%)	0 (0%)	0.296	1.0905
Expulsion 6 week	1 (2%)	2 (3.7%)	0.604	0.2690
Perforation 1 week	0 (0%)	1 (1.85%)	0.334	0.9349
Perforation 6 week	0 (0%)	0 (0%)	----	----
Missed threads	3 (6%)	0 (0%)	0.068	3.3362
Vaginal infection 1 week	0 (0%)	2 (3.7%)	0.169	1.8882
Vaginal infection 6 wk	0 (0%)	1 (1.85%)	0.334	0.9349
Unintended pregnancy	0 (0%)	0 (0%)	----	----

There was no failure in the insertion of the IUCD in the two groups. After analysis, the hemoglobin level was higher in group 2 (postpartum) compared to group 1 (intrapartum) after one and six weeks of follow-up with significant difference (P value= 0.000). There was one case of Bleeding and removal of the IUCD after one week in group 1 (intrapartum) and no case in group 2 (postpartum) with no significant difference (P value=0.296), there was a higher rate of bleeding and IUCD removal after six weeks of follow up, there were 4 cases of bleeding and IUCD removal in group 2 (postpartum) and 2 cases in group 1 (intrapartum), but with no significant difference (P value=0.457). After one week no cases of IUCD displacement and removal were noted in the two groups but after six weeks there were 2 cases of displacement and removal of IUCD in each group with no significant differences (P value= 0.937).

After one week there was one case of expulsion in group 1 (intrapartum) and no case of expulsion in group 2 (postpartum) with no significant difference (P value=0.296), after 6 weeks there were 2 cases of expulsion in group 2 (postpartum) and one case in group 1 (intrapartum) with no significant difference (P value=0.604). No significant difference regarding perforation after

one and six weeks. there were only 3 cases of missed threads in group 1 (intrapartum ) and no case of missed thread in group 2 (postpartum) but with no significant difference (P value=0.068), the rate of vaginal infection was higher in group 2 (postpartum), after one week 2 cases of vaginal infection in group 2 (postpartum) and no case in group 1 (intrapartum) with no significant difference (P value=0.169), after six weeks 1 case of vaginal infection in group 2 (postpartum) and no case of vaginal infection in group 1 (intrapartum) (P value=0.334), no cases of unintended pregnancy were noted in the two groups.

We used a multiple regression model to compare the two groups and rate of complications after six weeks; in the model we use all the following variables: age, parity, gravity and hemoglobin level before the CS to adjust for all the possible confounders. Using the multiple logistic regression model, the adjusted odds ratio for bleeding and IUCD removal after 6 weeks were 0.24 (95% CI: 0.02-2.30, P-value 0.217), the adjusted odds ratio for displacement and IUCD removal after 6 weeks were 0.54 (95% CI: 0.05-6.34, P-value 0.628), the adjusted odds ratio for expulsion after 6 weeks were 0.53 (95% CI: 0.04-6.63, P-value 0.620) as shown in **Table 3**.

**Table 3: Multivariable analysis of predictors of outcomes regarding the studied groups**

Complication	Group 1 Intrapartum group (n=50)	Group 2 Postpartum group (n= 54)	Adjusted Odds ratio	Confidence interval	P value
<b>Bleeding &amp; Removed 6 week</b>	2 (4%)	4 (7.41%)	0.24	0.02-2.30	0.217
<b>Displaced &amp; Removed 6 week</b>	2 (4%)	2 (3.7%)	0.54	0.05-6.34	0.628
<b>Expulsion 6 week</b>	1 (2%)	2 (3.7%)	0.53	0.04-6.63	0.620

## **Discussion**

The utilization of intrauterine devices (IUDs) as a reliable method of contraception has witnessed a significant surge, owing to their effectiveness and long-term benefits [5]. However, the ideal timing for IUD insertion, especially during or immediately after a cesarean section, remained a subject of interest and clinical investigation [6]. Non-hormonal Copper IUDs (Cu-IUDs) have gained prominence due to their non-hormonal nature and durability, making them an appealing choice for postpartum contraception [7].

These collective findings, including our own, indicate a robust pattern of similarity in baseline characteristics among participants across various studies and settings. This consistency reinforces the notion that the timing of Cu-IUD insertion, whether during cesarean section or postpartum, does not substantially influence these baseline characteristics. Therefore, healthcare providers can confidently base their decisions on clinical appropriateness and patient preferences, with less concern about introducing variations in these fundamental factors. This not only enhances the generalizability of our results but also underscores the importance of personalized patient care in the domain of contraceptive decision-making.

This study meticulously examined various complications associated with Cu-IUD insertion, including bleeding and IUD removal, displacement, expulsion, perforation, missed threads, vaginal infection, and unintended pregnancy.

This study found no cases of failed IUD insertion in either the intrapartum or postpartum group. This result demonstrates that both methods of Cu-IUD insertion, whether during cesarean section or postpartum, were technically successful, and this finding is consistent with previous research in the field. Aligned with our findings, a randomized

controlled trial revealed that immediate postplacental insertion of intrauterine Cu IUD is not linked to failed insertion when compared to standard insertion in postpartum women [8]. This consistency between our study and theirs supports the notion that immediate intrapartum insertion is a viable and technically successful option for Cu-IUD placement.

We observed significant differences in hemoglobin levels between the two groups. Specifically, participants in the postpartum group had higher hemoglobin levels after both one and six weeks. This difference suggests that postpartum Cu-IUD insertion may result in less immediate blood loss, or a quicker recovery of hemoglobin levels compared to intrapartum insertion. Conversely, immediate postplacental insertion of intrauterine Cu IUD is not associated with different hemoglobin levels compared to standard insertion in women who are postpartum at a Brazilian University Hospital [9]. The clinical significance of this finding merits further investigation.

Our analysis showed no significant differences in post-insertion pain between the two groups at both one and six weeks. This indicates that the timing of Cu-IUD insertion, whether during cesarean section or postpartum, did not significantly affect the experience of pain. The lack of a substantial pain difference is reassuring for both clinical practice and patient comfort.

In line with our results, another study also found no substantial differences between the two groups regarding post-insertion pain or bleeding [10].

However, in the study conducted at a municipal public maternity hospital in Porto Velho, Brazil, it was found that the main side effect in the first days of use, still in the puerperium, was pelvic pain in 20.36% of all IUDs inserted immediate postplacental [11].

After one week, there was one case of bleeding and IUCD removal in the intrapartum

group and none in the postpartum group. Although this difference was not statistically significant, it suggests a potential trend toward lower early complications in the postpartum group. However, after six weeks, the rates of bleeding and IUCD removal were higher in the postpartum group, though not significantly so. The longer-term data indicate that both groups had similar rates of this complication, suggesting that the timing of insertion may not be a critical factor.

In alignment with our findings, studies by [8, 12, 13] all yielded results indicating no significant impact on bleeding patterns following immediate post-placental IUCD placement.

Both groups had similar rates of IUCD displacement and removal after one week, with no cases noted. However, after six weeks, there were two cases in each group. The lack of significant differences in both early and late complications suggests that Cu-IUCD displacement and removal may be unrelated to the timing of insertion. While there was one case of expulsion in the intrapartum group after one week and none in the postpartum group, this difference was not statistically significant. After six weeks, the rates of expulsion remained similar between the groups. These findings suggest that the risk of expulsion is not significantly influenced by the timing of Cu-IUCD insertion.

Additionally, Abdel Ghany et al. found no significant distinctions in IUCD displacement and expulsion rates between the study groups [10]. However, Sharma's study suggested that there were higher rates of expulsion and removal in cases of vaginal insertions compared to cesarean insertions [14]. Additionally, in a Brazilian University Hospital, immediate postpartum insertion of copper IUCD is associated with higher rates of expulsion compared to standard insertion [9]. This suggests that other factors, aside from timing, may contribute to expulsion risk.

No cases of perforation were observed in either group at any time point. This is

reassuring, as perforation is a rare but serious complication associated with IUCD insertion. This finding aligns with the results reported in various studies, where no instances of perforation or pelvic inflammatory disease (PID) were observed in cases of transcesarean IUCD insertion [15-17].

Furthermore, a recent retrospective cohort study based on electronic medical records from Kaiser Permanente Southern California analysed 24,959 IUCD insertions. This study revealed a statistically significant increase in the risk of perforation with IUCD placement at 4-8 weeks postpartum compared to 9-36 weeks postpartum (0.78% versus 0.46%, respectively). The risk of perforation was found to decrease for IUCD insertions performed after 22 weeks postpartum [18].

Therefore, IUCD insertion timing should be based on individual desire for IUCD contraception and patient convenience to assure an IUCD insertion can occur. Careful follow-up of individuals at higher risk of uterine perforation is warranted.

After six weeks, the intrapartum group had a higher rate of missed threads compared to the postpartum group, but this difference was not statistically significant. The finding implies that the timing of insertion does not significantly affect the likelihood of missed threads. Similarly, Abdel-Ghany et al. found that, at the end of the follow-up period, there was a notable increase in the incidence of missed threads in the first group (immediate insertion) compared to the second group (insertion six weeks or more after delivery). This difference was attributed to variations in thread length at the time of insertion and subsequent adjustments made during follow-up screening visits [10].

The rate of vaginal infection was slightly higher in the standard group after one week, but not after six weeks. These differences were not statistically significant. Vaginal infection rates may be more influenced by individual patient factors and hygiene

practices than by the timing of IUD insertion.

In a recent systematic review [19], among the eight studies that documented data on infection rates following immediate postpartum IUD insertion, two of them reported cases of wound infections occurring immediately after the insertion of a copper IUD during caesarean deliveries [20, 21].

Importantly, no cases of unintended pregnancy were observed in either group throughout the study. This underscores the effectiveness of Cu-IUDs as a contraceptive method, regardless of the timing of insertion. The results from two studies were consistent with and confirmed our findings [8, 10].

### **Conclusions**

Our study has provided valuable insights into the efficacy and safety of intrapartum and postpartum Cu-IUD insertion during cesarean section. The results suggest that both methods are valid options for contraception, with no significant differences in complication rates after controlling for potential confounders. The decision regarding the timing of Cu-IUD insertion should be tailored to the individual patient's preferences and clinical context.

### **Based on the results of the study, several key recommendations can be made**

Healthcare providers should consider offering Cu-IUD insertion as a viable option to women during cesarean deliveries, allowing them to make informed choices regarding contraception at this crucial time. It is crucial to monitor the hemoglobin levels of women after Cu-IUD insertion. Healthcare providers should continue to offer these options and emphasize the importance of post-insertion follow-up to identify and manage any complications early. Further research with larger sample sizes and longer follow-up periods is recommended to confirm the safety and effectiveness of intrapartum and postpartum Cu-IUD insertion during cesarean sections.

**Financial support and sponsorship:** Nil

**Conflict of Interest:** Nil

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# Pregnancy Outcome for Pregnant Women with Common Cardiac Problems at Mansoura University Hospital

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## **Abstract**

The presence of heart disease.

**Background :** Pregnancy in the presence of heart disease (HD) poses a high risk of maternal mortality and morbidities including heart failure (HF), stroke and arrhythmias. The physiologic circulatory alterations related to pregnancy worsen the haemodynamic changes that are already present in these females. The fetus is also not spared as intrauterine growth restriction (IUGR) and prematurity also significantly increased.

**Aim :** To assess maternal & fetal outcomes for pregnant women with common cardiac problem at Mansoura University hospital.

**Methods:** This cross-sectional study included 90 pregnant females aged between 18 to 40 years with congenital heart disease (CHD), with rheumatic heart disease (RHD) who underwent elective abortion. The cases were followed up till delivery to determine the primary and secondary outcomes. The primary outcome was the rate of maternal complication as heart failure. The secondary outcome included changes in NYHA functional class, cardiovascular complications, post-partum complications, delivery mode and perinatal outcomes.

**Results:** Rheumatic heart diseases were the most common in 81.1% while the non-rheumatic heart diseases were detected in 18.9%. The history of previous abortion, the degree of mitral valve affection, the amount of intraoperative blood loss, the incidence of ICU admission and the incidence of puerperal pyrexia were statistically significantly higher in the non-rheumatic heart diseases (47.1%) as compared to the rheumatic heart diseases (30.1%). The mean ejection fraction, the 1- and 5- minutes APGAR scores, and the birth weight of the neonates were statistically significantly lower in the non-rheumatic heart diseases.

**Conclusion:** We concluded that heart diseases in mothers are not absolute contraindications for pregnancy, but there were associated with serious outcomes on both the mothers and offsprings. The non-rheumatic heart diseases (mainly CHD) are associated with worse outcomes compared with the mothers with RHD.

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**Keywords:** Heart diseases, Pregnancy, Arrhythmia, Rheumatic Heart Diseases, Congenital Heart Diseases, New York Heart Association.

## **INTRODUCTION**

HD is the major cause of maternal death with a rate of 2.27/100,000 maternities. However, the incidence of HD during gestation has remained constant at 0.9% over many years, indicating that its severity and/or the risk it poses during gestation is increasing [1]. The major reason for that seems to be the high incidence in a pre-existing undiagnosed ischaemic heart disease. This is because of lifestyle changes, the presence of risk factors e.g. obesity, diabetes and smoking, and also pregnancies in older females. Furthermore, females who have complex pre-existing HD survive into adulthood and considering pregnancy [2].

Pregnancies in females with HD pose a risk of maternal mortality and serious morbidities including HF, stroke and cardiac arrhythmias. There may be also neonatal morbidity and mortality as IUGR and prematurity significantly increased [3]. The causes of maternal HD are diverse and its treatment is complex. The incidence of HD during pregnancy ranges between 0.9 and 3.1 % [4]. In developing countries, RHD accounts for 50–88 % of all HD in pregnancy [5]. CHD is less common however most CHD cases get pregnant with undiagnosed or untreated lesion [6].

The physiologic circulatory alterations during gestation worsen the haemodynamic changes which are already present. Pregnancy is a hypercoagulable state, this it enhances the risk of thromboembolic events particularly in those with artificial valves [7]. Cardiac intervention might be necessary for worsening cardiac condition in the pregnant woman. Such interventions together with cardiac drugs might pose a risk to the fetus [8, 9]. So, this study assessed maternal and

fetal outcomes for pregnant females with common cardiac problem at Mansoura University hospital.

## **PATIENTS AND METHODS**

This cross-sectional study was conducted at Obstetrics & gynecology Department, Mansoura University Hospitals, Mansoura, Egypt in the period between May 2021 and May 2023. The study included 90 pregnant females between 18 to 40 years old with heart diseases who underwent elective termination of pregnancy. We included females with CHD, with RHD, with Surgically Corrected Congenital Heart Disease, with complicated cardiac disease and with Cardiac arrhythmias. But we excluded pregnant females with cardiac problem who underwent emergent termination of pregnancy. A written informed consents were taken from all participants prior to participation after explaining the aim of the research, and the procedures that were commenced.

### **Ethical approval**

The study obtained its approval from the institutional review Board, Faculty of Medicine, Mansoura University. Confidentiality and privacy were maintained throughout the study. Patients were free to withdraw at any time with no consequences. Patients' data were not and will not be utilized for any other purpose.

### **Methods**

The cases were subjected to thorough history taking included personal history (age, residence, occupation and smoking habit), Obstetrical history (gravidity, parity, mode of prior deliveries and Previous obstetric complications), present history of underlying cardiac lesion with analysis of type, onset, course and duration, and past history (previous surgeries, medical diseases, cardiac interventions before gestation, drugs, anticoagulant agents). Patients

were classified based on New York Heart Association (NYHA) functional class.

NYHA Classification of HF Stages [10] included class I that shows no symptoms and no limitations of regular activities, e.g. dyspnea on walking or climbing stairs, Class II shows mild symptoms (mild dyspnea and/or angina) and mild limitations in regular activities, class III shows significant limitations of ordinary activities because of symptoms, even with less-than-ordinary activities, e.g. walking a short distance (20—100 meters) and comfortable only at rest, and Class IV shows severe limitation and symptoms at rest, mostly bed-bound cases.

The examination included general examination (heart rate, blood pressure, temperature, respiratory rate, congested neck vein, hepatosplenomegaly, edema lower limb), laboratory investigations included complete blood count (CBC), electrocardiography and echocardiography were done to assess ejection fraction, LV and RV functions, thickness of LV and RV walls, valve function (stenosis/regurgitation), and cardiac devices (mechanical valve, PPM, closure device), and obstetric ultrasound to assess fetal well-being, and fetal echo to assess fetus heart.

We collected patients' data about gestational age at termination, type of cardiac disease (CHD, RHD, surgically corrected congenital Heart Disease, Cardiac arrhythmias), maternal complication as antepartum hemorrhage, postpartum hemorrhage, heart failure and follow up for six weeks postpartum, mode of delivery, bleeding and blood transfusion during delivery. The fetus' data included fetal weight at delivery, APGAR score at one and five minutes, admission to neonatal intensive care unit (NICU) and postnatal echocardiography.

### **Outcomes**

This was defined as something that follows as a result or consequence. Primary outcome

included rate of maternal complication as ICU admission, while secondary outcome included changes in NYHA functional class, cardiac complications, maternal complication (antepartum hemorrhage, postpartum hemorrhage, heart failure) after follow up for six weeks, post-partum complications, delivery mode, and perinatal outcomes [IUGR, prematurity, stillbirths, low birth weight (LBW) and birth defects].

### **Statistical Analysis**

Data were analysed using IBM SPSS Statistics for Windows, V 22.0. Armonk, NY: IBM Corp. Qualitative data were expressed as frequencies and percentages. Quantitative data were expressed as median (minimum and maximum, interquartile range) for non-normally distributed data and means  $\pm$  SDs for normally distributed data following testing normality by Kolmogorov-Smirnov test. Student T-Test and Mann Whitney Tests were utilized to evaluate the significance of difference between 2 independent groups with parametric data and non-parametric data, respectively. Chi-Square test was used to compare  $\geq 2$  groups. Monte Carlo test as correction for Chi-Square test when  $> 25\%$  of cells have count  $< 5$  in tables ( $2 \times 2$ ). Fischer's exact test as correction for Chi-Square test when  $> 25\%$  of cells have count  $< 5$  in tables ( $2 \times 2$ ). The significance was set at (0.05) level.

### **RESULTS**

As shown in table (1), the mean age of included females was  $29.83 \pm 5.44$  years while the median age was 29 years (range=18-40 years). The mean number of Gravities was  $3.32 \pm 1.34$  while the median number was 3 (range= 1-7). The mean number of parities was  $1.82 \pm 1.13$  while the median number was 2 with range between 0 and 6. Previous abortion was reported in 30 cases (33.3%) while previous still birth was shown in 1 case only (1.1%). Among the cases, 77.8%

had previous CS and 20% had previous vaginal delivery. Regarding the type of heart diseases, RHD was the most common in 81.1% while the non-rheumatic heart diseases were detected in 18.9%. The types of non-rheumatic heart diseases included pulmonary hypertension in 2 cases, cardiomyopathy/ chronic hypertension in one patient, chronic hypertension in one patient, CHD in 9 cases, dilated cardiomyopathy in 1 case, ischemic heart disease in 2 cases and arrhythmogenic heart disease in 1 cases.

**Table (1): Demographic data, obstetric history and Cardiac history in the study cases**

Variables	Study cases (N = 90)	
Age (years)		
Mean $\pm$ SD	29.83 $\pm$ 5.44	
Median (range)	29 (18 - 40)	
Gravidities		
Mean $\pm$ SD	3.32 $\pm$ 1.34	
Median (range)	3 (1 - 7)	
Parities		
Mean $\pm$ SD	1.82 $\pm$ 1.13	
Median (range)	2 (0 - 6)	
Previous obstetric complications		
Previous abortion	30	33.3
Previous still birth	1	1.1
CS		
0	20	22.2
1	30	33.3
2	23	25.6
3	17	18.9
Vaginal delivery		
0	72	80.0
1	4	4.4
2	8	8.9
3	4	4.4
4	1	1.1
5	1	1.1
Type of heart disease		
Rheumatic heart diseases	73	81.1
non-rheumatic heart diseases	17	18.9
Types of non-rheumatic heart diseases		
Pulmonary hypertension	2	2.2
Cardiomyopathy/chronic hypertension	1	1.1
Chronic hypertension	1	1.1
Congenital heart disease	9	10
Dilated cardiomyopathy	1	1.1

Ischemic heart disease	2	2.2
Arrhythmogenic heart disease (SVT)	1	1.1

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

Categorical data expressed as Number (%)

Table (2) demonstrates a non-significant difference among RHD cases and cases with non-rheumatic heart diseases in terms of age, gravidity, parity, CS, vaginal delivery and previous stillbirth, however, the history of previous abortion was statistically significantly higher in the non-rheumatic heart diseases (47.1%) as compared to the rheumatic heart diseases (30.1%). The mean ejection fraction was significantly lower in the non-rheumatic heart diseases ( $p=0.002$ ). Also, there was higher degree of heart affection the non-rheumatic heart diseases ( $p=0.005$ ), there were 23.5% and 11.8% with NYHA class 3 and 4 in the non-rheumatic heart diseases while there were no cases with class 3 or class 4 in the rheumatic heart diseases.

**Table (2): Comparison of the demographic data, obstetric history, and cardiac disease severity in the cases according to the nature of cardiac diseases**

	Groups		Test of significance	P value
	Rheumatic heart disease (n= 73)	Non-rheumatic heart diseases (n= 17)		
<b>Age (Years)</b>	30.13 ± 5.28	28.59 ± 6.06	t= 1.049	0.297
<b>Gravidity</b>	3 (1 – 7)	3 (1 – 7)	z = - 0.480	0.631
<b>Parity</b>	2 (0 – 5)	2 (0 – 6)	z = - 0.220	0.826
<b>CS</b>	1 (0 – 3)	2 (0 – 3)	z = - 0.947	0.344
<b>Vaginal delivery</b>	0 (0 – 5)	0 (0 – 3)	z = - 0.871	0.384
<b>Previous abortion</b>	22 (30.1%)	8 (47.1%)	$\chi^2= 4.253$	<b>0.005*</b>
<b>Previous stillbirth</b>	1 (1.4%)	0 (0%)	FET = 0.235	0.627
<b>Ejection fraction (%)</b>	64.15 ± 6.17	58.11 ± 7.02	t = 4.218	<b>0.002*</b>
<b>NYHA classification</b>				
Class 1	24 (32.9%)	1 (5.9%)	MC = 6.459	<b>0.005*</b>
Class 2	49 (67.1%)	10 (58.8%)		
Class 3	0 (0%)	4 (23.5%)		
Class 4	0 (0%)	2 (11.8%)		

P: probability. Quantitative data expressed as mean ± SD/ median (Range), Categorical data expressed as Number (%). MC: Monte-Carlo test, t: Independent samples t-test, FET: Fisher's exact test, z: Mann-whitney U-test

Table (3) demonstrates a non-significant difference between the cases with rheumatic heart disease and the cases with non-rheumatic heart diseases regarding the affection of aortic valve, pulmonary valve or the tricuspid valve. However, the degree of mitral valve affection was significantly higher in cases with RHD ( $p < 0.001$ ). No significant difference existed between RHD cases and cases with non-rheumatic heart diseases regarding the delivery mode ( $p= 0.098$ ) and GA at delivery ( $p = 0.921$ ). The amount of intraoperative blood loss was significantly higher in cases with non-rheumatic heart diseases compared with cases with rheumatic heart diseases ( $p= 0.030$ ). Also, there was statistically significant higher requirement of blood transfusion in the non-rheumatic heart diseases ( $p=0.005$ ).

**Table (3): Comparison of the valve affection and operative data in the cases according to the nature of cardiac diseases**

	Groups		Test of significance	P value
	Rheumatic heart disease (n= 73)	Non-rheumatic heart diseases (n= 17)		
<b>Mitral valve</b>				
Normal	8 (11%)	10 (58.8%)	MC = 20.298	< <b>0.001*</b>
Affected	44 (60.3%)	6 (35.3%)		
Replacement	21 (28.8%)	1 (5.9%)		
<b>Grade of affection</b>	<b>(N= 44)</b>	<b>(N = 6)</b>		
Mild	3 (6.8%)	0 (0%)	MC = 0.511	0.775
Moderate	25 (56.8%)	4 (66.7%)		
Severe	16 (36.4%)	2 (33.3%)		
<b>Aortic valve</b>				
Normal	47 (64.4%)	15 (88.2%)	MC = 3.705	0.157
Affected	16 (21.9%)	1 (5.9%)		
Replacement	10 (13.7%)	1 (5.9%)		
<b>Grade of affection</b>	<b>(N= 16)</b>	<b>(N = 1)</b>		
Mild	6 (37.5%)	1 (100%)	FET = 1.512	0.218
Moderate	10 (62.5%)	0 (0%)		
<b>Tricuspid valve</b>				
Normal	38 (52.1%)	11 (64.7%)	$\chi^2 = 0.890$	0.346
Affected	35 (47.9%)	6 (35.3%)		
<b>Grade of affection</b>	<b>(N= 16)</b>	<b>(N = 1)</b>		
Mild	6 (17.6%)	1 (16.7%)	MC = 3.585	0.167
Moderate	19 (55.9%)	5 (83.3%)		
Severe	9 (26.5%)	0 (0%)		
<b>Pulmonary valve</b>				
Normal	63 (86.3%)	14 (82.4%)	FET = 0.216	0.786
Hypertension	10 (13.7%)	3 (17.6%)		
<b>Mode of delivery</b>				
CS	67 (91.7%)	17 (100%)	FET = 2.859	0.098
Vaginal delivery	6 (8.3%)	0 (0%)		
Amount of intraoperative blood loss (cc)	389 (215-1100)	842 (430-2500)	z = - 2.542	<b>0.030*</b>
Gestational age at delivery (Weeks)	37.16 ± 1.80	37.12 ± 1.45	t= 0.100	0.921
Intraoperative blood transfusion	0 (0%)	2 (23.5%)	FET = 4.625	<b>0.005*</b>

P: probability, Quantitative data expressed as mean ± SD, Categorical data expressed as Number (%)

MC: Monte-Carlo test, FET: Fisher's exact test/ t: Independent samples t-test z: Mann-whitney U-test

Regarding the maternal outcomes in the two study groups, table (4) shows a non-significant difference between RHD cases and cases with non-rheumatic heart diseases regarding the Postpartum haemorrhage (p= 0.516) and the wound healing or infection at follow up (p = 0.244). The incidence of ICU admission (p= 0.042) and the incidence of puerperal pyrexia (p= 0.028) were statistically significantly higher among cases with non-rheumatic heart diseases compared to the cases with rheumatic heart diseases, no significant difference existed between cases with rheumatic heart disease and the cases with non-rheumatic heart diseases as regards the number of fetii (p= 0.494), abortion (p = 0.228), IUGR (p= 0.0727) and neonatal mortality (p= 0.924). The 1- and 5-minutes APAR scores were statistically significantly lower in the cases with non-RHD (p= 0.002 and 0.001 respectively). The birth weight of the neonates was significantly lower in non-RHD cases (p= 0.040). Moreover, NICU admission (p= 0.004) and presence of congenital anomalies (p= 0.018) in the neonates was statistically significantly higher in this group.

**Table (4): Comparison of the maternal outcomes and foetal outcomes in the cases according to the nature of cardiac diseases**

	Groups		Test of significance	P value
	Rheumatic heart disease (n= 73)	Non-rheumatic heart diseases (n= 17)		
ICU admission	0 (0%)	3 (17.6%)	FET = 2.975	<b>0.042*</b>
Postpartum haemorrhage	0 (0%)	1 (5.9%)	FET = 0.423	0.516
Puerperal pyrexia	1 (1.4%)	4 (23.6%)	FET = 3.216	<b>0.028*</b>
<b>Wound at follow up</b>				
Healed non-complicated	73 (100%)	15 (88.2%)	FET = 1.278	0.244
Wound sepsis	0 (0%)	2 (11.8%)		
<b>Number of fetii</b>				
Single foetus	68 (95.8%)	16 (100%)	FET = 0.468	<b>0.494</b>
Two fetii	3 (4.2%)	0 (0%)		
1 minute APGAR score	8 (5 - 8)	7 (5 - 8)	z = - 3.143	<b>0.002*</b>
5 minute APGAR score	10 (6 - 10)	6 (6 - 10)	z = - 3.318	0.001*
Birth weight (gm)	2520 ± 421.73	2253.13 ± 613.04	t= 2.086	0.040*
Abortion	6 (8.5%)	0 (0%)	FET = 1.452	0.228
IUGR	3 (4.2%)	1 (6.3%)	FET = 0.122	0.727
NICU admission	9 (12.7%)	7 (43.8%)	FET = 8.401	0.004*
Mortality	4 (5.6%)	1 (6.3%)	FET = 0.009	0.924
Congenital anomalies	1 (1.4%)	4 (25%)	FET = 4.015	0.018*

P: probability. Categorical data expressed as Number (%)

FET: Fisher’s exact test/ t: Independent samples t-test z: Mann-whitney U-test

Table (5) shows that the highest percentage of the cases were classified as NYHA class II (64.4%) followed by NYHA class I in 28.9%, NYHA 3 in 4.4% and NYHA 4 in 2.2%. LMWH / Beta blockers were used in 93.3% of the cases. The mean ejection fraction among the included cases was 61.29 ± 8.51 % with range between 35 and 75%. The mitral valve was the most affected vale in 80% of cases, tricuspid vale in 43.3%, aortic valve in 34.4% and then pulmonary vale in 14.4%.

**Table (5): Dyspnea severity, treatment and Echocardiographic in the cases of the study**

Variables	Study cases N = 90	
<b>NYHA classification</b>		
Class 1	26	28.9
Class 2	58	64.4
Class 3	4	4.4
Class 4	2	2.2
<b>Medications</b>		
Beta blocker	3	3.3
LMWH / Beta blocker	84	93.3
LMWH / Beta blocker/long-acting penicillin	1	1.1
Methyl- dopa	2	2.2
<b>Ejection fraction (%)</b>		
Mean $\pm$ SD	61.29 $\pm$ 8.51	
Median (range)	60 (35 - 75)	
<b>Mitral valve</b>		
normal	18	20
Mitral valve Stenosis	10	11.1
Mitral valve replacement	25	27.8
Mitral valve prolapse	1	1.1
<b>Mitral valve Regurgitation</b>	36	40
<b>Aortic valve</b>		
Normal	59	65.6
Stenosis	1	1.1
Replacement	11	12.2
<b>Aortic valve Regurgitation</b>	19	21.1
<b>Pulmonary valve</b>		
normal	77	85.6
pulmonary hypertension	12	13.3
pulmonary Regurgitation	1	1.1
<b>Tricuspid valve</b>		
Normal	51	56.7
Tricuspid Regurgitation	39	43.3
<b>Synthetic valve</b>		
No	60	66.7
Well-functioning	28	31.1
Good functioning valve prothesis	2	2.2

Continuous data expressed as mean $\pm$ SD and median (range)

Categorical data expressed as Number (%).

Table (6) shows that the general anathesia was used in 11.1% of the cases. Caesarean section was the most common ode of delivery in 93.3%. the amount of blood loss ranged from 215 and 2500 cc. four cases (4.4%) required intraoperative blood transfusion.

**Table (6): Operative data in the cases of study**

Variables	Study cases N = 90	
<b>Anesthesia</b>		
General	10	11.1
Spinal (epidural)	80	88.9
<b>Mode of termination</b>		
Caesarean section	84	93.3
Vaginal delivery	6	6.7
<b>Blood loss intraoperative (cc)</b>		
Mean ± SD	459.57 ± 281.27	
Median (range)	389 (215 - 2500)	
<b>Intraoperative blood transfusion</b>		
No	86	95.6
Yes	4	4.4
<b>Number of blood units</b>		
Mean ± SD	2.34 ± 0.69	
Median (range)	2 (1 - 4)	

Continuous data expressed as mean±SD and median (range), Categorical data expressed as Number (%)

Table (7) shows that the maternal outcomes included puerperal pyrexia in 5 cases (5.6%), ICU admission in 3 cases (3.3%), wound infection in 2 cases (2.2%) and postpartum haemorrhage in 1 case only (1.1%). The mean duration of hospital stay was  $3.74 \pm 1.78$  days with range between 2 and 15 days. Regarding the adverse neonatal outcomes included IUGR in 4 cases (4.6%), NICU admission in 16 cases (18.4%), neonatal mortality in 5 cases (5.8%) and congenital anomaly in 5 cases (5.8%). The median APGAR score at 1 minute was 8 (range= 5-8) while the median APGAR score at 5 minutes was 10 (range= 6-10). The mean GA at delivery was  $37.16 \pm 1.73$  weeks (range= 29-49) while the mean birthweight was  $2470.85 \pm 470.76$  rams with range between 1000 and 3600 grams.

**Table (7): Maternal outcomes in the cases of study**

Maternal Complications	Study cases N = 90	
ICU admission	3	3.3%
Postpartum haemorrhage	1	1.1%
Puerperal pyrexia	5	5.6%
<b>Wound at follow up</b>		
Healed non-complicated	88	97.8%
Wound sepsis	2	2.2%
<b>Duration of hospital stay (Days)</b>		
Mean ± SD	3.74 ± 1.78	
Median (range)	3 (2 – 15)	

<b>Fetal Outcomes</b>		
<b>Number of fetus</b>	<b>N = 87</b>	
Single fetus	84	11.1%
Two feti	3	88.9%
<b>GA at delivery (Weeks)</b>		
Mean $\pm$ SD	37.16 $\pm$ 1.73	
Median (range)	38 (29 - 40)	
<b>Neonatal outcomes</b>		
IUGR	4	4.6%
NICU admission	16	18.4%
Mortality	5	5.8%
Congenital anomaly	5	5.8%
<b>APGAR score</b>		
1 minute	8 (5 - 8)	
5 minutes	10 (6 - 10)	
<b>Birth weight (grams)</b>		
Mean $\pm$ SD	2470.85 $\pm$ 470.76	
Median (range)	2600 (1000 – 3600)	

Continuous data expressed as mean $\pm$ SD and median (range), Categorical data expressed as Number (%)

## **DISCUSSION**

Pregnancy and the peripartum period cause prolonged physiologic stress on mother's heart. Although the majority of cardiac diseases are well-tolerated during gestation with good outcome, some diseases as linked to morbidities and death of the mother and the fetus [11].

HD that complicate pregnancy is a key non-obstetric and an 'indirect' cause of maternal death, since it is not related to any complication of the pregnancy itself [12]. Arrhythmias and HF the most common cardiac complications during gestation. Both conditions are associated with maternal death, prematurity, LBW, and neonatal death [5]. The prevalence antenatal heart diseases differs between developed and developing countries [13].

In developing countries, RHD accounts for 50–88 % of all cardiac diseases during gestation [5]. In Egypt, HD is the commonest indirect cause of death of the mother during pregnancy [14]. In pregnant females, mitral

stenosis (MS) is the commonest rheumatic heart valve disease, which might be linked to pulmonary oedema, and arrhythmia during pregnancy or soon post-delivery [15].

This study assessed maternal and fetal complications of 90 pregnant females with common cardiac problem at Mansoura University hospital. In our study, rheumatic heart diseases were more common than non-rheumatic heart diseases representing (81.1% and 18.9%, respectively). CHD was the most common type of non-RHD and was found in 9 cases (10%) while in the RHD group, the mitral valve was the commonest type in 80% of these patients. Salam et al., included 90 pregnant females complicated by HD. The prevalence of HD was 4.3%. The main cardiac lesion was RHD (56.6%) whereas CHD was present in 13.3%. Among females with RHD, MS observed in 21 (23.3%) females was the commonest lesion while multiple heart lesions were observed in 21 (24.4%) females. Among those with CHD, mitral valve prolapse was the commonest lesion in 5 (5%) females [16]

In this study, the mean age was  $29.83 \pm 5.44$  years and there was high prevalence of either primigravidae or primipara. Salam et al., included 90 pregnant females with congenital heart diseases and showed that most of cases (74.5%) aged 20-30 years old and the majority of them were either primigravidae or primipara (60%) [16].

Beriye et al. demonstrated that the prevalence of valvular heart disease (VHD) among pregnant females was 0.6%. Out of 29 pregnancies, 28 (96.6%) had RHD. MS (75.9%) was the commonest valvular lesion and 16 (55.2%) had severe MS [17]. Behera and Moharana showed that the principal lesion was RHD (68.1%) followed by CHD (22.7%) and cardiomyopathies (6.25%). The commonest valvular pathology in our study is MS (46.6%), which agrees with Manohar et al., (38.6%) [18]. This could be explained by the lack of preventive measures and inappropriate administration of secondary antibiotics as a prophylaxis against streptococcal infection with subsequent occurrence of valvular lesions.

Our results conflict with Lima et al., who examined 81,295 cases with heart disease and 39,894,032 without. CHD was the commonest lesion (33,982/ 81,295 cases; 41.8%), followed by VHD (25,138/ 81,295 cases; 30.9%), cardiomyopathies (16,926 / 81,295 cases; 20.8%), and pulmonary hypertension (5,250 of 81,295 cases; 6.5%) [19]. The difference could be explained as the latter study was conducted in the US and there is relatively higher prevalence of non-RHD in the developed world due to efficient screening programs and early treatment of infections.

In this work, the highest percentage of pregnant females was classified as NYHA class II (64.4%) followed by NYHA class I in 28.9%. Behera and Moharana who included 22 pregnant females with cardiac diseases and showed that most of cases were in NYHA class II (50%) followed by NYHA class I in 22.7% [18].

In females with HD, planned C-section did not improve maternal outcomes and was detrimental to fetal outcomes [20]. Thus, vaginal delivery is advised in almost all females, and C-section is reserved for selected cases with severe pathology (e.g. advanced HF or pulmonary hypertension, alarming aortic dilatation or spontaneous labor during oral administration of anticoagulants) [21].

In our study, 88.9% of the included cases delivered by CS and this could be explained due to the attitude of high CS rate in Egypt. In our study, the maternal outcomes included puerperal pyrexia in 5 cases (5.6%), ICU admission in 3 cases (3.3%), wound infection in 2 cases (2.2%) and postpartum hemorrhage in 1 case only (1.1%). Steiner et al., that analyzed the outcomes in 245 pregnancies with heart diseases, postpartum hemorrhage was reported in 24 cases (9.9%), preeclampsia in 23 cases (9.5%) and pregnancy composites in 80 cases (32.7%) [22].

Magun et al., included 306 pregnant females (median age 29 years) with CVD were seen. The reported maternal outcomes were gestational diabetes in 11.4%, gestational hypertension in 9.5%, and pre-eclampsia in 12.1% of females. In addition, 27 females (8.8%) required ICU admission. One mortality occurred within 12 months after delivery in a female with Eisenmenger syndrome [23]. Out of 90 pregnant females in their study, Salam et al., reported that 4 (4.4%) females died and 9 (9%) females had first trimester abortion [16].

In our study, the adverse neonatal outcomes included IUGR in 4 cases (4.6%), NICU admission in 16 cases (18.4%), neonatal mortality in 5 cases (5.8%) and congenital anomaly in 5 cases (5.8%). The mean GA at delivery was  $37.16 \pm 1.73$  weeks (range= 29 -40 weeks) while the mean birthweight was  $2470.85 \pm 470.76$  grams with range between 1000 and 3600 grams. Khanna et al., included 80 patients with heart diseases, abortion was reported in 7 cases (8.7%), intra-uterine fetal death in 1 case only (1.2%), IUGR in 4 cases

(5%), oligohydramnios in 11 cases (13.7%), preterm in 19 cases (23.7%), LBW (<2.5 kg) in 40 cases (50%) and very-low-birth-weight (<1.5 kg) in 3 cases (3.7%) [24]. The adverse neonatal outcomes reported by Steiner and his colleagues included intrauterine Growth Restriction in 19 cases (7.9%), small for Gestational Age in 7 cases (2.9%), neonatal Intensive Care Unit Stay in 60 cases (24.7%) and preterm Birth in 42 cases (17.14%) [22].

Beriye et al., showed that the mean birth weight of newborns was 2640 ( $\pm$ 690) grams (range= 1200 - 3900 grams). Eleven (39.3%) newborns were admitted to NICU with diagnosis. Ten (35.7%) neonates were LBW. Seven (25%) neonates were SGA having mean weight of 1921( $\pm$ 565) grams. Nine (32.1%) neonates had low fifth minute APGAR score [17].

Salam et al., among all newborns born alive none had CHD. There were 77 (85.6%) live births observed in these females. In addition, 56 (72.8%) weighted > 2 Kgs [16]. Priya et al. demonstrated that half of neonates had a birth weight between 2.5 and 3.5 kg. However about 30% of newborns were of LBW (<2.5 kg). Authors suggested that heart disease itself could be a risk factor for LBW [25].

In this study, a significant relationship existed between non-rheumatic heart diseases and occurrence of adverse maternal outcomes. The incidence of ICU admission and puerperal pyrexia was statistically significantly higher among the cases of this group. Liu et al., showed that pregnancies with CHD were associated with longer hospital stay, more frequent hospitalizations, more cost, greater mortality rates, as well as higher likelihood of adverse outcomes compared to pregnancies without CHD [26].

In our study, the incidence of unwanted neonatal outcomes was statistically significantly greater in the cases with non-rheumatic heart diseases. The 1- and 5-minutes APAR scores were significantly lower in the

cases with non-rheumatic heart diseases. The birth weight of the neonates was significantly lower in non-rheumatic heart diseases cases. Moreover, NICU admission and presence of congenital anomalies in the neonates was statistically significantly higher in this group. Liu et al., who showed that newborns born to mothers with CHD had more likelihood to be a pre-term or a LBW neonate. Furthermore, they have more likelihood to have a growth restriction because of the drugs administered by the mother [26]. This was in accordance with who showed that neonatal complications likely followed a pattern comparable to maternal and obstetrical outcomes. Complications were highest in the neonates born to mothers with cardiomyopathies and pulmonary hypertension and lower in RHD mothers [27].

This study has some limitations, mainly the small sample size included and being a single center study. Also, the lack of the control group limit the power of the obtained results as it didn't actually reflect the burden or the magnitude of the condition.

## **CONCLUSION**

We concluded that heart diseases in mothers are not absolute contraindications for pregnancy, but there were associated with serious outcomes on both the mothers and offsprings. The non-rheumatic heart diseases (mainly the congenital heart diseases) are associated with worse outcomes as compared to the mothers with rheumatic heart diseases.

**Conflict of interest:** None.

**Funding:** This research didn't receive any specialized grant from funding agencies.

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# Factors affecting surgery-related decline in ovarian reserve in women with endometriomas

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## Abstract

**Background:** Endometriosis is a main cause of female infertility. Surgical treatment of ovarian endometriomas raised great concerns about future fertility and the possible decline in ovarian reserve.

**Objective:** Evaluate factors associated with the decline in ovarian reserve after surgical excision of the endometriomas.

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**Study design:** This cross-sectional study was conducted in tertiary hospital from 1/11/2020 to 31/7/2022. We recruited eligible patients during the study duration according to predetermined inclusion and exclusion criteria. Eligible patients were subjected to ultrasound examination to diagnose ovarian endometrioma, its diameter, and the AFC of the affected. The AMH was also withdrawn. Patients were prepared for laparoscopic cystectomy. After three months, patients were subjected to reevaluation, including recurrence of the cyst, AFC, AMH levels, and patient satisfaction using the endometriosis treatment satisfaction questionnaire.

**Results:** Sixty patients were recruited throughout the study duration. The mean age was  $30.33 \pm 7.95$ . The recurrence rate was 19/60 (31.7%). There was a significant reduction in the cyst diameter, AFC, and AMH after surgical excision (p-value  $<0.001$ ). Only preoperative AFC and AMH levels were significant predictors for each marker individually (p $<0.001$ ). There was a significant increase in all domains of the endometriosis treatment satisfaction questionnaire and the total score (p-value  $<0.001$ ).

**Conclusion:** Surgical removal of endometriomas was associated with a significant decline in ovarian reserve. The decline in AFC and AMH was independent of other patient-related factors but for preoperative AMH, which affected post-operative AMH levels significantly.

**Keywords:** Ovarian reserve; Endometriosis; Surgery; Predictors; Satisfaction.

### **Introduction:**

Endometrioma is a cystic lesion in the ovary developed due to the presence of ectopic endometrial cells. It occurs in 17-44% of patients with endometriosis (1). Different management options are available, with surgical excision representing the mainstay treatment (2). However, several concerns

were raised about the deleterious effect of surgical excision on ovarian reserve. This was rendered to the concomitant removal of healthy ovarian tissue (3). The ovarian reserve is a reflection of the reproductive capacity of women (4). Its markers included antral follicle count (AFC) and anti-mullerian hormone (AMH) (5). Endometriomas result in decreased ovarian reserve due to inadequate blood supply caused by the pressure effect of the endometriomas on the capsule and the local inflammatory reaction destroying the follicles (6). The AFC, although reliable, has some limitations as inter-cycle variation and the difficulty in obtaining accurate results because of the presence of endometriomas (7). The AMH is a reliable one without the limitations above (8). It has been noted that endometriomas managed conservatively lead to decreased ovarian reserve, and surgical excision leads to further decline (9). Other factors implicated in reducing ovarian reserve included age, size of the endometrioma, removal of ovarian tissue, the surgeon's expertise, and the endometrioma's site (3, 10, 11). Accordingly, this study was conducted to evaluate possible factors associated with reducing the ovarian reserve in women undergoing surgical excision of ovarian endometriomas.

### **Methods**

This cross-sectional study was conducted in the obstetrics and gynecology department at a tertiary hospital from 1/11/2020 to 31/7/2022. We recruited eligible patients during the study duration according to predetermined inclusion and exclusion criteria. Inclusion criteria: a) unilateral endometrioma, b) unilocular endometrioma of any size, c) age 18-45 years, d) regular cycles, e) no previous history of ovarian operations, and f) patients undergoing surgical excision of the endometrioma by laparoscopy. Exclusion criteria: a) suspected or confirmed malignancy, b) women within two years of menarche, c) women on progesterone only

or combined hormonal contraception, d) women refusing to participate in the study, and f) women preferring medication for the management of endometriomas.

After a detailed explanation of the study's aim and procedure, informed consent was obtained from all eligible study participants. Eligible patients were subjected to the following:

1. Complete personal and medical history.
2. Ultrasound examination, either transabdominal for virgins or transvaginal for sexually active women, to diagnose ovarian endometrioma. It was diagnosed as a unilocular cystic lesion with a ground glass echogenicity of the fluid and a regular thick wall (12). The AFC was evaluated on days 2-3 of the cycle by determining the number of follicles measuring 2-10 mm (13). The AFC of the affected ovary was considered for pre- and post-therapy evaluation.
3. Routine preoperative laboratory investigations such as complete blood count, coagulation profile, and liver function test was withdrawn. The AMH was also withdrawn.
4. Patients were prepared for laparoscopic cystectomy. Bipolar cauterization was used to achieve hemostasis.
5. After three months, patients were subjected to reevaluation, including recurrence of the cyst, AFC, and AMH levels.
6. Patient satisfaction was evaluated after intervention using an endometriosis treatment satisfaction questionnaire. The questionnaire included six questions that evaluated patient satisfaction after surgical excision of the endometrioma regarding endometriosis-related pain before or during periods, during or after sexual activity, endometriosis-related pain, any bleeding or spotting, tolerability, and overall satisfaction. Each question

has seven scales to answer, ranging from extremely satisfied to extremely dissatisfied, with scores of 6 to 0. A higher score indicates a more remarkable improvement (14).

### **Ethical approval**

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

### **Statistical analysis**

Data were statistically described as mean and standard deviation, frequencies (number of cases), and percentages when appropriate. P values of less than 0.05 were considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA), release 23 for Microsoft Windows. Wilcoxon Wallis test was used to evaluate the difference between ovarian reserve markers before and after surgery.

### **Results**

Sixty patients were recruited throughout the study duration. The mean age was  $30.33 \pm 7.95$ . The study population was either virgins or married/divorced/widowed equally. The mean parity of the married/divorced/widowed patients was  $1.27 \pm 0.69$  (**Table 1**).

The recurrence rate after excision was 12/60 (20%). There was a significant reduction in the cyst diameter, AFC, and AMH after surgical excision ( $p$ -value  $<0.001$ ) (**Table 2**).

Age, parity, history of infertility, and endometrioma diameter did not affect the ovarian reserve after cystectomy. Only preoperative AFC and AMH levels were significant predictors for each marker individually ( $p < 0.001$ ) (**Table 3**).

There was a significant increase in all

domains of the endometriosis treatment satisfaction questionnaire as well as the total score (p-value <0.001) (Table 4).

## **Discussion**

Surgical excision of ovarian endometriomas is cornerstone management; however, the decline in ovarian reserve represented a challenge. Variable methods were reported as fenestration and irrigation, cyst wall ablation, cystectomy, and other methods in combination (15). The current study evaluated possible factors contributing to the decline in ovarian reserve after cystectomy.

The mean age of the recruited patients was  $30.33 \pm 7.95$ . This was similar to previous results (16, 17), as endometriomas affect women in their childbearing years (18). After surgical excision, recurrence was noted in 20% of the participants. The recurrence rate after endometrioma excision was reported to be high. It ranged from 29-56% after 2 years while after 5 years it was 43% (19) without post-operative medical treatment. Another study reported a recurrence rate of 6.4% (20). The current study provided no medical treatment after surgery, while the follow-up period was only three months. Immune cells and extracellular matrix metalloproteinase lead to the proliferation and survival of endometriotic cells, explaining recurrent endometriosis (21).

There was a significant decline in the AFC and AMH levels after surgical excision. A meta-analysis reported no change in the AFC after cystectomy. However, the detailed analysis reported decreased AFC in the operated ovary than the normal one (22). This was rendered to compression of the ovarian capsule by the endometrioma leading to underestimation of the AFC (23), limiting its reliability in evaluating the ovarian reserve (24). Another reported a significant decline in AMH levels after the excision of unilateral endometriomas (3). Although conflicting results were reported, the eventual

conclusion pointed to AMH reduction (11). An earlier study reported a persistent decline in AMH levels at 1 and 6 months after excision. Although some increase was noted at six months, the results were below those obtained at baseline (25). This was explained by the accidental removal of healthy ovarian tissue during the operation (8).

Age, parity, history of infertility, and endometrioma diameter did not affect the ovarian reserve after cystectomy. Preoperative AMH and AFC were significant predictors for the decline in each marker individually. It has been reported that age and endometrioma size were not related to the decreased AMH levels (3, 11). Another factor that contributed to the decline in AMH was the laterality (8); however, we recruited patients with unilateral endometriomas only. Also, preoperative AMH correlated significantly with the decrease noted postoperatively. Women with increased AMH reported more decline post-operative. This was due to the presence of primordial follicles in large numbers in the ovarian tissue that was removed inadvertently (26, 27). An additional contributing factor is the method of hemostasis used during excision. Hemostasis would be achieved using sutures or bipolar cauterization. The current study depended on bipolar cauterization in all cases. Suturing leads to increased intraovarian pressure and ischemia due to suture tightening, which might affect the ovarian reserve (28). However, bipolar cautery was associated with tremendous damage to ovarian reserve (29, 30).

There was a significant improvement in patients' satisfaction after the operation. There was an improvement in all pain aspects. The mean ETSQ score increased significantly from  $12.65 \pm 3.31$  to  $21.22 \pm 2.93$ . This agreed with previous results, where 42.5% and 45.2% were satisfied and very satisfied with endometriosis treatment at three months (31). Similar results were reported by an earlier one (32). However, the former used gonadotropin-releasing

hormone agonists (GnRHa) and combined oral contraceptives (COC) after the operation in their recruited patients, which might affect pain scores. Also, they reported a minor change in dysmenorrhea, contradicting the current results. This would be due to other pelvic pathologies such as adenomyosis (31). As surgery didn't impact the pathogenesis of endometriosis, recurrent symptoms were the cause of declining satisfaction at 12 months (32).

### **Strength and limitations**

This study adopted a fixed technique for endometrioma removal performed by the same surgical team. Follow-up was for three months only. When possible, we resected pelvic endometriotic lesions, which might affect the pain scores. Dyspareunia scores were excluded among non-sexually active participants to avoid bias.

### **Conclusion**

Surgical removal of endometriomas was associated with a significant decline in ovarian reserve. The decline in AFC and AMH was independent of other patient-related factors but for preoperative AMH, which affected post-operative AMH levels significantly. Patients were satisfied after the intervention.

**Conflict of interest:** None.

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**Table 1: Basic demographic data of the studied population (N= 60)**

Age (years) (Mean ± SD)		30.33 ± 7.95
Occupation N (%)	Not working	29 (48.33%)
	Working	31 (51.67%)
Residence N (%)	Urban	28 (46.67%)
	Rural	32 (53.33%)
Marital status N (%)	Virgin	30 (50%)
	Married/Divorced/Widowed	30 (50%)
Parity (Mean ± SD)		1.27 ± 0.69

**Table 2: Comparison of the ovarian reserve before and after intervention**

Group	Before	After	P-value
Cyst diameter (cm) (Mean ± SD)	5.39 ± 1.62	0.4 ± 0.7	<0.001a
Anti-Mullerian hormone (ng/ml) (Mean ± SD)	1.77 ± 0.4	1.52 ± 0.43	<0.001a
Antral follicular count (Mean ± SD)	5.33 ± 2.13	3.4 ± 1.63	<0.001a

<sup>a</sup>Wilcoxon Wallis test

**Table 3: Factors affecting the ovarian reserve after surgical excision.**

<b>AFC</b>			
	<b>Beta</b>	<b>95% confidence interval</b>	<b>P value</b>
<b>Constant</b>	3.612	-0.121- 7.346	0.057
<b>Age</b>	0.013	-0.082- 0.108	0.783
<b>Parity</b>	0.180	-0.860- 1.221	0.724
<b>Infertility</b>	-0.313	-1.694- 1.068	0.645
<b>Endometrioma diameter</b>	-0.190	-0.639- 0.258	0.390
<b>AFC (preoperative)</b>	0.546	0.405- 0.687	<0.001
<b>AMH</b>			
<b>Constant</b>	1.186	0.227- 2.144	0.017
<b>Age</b>	-0.001	-0.026- 0.023	0.921
<b>Parity</b>	0.105	-0.163- 0.372	0.428
<b>Infertility</b>	0.158	-0.197- 0.512	0.368
<b>Endometrioma diameter</b>	0.039	-0.076- 0.154	0.488
<b>AMH (preoperative)</b>	-0.139	0.937- 1.109	<0.001

**Table 4: Patient satisfaction after surgical excision of the endometrioma**

<b>Variable</b>	<b>PRE</b>	<b>POST</b>	<b>P value</b>
<b>Endometriosis-related pain before or during periods</b>	1.93 ± 1.23	3.43 ± 1.13	<0.001a
<b>Endometriosis-related pain during or after sexual activity</b>	2.03 ± 1.46	3.43 ± 1.2	<0.001a
<b>Endometriosis related pain</b>	2.33 ± 1.37	3.68 ± 1.14	<0.001a
<b>Any bleeding or spotting</b>	2.13 ± 1.37	3.8 ± 1.2	<0.001a
<b>Tolerability</b>	1.88 ± 1.37	3.33 ± 1.05	<0.001a
<b>Overall satisfaction</b>	2.33 ± 1.4	3.53 ± 1.19	<0.001a
<b>ETSQ total score</b>	12.65 ± 3.31	21.22 ± 2.93	<0.001b

<sup>a</sup> Wilcoxon Wallis test, <sup>b</sup> Paired sample t-test.

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# Efficacy and Safety of Transversus Abdominis Plane Block and Patient-Controlled Analgesia for Pain Relief after Cesarean Delivery

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## Running Title

Transversus Abdominis Plane Block, Patient-Controlled  
Analgesia

**Funding:** No

**Conflict of interest:** No

## Abstract

**Objectives:** The target of this research is to assess the efficiency of intravenous patient-controlled analgesia in comparison to ultrasound-guided TAP block in the first twenty-four hours after cesarean surgery in pregnant women who have had cesarean section.

**Background:** However, women's happiness continues to be an issue, despite the fact that pain treatment after cesarean section birth is highly crucial. It is helpful to identify the most appropriate analgesic method, medications, & dosage, as well as to provide effective therapy for postoperative pain, when the pain intensity of post-cesarean delivery is appropriately assessed.

**Methods:** A cross-sectional research has been conducted on 84 women at Faculty of Medicine, Menoufia university hospitals and Berket El-Saba General Hospital, who were admitted for delivery by elective cesarean Section.

Individuals were separated into two groups: "group I" (n = 42) consisted of women who were given TAP block, & "group II" (n = 42) consisted of women who were given PCA.

**Results:** Following the operation, the patient's heart rate, respiration rate, pain score, intestinal motility, nausea, & vomiting were evaluated at 2, 4, 6, 12, & 24 hours after the procedure. The "patient-controlled analgesia group" had a considerably lower level of pain compared to the "TAP group" (p value of 0.009 at 2 hours postoperative & 0.031 at 4 hours; respectively). In addition, women who were in the "patient-controlled analgesia group" had substantially greater levels of nausea & vomiting compared to those who were in the "TAP group" (p value = 0.007). It was more noticeable in the "TAP group" than in the "PCA

category" when it came to the motility of the digestive tract.

Regarding duration of analgesia, time of first analgesia, and time of first ambulation were significantly lower in TAP block collection compared to PCA collection.

**Conclusions:** transversus abdominis plane block was favored because it prevented the systemic impact of opioids that were utilized in Patient Controlled Analgesia. Patient Controlled Analgesia was better than TAP block since it covered visceral discomfort. In addition, Patient Controlled Analgesia may be administered without much difficulty, while transversus abdominis plane block requires further training as well as an intraoperative ultrasound equipment. When modifying the dosages, there were very few complications & adverse effects associated with any of the two.

**Keywords:** Transversus abdominis plane block, CS, PCA, Ultrasound guided analgesia, Pain score.

## **Introduction**

There has been a significant increase in the number of cesarean deliveries all across the globe, involving in Egypt, according to most recent research. [1]

Throughout the first forty-eight hours after surgery, a cesarean section that is not complex may, in most cases, cause moderate to severe pain. [2]

As a result, pain management is essential since it has an impact on the mother as well as the care that she provides for the infant. Women having cesarean birth have extra strong reasons to obtain appropriate pain treatment as early mobilization constitutes a crucial component that minimizes the risk of thrombo-embolic illness which is known to be elevated during puerperium & pregnancy. [3]

Controlling postoperative pain may be accomplished via a wide variety of approaches. On the other hand, the hunt

for the most effective approach is still underway. Several different procedures have been implemented. In spite of this, the most effective method of administering opioids is still the use of several routes. [4]

During a cesarean delivery, the TAP block is a viable main analgesic that may be utilized for women who are not getting neuraxial morphine for whatever reason. This is a possibility. One kind of thoracolumbar nerve field block is known as the TAP block. This type of block is carried out in the fascial plane, which means that it is carried out across the transversus abdominis muscles & the internal oblique muscular group. Around the midaxillary line, the anterior major rami divides into the lateral and anterior dermal nerves. It has a path that runs amongst the transversus abdominis muscles & the internal oblique. They are the nerves that are in charge of the surface of the skin. [5]

IV patient-controlled analgesia, often known as PCA, is now being used extensively in the field of post-cesarean pain management. The objective of utilising patient-controlled analgesia is to successfully manage pain at a dosage & schedule that is desired. Providing individuals with the ability to deliver a predefined bolus amount of medicine on demand is one way to accomplish this goal. It was possible to deliver each bolus, either on its own or in conjunction with another drug. Opioids & local anesthetics are probably the two types of analgesics that are used the most often, however there are additional options available. [6]

We wanted to determine whether or not an ultrasound-assisted TAP block or an intravenous PCA was more effective in providing pain relief in the first twenty-four hours after a cesarean section in patient women. Postoperative pain at 2, 4, 6, 12, & 24 hours was the major outcome examined in this study. Intestinal mobility, nausea, early mobilization, heart rate, vomiting, & respiration rate were those that were considered secondary results.

## **Methods**

A cross-sectional research has been conducted on 84 women at Faculty of Medicine, Menoufia university hospitals and Berket El-Saba General Hospital, who were admitted for delivery by elective cesarean section.

An approval was obtained from Ethics Committee in Menoufia University Hospital and Berket El-Saba Hospital.

Randomization was used to divide individuals into 2 categories. according to a sequence generated computerized software program with a ratio 1 : 1. This sequence was distributed consequently in numbered envelopes

**Group I (TAP-block):** included 42 patient utilising ultrasound guided transversus abdominis plane (USG-TAP) block procedure. **Group II (PCA):** involved 42 individuals utilising patient-controlled analgesia procedure.

**Inclusion criteria:** Singleton pregnant women aged from twenty to thirty five years, Pregnant at thirty seven to fourty two weeks, with body mass index 25–35 kg/m<sup>2</sup> and hemoglobin level above 10 g/dl undergoing elective cesarean section.

**Exclusion criteria:** Uncooperative patients with multiple gestation, BMI more than 35 kg/m<sup>2</sup>, or having chorioamnionitis, or hypersensitivity or contraindications to opioids, or high risk pregnancy, or infection at site of injection.

Under the guidelines of the research protocol, each and every participant was asked to provide their written informed consent about the procedure.

Both groups were subjected to:

An antibiotic prophylaxis 60 minutes at least before skin incision in the form of single-dose intravenous injection of 1gm Cefazoline.

Standard methods were used to monitor them, including pulse oximeter, heart rate,

non-invasive arterial blood pressure, & the duration of cesarean section.

All operations were performed under regional spinal anesthesia.

The transversus abdominis plane block was guided by ultrasonography & performed after the incision had been closed in the collection that received the transversus abdominis plane block. since of this, the injection is completely painless, & the patient would not be able to perceive it since they are still under the influence of spinal anesthetic. In order to accomplish the TAP block, 0.25% bupivacaine was used (25 ml on each side being administered).

Utilizing a sono-sensitive short bevel needle with a gauge of 22 gauge, the approach involves inserting the needle in a sagittal plane around three to four centimeters medial to the ultrasound probe. In order to get a picture of the skin puncture & the superficial course, the probe is moved slightly anteriorly. After that, it is moved progressively posteriorly, following the needle until it reaches the right place in the transverse abdominis plane. By directing the needle point into the plane that is below the internal oblique & above the transversus abdominis muscle, the needle is precisely positioned. A modest amount of local anesthetic, one milliliter, of bupivacaine 0.25% is injected to open the plane among the two muscles. This may be followed by the insertion of the entire dosage of local anesthetic. It is necessary to reposition the needle if the 1 milliliter dosage seems to be somewhere inside the muscle rather than in between the muscles.

**In PCA group:** The PCA system (100 ml disposable infusion pump) was carefully explained to individual before cesarean section & its filled by 40 ml nalbuphine, 30 ml ketorolac, 3 mg granytryl, 2 ampules of ranitidine and completed by normal saline via IV patient-controlled analgesia device. The patient-controlled analgesia pump was programmed to have a basal infusion rate

of 2 milliliters per hour, a loading dose of 2 milliliters, a bolus of 2 milliliters, & a lockout interval of ten minutes.

After surgery: Visual analogue scale from 1 to ten was recorded by a blinded investigator at 2, 4, 8, 12, 24 hours during rest and during mobilization.

All women were received 1gm of paracetamol orally every 8 hours.

The rescue pain analgesia was given postoperatively in the form of Nalufin 4mg bolus IV (if VAS pain score is 4 or more) given upon patient request.

### **Statistical analysis**

A table of the collated data was created using Microsoft Excel®. The SPSS (Statistical Package for the Social Sciences) version 28 (IBM Inc., Chicago, IL, USA) was utilized to conduct the statistical analysis. The Shapiro-Wilk test was employed to examine the variables' distribution pattern.

#### **I- Descriptive**

1. The mean value & standard deviation ( $X \pm SD$ ) are used to analyze quantitative data that follows a normal distribution.
2. For quantitative data that is not regularly distributed, the median & the interquartile range (median (interquartile 25 – 75)) are used.
3. Frequency & percentage for qualitative data.

#### **II- Analytic: which include the following tests:**

- Chi-square test of independence ( $\chi^2$ ): Used to evaluate whether there is a substantial variance amongst qualitative data.
- Independent t-test: Used to evaluate whether there is a substantial variance amongst normally distributed quantitative data.

- Mann-Whitney U test: Used to assess whether there is a significant difference between non-normally distributed quantitative data.
- P value: P-value set at 0.05 where P value < 0.05 was considered statistically substantial.

### **Results**

Age, BMI, GA, and parity were not significantly different across the groups that were investigated.

The length of time that each of the groups under study underwent surgery did not vary significantly from one another, but duration of analgesia, time of first analgesia, and time of first ambulation were significantly lower in TAP block group compared to PCA group with P value less than 0.05. [Table1]

The Visual analogue scale score was significantly higher in TAP block group at 2 and 4 hours after operation compared to PCA group. The P value was 0.009 at 2h and 0.031 at 4h which was significant, but was observed no substantial variance amongst the groups at 8, 12, and 24 hours after the operation.

Was observed no substantial variance in the number of patients with local anesthesia complications between the studied groups. The number of patients who suffered from nausea & vomiting was significantly higher in PCA group compared to TAP block group.

### **Discussion**

With the goal of reducing the likelihood of death & disability, surgical procedures & anesthesia are considered to be essential components of medical treatment. In addition, the use of anaesthetics helps to lessen the instances of acute pain that occur during & soon after surgical procedures. [7]

When compared to systemic opioids, the

peripheral regional analgesic approach may give improved analgesia & avoid unwanted side effects. The method can be administered as a single or continuous infusion.

After receiving a comprehensive description of the procedures, as well as the benefits & drawbacks of each methodology, the ladies who participated in our research agreed with both applications. One of the pain scales that is utilized in medicine the most often is the VAS. As the best response scale, it is strongly recommended for use in evaluating pain in people who do not have cognitive impairment. [8]

Even though the VAS (which is used for assessing pain) revealed a reduction in the degree of pain feeling in both groups within the first twenty-four hours after surgery, the VAS values were much lower in the patient-controlled analgesia group than they were in the transversus abdominis plane block group. This was shown by the aforementioned research.

The TAP block was reviewed & compared to normal or control practice for the purpose of providing immediate pain relief after CS in a meta-analysis that was carried out by Champaneria (2016). The research came to the conclusion that TAP block was more effective than patient-controlled analgesia. This means that TAP block considerably reduces pain at rest when compared with placebo or with no transversus abdominis plane block at all. [9]

According to the findings of a meta-analysis conducted by Mishriky, post-cesarean TAP block is related with decreased pain levels both at rest (six & twelve hours) & with movement (six & twelve hours). [16] According to the information that is now available, the transversus abdominis plane block seems to be useful for postoperative analgesia. The investigations came to the conclusion that transversus abdominis plane block eliminates the need for opioids & has the potential to decrease pain ratings during

the first twelve hours after cesarean section . [10]

In 2018, Ng conducted a meta-analysis to compare the effectiveness of a high dosage of TAP block to that of a modest dose that was administered. As a consequence of their meta-analysis, the researchers found that both collections (low-dose & high-dose categories) had comparable effects in terms of postoperative analgesia & opioid-sparing (opioid intake, time-to-first request, & 24-hour pain levels). As a consequence of this, it was eventually determined that there would be no further benefit associated with the use of local anesthetics over a certain dose threshold. In addition, low-dose techniques for post-cesarean transversus abdominis plane block have the potential to lessen the likelihood of local anesthetic toxicity while yet preserving the effectiveness of the analgesic agents. [11] According to the findings that we obtained, this is consistent.

According to the findings of our research, nalbuphine was selected as an alternative to morphine in order to mitigate the well-known adverse effects of morphine, which include respiratory depression, itching, & postoperative nausea & vomiting. On the contrary, nalbuphine, which is both a  $\mu$  antagonist and a  $k$  agonist, exhibits a ceiling effect in its respiratory depression. As a result, it is regarded as a safer alternative to morphine. When compared to morphine, the occurrence of side effects such as pruritis & PONV during treatment with nalbuphine is much reduced. [12] During the postoperative phase, Yeh studied individuals who had undergone open gynecological procedures & utilized various combinations of morphine & nalbuphine. He discovered that there was no variation in the amount of PCA that was required. [13]

It is possible that the systemic impact of the combined medicines of PCA, which influence visceral pain, is the reason why PCA is better than TAP block in terms of pain relief after CS & patient satisfaction. This is in contrast

to transversus abdominis plane block, which only operates on somatic pain in the anterior abdominal wall during the procedure.

On the other hand, Erbabacan came to the conclusion that, in instances when lower abdominal procedures are being performed, 30 milliliters of transversus abdominis plane block is just as effective as intravenous patient-controlled analgesia in terms of pain relief. In addition, when intravenous patient-controlled analgesia was compared to TAP block, it was found that TAP block was considered to be a more superior method. This was due to the fact that it was able to avoid the systemic effects of morphine, which was utilized for PCA, & because its analgesic impact began sooner. [14] It is However, this research was conducted on lower abdominal procedures rather than cesarean sections, which do not take into account the discomfort that is associated with post-operative uterine contractions.

In contrast to the findings that we obtained, a research that was carried out by Erbabacan revealed that the values of heart rate were discovered to be considerably lower in the transversus abdominis plane block group compared to the patient-controlled analgesia collection. According to the findings of our research, there was no discernible variation in heart rate amongst the groups that were evaluated at the beginning of the investigation, five, ten, thirty, & forty minutes after the operation.

The results of our investigation showed that there were no variances between the effects of transversus abdominis plane block & IV patient-controlled analgesia on respiratory rate. This might be attributed to the fact that both groups reported experiencing modest levels of discomfort. In terms of nausea & vomiting, it was discovered that the women who were in the "PCA group" experienced much more of them than those who were in the "TAP block group" (Table 2). Reductions in postoperative nausea & vomiting, as well as antiemetic needs, have been reported.

This difference may be due to the dosage of nalbuphine that was administered to the PCA group.

While Siddiqui performed a meta-analysis to analyze the therapeutic efficacy of transversus abdominis plane block on nausea alone, he discovered that there was no significant decrease in nausea score. This finding contradicts the findings that we obtained at the time. Nevertheless, this might be because of the various dosages that were administered. [15]

Similarly, Mäkelä conducted an investigation on 205 individuals & analyzed oxycodone, which has an emetic effect. The researchers came to the conclusion that individuals who received intravenous PCA reported higher nausea after 4 hours & more vomiting at 8 hours ( $p = 0.001$  and  $p = 0.01$ , respectively) [16]

However, we are able to explain this discrepancy through utilizing different dosages than we used in our research. Those investigations did not concur with our findings. Auscultation with a stethoscope was performed at intervals of 2, 6, & 24 hours in order to assess the motility of the digestive tract. In the "TAP block group," it was heard sooner than in the "PCA group," according to the observations. PCA medications have a systemic impact, which might be the cause of this phenomenon. The authors of the Cochrane study, Charoenkwan and Matovinovic, came to the conclusion that early postoperative eating is safe & facilitates speedier recovery of bowel function, a shorter hospital stay, & greater levels of satisfaction following major gynecological surgery. [17]

In terms of the early mobilization of women in the groups that were tested, PCA had a role in delaying patient mobilization owing to its sedative impact. This was in comparison to patients who received TAP block. According to the findings of Mäkelä, the average amount of time required for mobilization was seventeen hours, which was far higher than the six-hour guideline [16]

As a result of the main mechanism of the treatment and the pharmaceuticals that are used, it has been stated that the PCA technique is associated with a number of difficulties and typical adverse effects. Among the most prevalent difficulties associated with PCA pumps are the failure to employ anti-reflux valves, pumps that "run away," patient-controlled analgesia via proxy, poor syringe positioning, & machine manipulation. [18]

TAP block in cesarean birth is effective as a main means of analgesia in women who are not receiving neuraxial morphine for any reason. However, as a result of anatomical changes that occur after cesarean delivery, it may be difficult to execute the TAP block after the delivery. Nevertheless, the ultrasonographic anatomy is indicated as the optimal solution to this difficulty in order to conduct the block. This is true even after the cesarean birth. Visceral analgesia was not provided by the TAP block, which was the primary disadvantage of this technique. As a consequence of this, it is possible that this is the reason why several studies were unable to convincingly establish that TAP block is superior to alternative options.

During our review of the relevant literature, we came to the realization that the bulk of the studies that were conducted on both methodologies had been conducted on surgical procedures other than cesarean sections. We have high hopes that our study will open the way for more research on this subject, especially in light of the significant increase in the number of women who have cesarean sections & the increasing need for procedures that are painless.

### **Conclusion**

Because of its usefulness in alleviating pain after surgery, TAP block and IV PCA were both subjected to research. On the other hand, intravenous PCA was preferable than transversus abdominis plane block because it covered visceral pain, but

transversus abdominis plane block was favored since it avoided the systemic impact of opioids that were employed in patient-controlled analgesia. Additionally, patient-controlled analgesia could be done without much difficulty, while TAP block required additional training as well as an intraoperative ultrasound equipment. When changing the amounts of the medications that were utilized in both procedures, there were very few complications and adverse effects of either sort.

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**Table 1**

	<b>TAP block group (n =42)</b>	<b>PCA group (n =42)</b>	<b>Statistical test</b>	<b>P value</b>
<b>Duration of surgery (mins)</b> Mean $\pm$ SD Range	45.5 $\pm$ 7.9 35 - 60	45.5 $\pm$ 7.9 35 - 60	t =2.61	<b>0.011*</b>
<b>Duration of analgesia (mins)</b> Mean $\pm$ SD Range	843 $\pm$ 317 400 - 1440	1172 $\pm$ 208 480 - 1440	t =5.6	<b>&lt;0.001*</b>
<b>Need for rescue analgesia</b> Yes No	17 (40.5%) 25 (59.5%)	8 (19.0%) 34 (81.0%)	$\chi^2$ =4.56	<b>0.033*</b>
<b>Time of first analgesia (hours)</b> Mean $\pm$ SD Range	10.4 $\pm$ 2.4 7 - 15	15.2 $\pm$ 3.1 8 - 18	t =4.3	<b>&lt;0.001*</b>
<b>Time of first ambulation (hours)</b> Mean $\pm$ SD Range	5.4 $\pm$ 1.2 4 - 8.5	6 $\pm$ 1.3 4 - 8.5	t =-2.12	<b>0.037*</b>

**Table 2**

	<b>TAP block group (n =42)</b>	<b>PCA group (n =42)</b>	<b>Statistical test</b>	<b>P value</b>
<b>VAS at 2h</b> Median (IQR) Range	1 (0 - 1) 0 - 2	0 (0 - 1) 0 - 1	<b>U =626</b>	<b>0.009*</b>
<b>VAS at 4h</b> Median (IQR) Range	2 (1 - 3) 1 - 5	1 (0 - 2) 0 - 4	<b>U =649</b>	<b>0.031*</b>
<b>VAS at 8h</b> Median (IQR) Range	2 (2 - 3) 1 - 5	2 (1 - 3) 0 - 4	<b>U =704</b>	0.1
<b>VAS at 12h</b> Median (IQR) Range	1 (0 - 2) 0 - 3	0 (0 - 2) 0 - 4	<b>U =813</b>	0.507
<b>VAS at 24h</b> Median (IQR) Range	1 (0 - 1) 0 - 2	0 (0 - 1) 0 - 2	<b>U =739</b>	0.160

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# Clinical and ultrasonographic predictors of maternal morbidities in patients with placenta accreta spectrum

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## **Abstract**

**Background :** The incidence of placenta accreta has been markedly increased. Patients with this condition are exposed to many complications, including massive blood loss, hysterectomy and postpartum haemorrhage.

**Aim :** To predict maternal morbidities related to placenta accreta spectrum (PAS) using clinical and ultrasonographic criteria so proper preoperative preparation and counselling can be done.

**Patients and methods:** This study analysed 106 patients diagnosed by ultrasonography as having PAS and confirmed intraoperatively according to FIGO criteria. Planned caesarean sections were done, and the amount of blood loss was calculated. Patients were considered to have massive bleeding if the estimated blood loss was 2500 cc or more. The patients with hysterectomy, bladder injury, and postpartum haemorrhage were identified, and the association with clinical and sonographic signs were analyzed.

**Results:** In our study, some ultrasonographic signs such as placenta previa complete centralis, lacunae grading and bridging vessels were associated with massive intraoperative bleeding with Odds ratio 1.47 95% CI (1.35-1.75) (p=0.014) for lacunae grade 2 and 1.26 95% CI (1.07-1.61) (p=0.048) for bridging vessels. However, none of them was an independent predictor for massive intraoperative blood loss in regression analysis. The risk of hysterectomy was increased in patients with lacunae grade 3 (p <0.001), while the risk for bladder injury was significantly increased with bridging vessels

( p=0.048). None of the clinical characteristics have a relation to maternal morbidities.

**Conclusion:** None of the patient,s clinical characteristics statistically linked to maternal morbidities. The ultrasonographic signs of PAS could allow the prediction of maternal complications.

**Key words:** placenta accreta, intraoperative bleeding, hysterectomy, ultrasound color Doppler.

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## **Introduction**

Placenta accreta spectrum syndrome (PAS) represents a significant health problem; the complications include massive maternal bleeding, shock, hysterectomy and even maternal death <sup>(1,2)</sup>.

The increased incidence could be attributed to the markedly increased caesarean section rate in addition to previous uterine surgery, IVF pregnancy, and advanced maternal age <sup>(3,4)</sup>.

Accurate preoperative evaluation is essential to predict and manage the expected complications. Ultrasound is the most widely used tool for prenatal diagnosis. It depends on typical sonographic findings with two-dimensional (2D) and colour Doppler imaging <sup>(5,6)</sup>.

The ultrasonographic signs suggesting PAS include loss of retroplacental hypoechoic space, placental lacunae, myometrial thinning, bladder wall interruption, and placental bulge (6); when colour Doppler imaging is added to the 2D greyscale, the sensitivity and the negative predictive values were increased to 90% and 95%, respectively. The colour Doppler findings include ureterovesical hypervascularity, sub-placental hypervascularity and bridging vessels <sup>(7,8)</sup>.

It was reported that ultrasonographic signs could predict placental adhesion <sup>(9)</sup>; however, studies that linked ultrasonographic findings to maternal morbidity are limited. Precise antenatal diagnosis could help in planning a proper management <sup>(10)</sup>, thus decreasing maternal morbidity related to that significant health problem. The aim of this study is to evaluate the role of the patient's clinical criteria and ultrasonographic markers of PAS in predicting maternal morbidity.

## **Patient and method**

This prospective study was conducted at Mansoura University Hospital in the period from October 2021 to October 2023

after approval from the ethical committee of the Mansoura Faculty of Medicine (code number MS.21.06.1556).

The study initially included 122 patients with placenta accreta spectrum (PAS). Sixteen of them were excluded as they have other risk factors for bleeding; 12 had emergency caesarean sections for severe antepartum haemorrhage, 3 were twin pregnancies, and 1 had immune thrombocytopenic purpura (ITP). The remaining 106 were confirmed to have PAS by the ultrasonography according to Cali et al. <sup>(6)</sup> and all were confirmed intraoperatively according to FIGO <sup>(11)</sup>. The ultrasonography was done by the same experienced sonographer team. All participants had a history of one or more caesarean sections.

All patients were counselled, the management plan and the possible risks were explained, and informed consent was obtained.

Ultrasonographic examination at 34-36 weeks was done with a semi-full bladder to delineate the bladder-serosa interface. We used a 4.0–6.0-MHz curved transabdominal and 5.0–7.0-MHz transvaginal transducer if needed (Toshiba/Canon Aplio 500 Platinum Ultrasound Machine, Toshiba medical ultrasound, Otawara, Tochigi, Japan). The pulsed rate frequency of the colour Doppler ultrasound was initially set at 1.3 kHz, but it was then lowered to 0.9 kHz to identify the presence of placental lacunar flow. The diagnosis of PAS disorders was based on detecting at least two of the following criteria <sup>(6)</sup>.

- Loss of the retro placental sonolucent zone.
- Interruption of the uterine serosa-bladder wall interface.
- Turbulent placental lacunae with the high-velocity flow.
- The myometrial thickness is less than 1 mm.
- Increased vascularity of the uterine serosa-bladder wall interface.

- Increased vascularity in the parametrial region.

A planned caesarean section was performed for all cases by the same surgical team. The uterine incision was done at a level higher than the expected upper border of the placenta to avoid disturbing the placenta. All patients were intravenously given 100 micrograms of Carbetocin (papal 100 microgram Ferring pharmaceutical) after delivery of the fetus. Delayed cord clamping was done. Bilateral uterine artery ligation, and meticulous dissection of the bladder from the lower uterine segment was done. A Hypogastric artery is ligated when severe haemorrhage occurs. Once the baby was delivered, the suction container and gauze were replaced to avoid parietal blood loss counting and amniotic fluid contamination.

The equation used when calculating blood loss of a blood soaked item is wet weight of the item (in grams) - dry weight of the item (in grams) = milliliters of blood within the item<sup>(12)</sup>.

The volume in the suction apparatus was added to the gauze weight to calculate the total amount of blood loss. Patients were considered to have massive blood loss if the estimated blood loss exceeded 2500 cc<sup>(13)</sup>.

The secondary outcomes were hysterectomy, bladder injury, postpartum haemorrhage and the need for ICU admission.

Univariable and multivariable logistic regression was done to detect the association between the ultrasonographic criteria, patient's clinical characteristics and maternal complications.

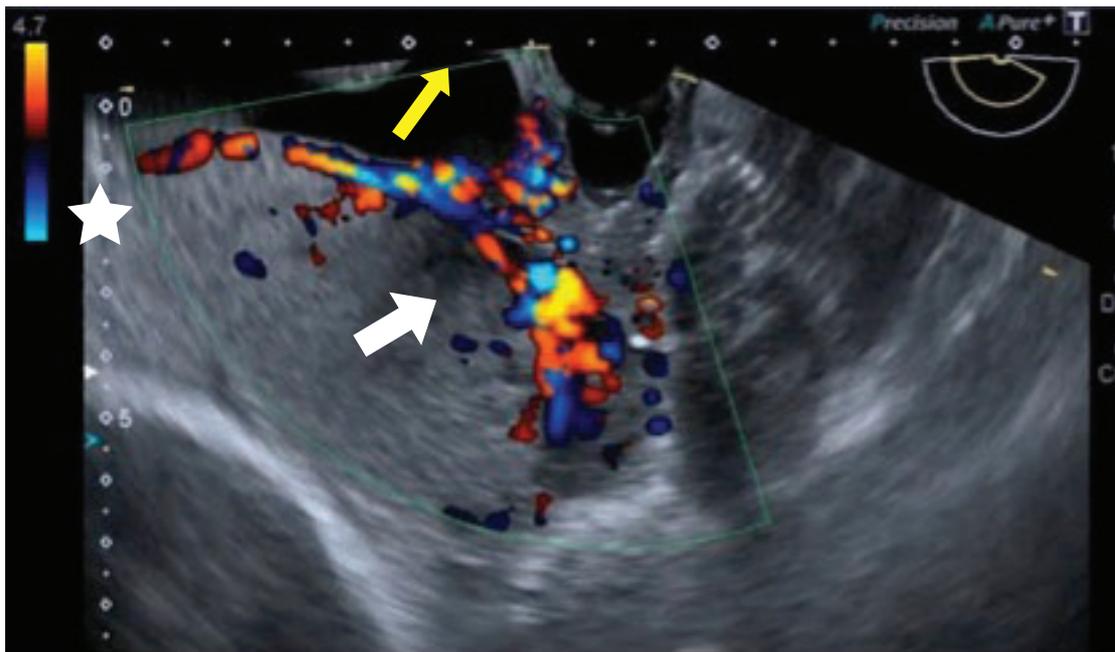


Figure (1): Transabdominal ultrasonographic examination showed retroplacental space hypervascularity (White arrow), placenta is homogenous, low lying (star), bladder (yellow arrow).

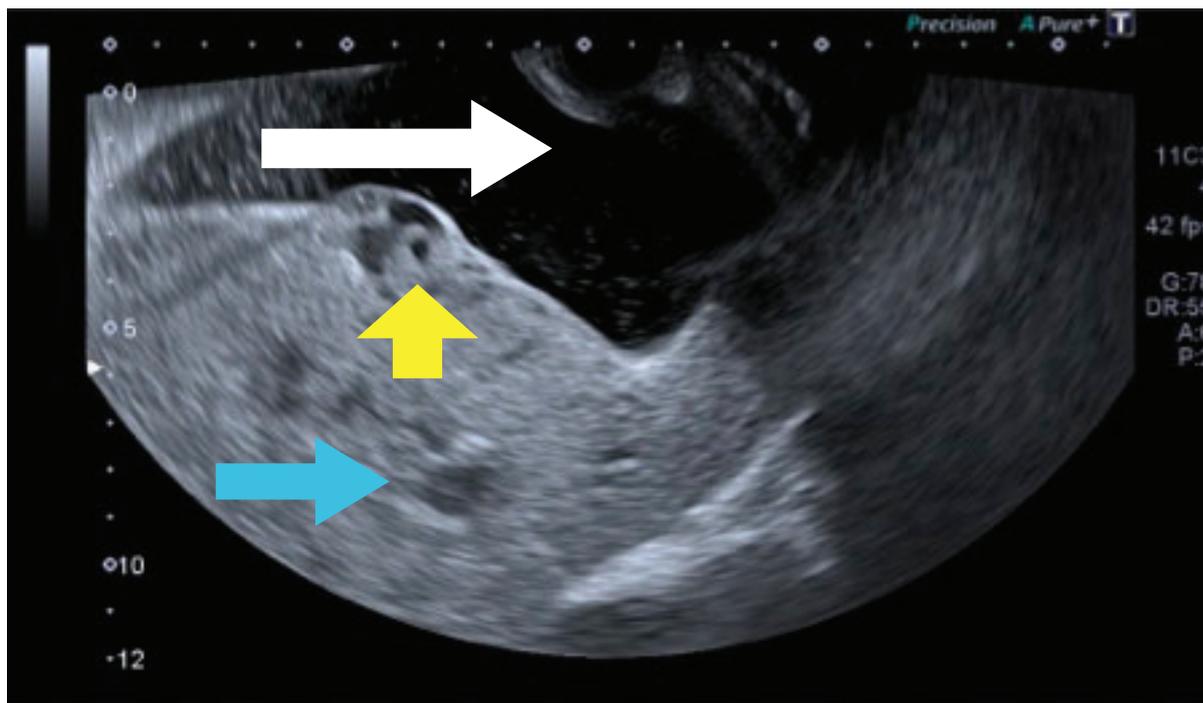


Figure (2): Transabdominal ultrasonographic examination showed focal percreta (yellow arrow), placenta is heterogenous, low lying (blue arrow), bladder (white arrow).

### **Statistical analysis and data interpretation**

Collected data was revised, coded, tabulated and introduced to a P.C. using Statistical Package for Social Science (**IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.**). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter.

### **Normality of data**

The Kolmogorov-Smirnov test was used to test normality. If the significance level is greater than 0.05, then normality is assumed.

### **Descriptive statistics**

- Mean  $\pm$  standard deviation (S.D.) were used for parametric numerical data, while median and range were used for non-parametric numerical data.
- Frequency and percentage were used for non-numerical data.

### **Results**

The patient's clinical data including age, BMI, gravidity, parity and Number of cesarean sections, are shown in table (1). The primary outcome was intraoperative blood loss, while the secondary outcomes were hysterectomy, postpartum haemorrhage, bladder injury and admission to intensive care unit (ICU).

There was no increased risk of intraoperative massive bleeding and other maternal morbidities based on maternal clinical data as shown in Table (2).

The study outcome was 65 / 106 (61.3%) patients had massive blood loss (2500 ml or more), 14 had cesarean hysterectomy, 8 had bladder injury, and 10 cases were admitted to the Intensive care unit (ICU). There are no reported cases of bowel injury or maternal mortality.

Regarding the intraoperative massive blood loss, 70% (46/65) of cases had placenta previa complete centralis, 46% (30/65) had

lacuna grade 3, and 75% (49/65) had bridging vessels. Hysterectomy, ICU admission and bladder injury were more common in complete centralis(92%,80%,75%), respectively, as shown in Table (3).

The presence of bladder invasion was significantly associated with Hysterectomy (p = 0.041), ICU admission (p = 0.015) and bladder injury (p= 0.02). Other variables didn't show significant association, as shown in Table (3)

There is a significant association between post partum haemorrhage and the placenta site (p= 0.008), as well as between hysterectomy and the grades of lacunae (p < 0.001). At the same time, bridging vessels were statistically significant with bladder injury (p = 0.048), as shown in Table (3).

The Odds ratio (OR) for clinical criteria and ultrasonographic signs was calculated by using univariate regression analysis. For massive blood loss; lacunae grade 2 OR 1.47, 95% CI (1.35-1.75) (P= 0.01), and bridging vessel OR 1.26 95% CI (1.07-1.61) (p= 0.04). However, by multivariate regression analysis, none were shown as independent risk factors for massive blood loss, as shown in Table (4)

**Table (1): Demographic data of the cases of the study.**

Variables	Mean ± SD
Age (years)	32.15 ± 5.36
BMI	27.35± 2.8
Gravidity	4.42 ± 1.45
Parity	2.69 ± 0.95
Previous C.S.	2.55 ± 1.03
Blood transfusion units	5.47 ± 2.88

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

Categorical data expressed as Number (%)

**Table (2): Maternal outcome in relation to clinical data**

Clinical data	Maternal outcome				
	Massive blood loss (N= 65)	Hysterectomy (N= 14)	ICU admission (N= 10)	Bladder injury (N= 8)	PPH (N= 8)
Age/years	32.23 ± 5.21	31.71 ± 3.97	32.70 ± 6.73	30.75 ± 4.86	35.38 ± 6.32
Test of significance	t= - 0.192 p = 0.870	t= 0.326 p=0.745	t= - 0.339 p = 0.735	t= 0.768 p= 0.444	t= - 1.789 p= 0.076
Gravidity	4 (2-9)	4 (2-9)	4 (2-6)	3 (2-6)	4 (2-6)
Test of significance	z= - 0.164 p=0.936	z= - 0.380 p= 0.704	z= - 1.965 p= 0.49	z= - 1.410 p= 0.158	z= - 0.148 p= 0.882
Parity	3 (1-5)	3 (1-4)	2 (1-3)	2 (1-4)	3 (1-4)
Test of significance	z= - 0.225 p = 0.822	z= - 0.32 p = 0.895	z= - 1.214 p= 0.225	z= - 1.004 p= 0.315	z= - 0.282 p= 0.778
Test of significance	z= - 0.548 p = 0.584	z = - 0.601 p = 0.548	z= - 1.555 p= 0.120	z= - 1.083 p= 0.279	z= - 0.492 p= 0.623
Previous C.S.	3 (1 - 5)	3 (0 - 4)	2 (1-3)	2 (1-4)	3 (1-4)
Test of significance	z= - 1.202 p = 0.229	z= - 0.127 p= 0.899	z= - 1.109 p= 0.267	z= - 1.465 p= 0.143	z= - 0.651 p= 0.515

Data are presented as mean ± S.D. or median (Range)

t: Independent samples t-test z: Mann Whitney U-test

\*: Statistically significant ( $p \leq 0.05$ )

**Table (3): Maternal outcomes to sonographic criteria.**

	Maternal outcome				
Sonographic criteria	Massive blood loss (N= 65)	Hysterectomy (N= 14)	ICU admission (N= 10)	Bladder injury (N= 8)	PPH (N= 8)
<b>Site of placenta</b>					
PPCC	46 (70.8%)	13 (92.9%)	8 (80%)	6 (75%)	3 (37.5%)
PPMDA	16(24.6%)	0 (0%)	0 (0%)	0 (0%)	3(37.5%)
PPMDP	2 (3.1%)	1 (7.1%)	2 (20%)	2 (25%)	1 (12.5%)
PPM	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)
<b>Test of significance</b>	MC = 3.865 P=0.569	MC = 7.112 P= 0.242	MC=1.695 P= 0.890	MC=1.210 P= 0.944	<b>MC= 15.644 P=0.008*</b>
<b>Grades of lacunae</b>					
<b>Grade 0</b>	0	0	0	0	0
<b>Grade 1</b>	12 (18.5%)	1 (7.1%)	0 (0%)	1 (12.5%)	0 (0%)
<b>Grade 2</b>	23 (35.4%)	1 (7.1%)	4 (40%)	2 (25%)	4 (50%)
<b>Grade 3</b>	30 (46.2%)	12 (85.7%)	6 (60%)	5 (62.5%)	4 (50%)
Test of significance	$\chi^2 = 4.636$ P=0.098	<b>MC = 13.694 P&lt;0.001*</b>	MC=3.959 P= 0.138	MC=1.802 P= 0.406	MC= 3.049 P = 0.218
<b>Bridging vessels</b>	49 (75.4%)	12 (85.7%)	8 (80%)	8 (100 %)	6 (75%)
Test of significance	$\chi^2 = 3.329$ P=0.068	FET = 2.135 P = 0.144	FET=0.638 P = 0.424	<b>FET = 3.912 P= 0.048*</b>	FET = 0.152 P = 0.697
<b>Bladder invasion</b>	20 (30.8 %)	7 (50%)	6 (60%)	5 (62.5%)	3 (37.5%)
Test of significance	$\chi^2 = 0.984$ P=0.321	<b><math>\chi^2 = 4.161</math> P = 0.041*</b>	<b>FET= 5.920 P = 0.015*</b>	<b>FET= 5.377 P = 0.020*</b>	FET = 0.448 P= 0.503

Data are presented as Numbers and per cent within groups

$\chi^2$ : Chi-square test MC: Monte-Carlo test FET: Fischer's exact test\*: Statistically significant ( $p \leq 0.05$ )

PPCC: placenta praevia complete centralis

PPMDA: placenta praevia major degree anterior.

PPMDP: placenta praevia major degree posterior.

PPM: placenta praevia marginalis.

**Table (4): Univariate and multivariate regression analysis for prediction of massive blood loss (n= 65)**

Predictors	Univariate regression				Multivariate regression			
	P value	Odds ratio	95% C.I. for odds ratio		P value	Odds ratio	95% C.I. for odds ratio	
			Lower	Upper			Lower	Upper
Age	<b>0.846</b>	1.240	0.823	1.636				
Gravidity	<b>0.892</b>	0.320	0.032	3.184				
Parity	0.749	1.174	0.622	1.572				
Abortion	0.746	0.609	0.274	1.357				
Previous CS	0.150	0.329	0.095	1.135				
Lacunae grade 2	<b>0.014*</b>	1.472	1.355	1.755	0.214	1.23	0.71	1.46
Lacunae grade 2	0.882	0.716	0.128	1.487				
Bridging vessels	<b>0.048*</b>	1.267	1.073	1.614	0.348	1.245	0.60	1.52
Bladder invasion	0.532	1.254	0.630	1.245				

CI: Confidence interval OR: Odd's ratio

## **Discussion**

Accurate preoperative evaluation of patients with PAS is mandatory to prevent the complications associated with that condition. In this study, we tried to predict the maternal complications related to PAS based on clinical and ultrasonographic findings. We hoped to optimize the delivery environment and explain the risks to the patients during preoperative counselling.

Although the relation between different sonographic signs and placenta accreta are well established, the link between these signs and maternal complications are lacking. Various ultrasonographic signs such as placental lacunae, loss of retroplacental clear zone, myometrial thinning, and interruption of bladder myometrial interface were associated with placenta accreta. The lacunae were the most predictive sign of placenta accreta<sup>(14,15)</sup>.

In our study it was found that ultrasonographic signs such as placenta previa complete centralis, increased lacunae grading and bridging vessels were associated with massive intraoperative bleeding with an Odds ratio of 1.47 for lacunae grade 2 and 1.26 for bridging vessels. However, none of them

was an independent predictor for massive intraoperative blood loss in regression analysis. Hysterectomy was significantly related to lacunae grading and bladder invasion, while bladder injury was related to bridging vessels and bladder invasion.

We used 2 D ultrasonography in combination with color Doppler. Adding colour Doppler to two D ultrasonography increases the diagnostic accuracy of placenta accreta<sup>(7,8)</sup>, and adds a great benefit. It can identify the areas with the highest vascularity, which may be taken in consideration when planning appropriate surgery, such as postponing dissection of these highly vascular areas and early stepwise devascularisation of the uterus, thus reducing intraoperative blood loss.

The clinical findings, including age, parity and Number of previous caesarean sections, although they can increase the grade of PAS, were not statistically significantly associated with maternal morbidities.

A scoring system developed by Chong et al. based on various ultrasonographic signs such as lacunae, retro-placental vascularity and loss of the retroplacental clear zone

among other criteria <sup>(16)</sup>. They discovered that higher scores were associated with massive blood loss and hysterectomy, but the method of calculation of blood loss was not straightforward and the definition of PAS was ambiguous.

Hussein et al found that adding added 3D power Doppler to 2D ultrasound and colour Doppler can increase the diagnostic performance and predict the severity of blood loss during planned caesarean hysterectomy for patients with PAS. Numerous coherent vessels involving the serosa– bladder interface” are independent predictors of major blood loss <sup>(17)</sup>

Our study have some strength points. First, the ultrasonographic examination was done by the same expert team, and the surgical interference was performed by the same surgical team. This could reduce the possibility of bias. second, The diagnosis of placenta accreta was confirmed surgically according to well defined terminology of FIGO classification.

The relatively small sample size is one of the limitations in our study as it was done in a single tertiary centre. The findings were not confirmed by pathological examination but this could be explained by conservative management of most cases. The surgeon was not blind to the result of ultrasound scanning. Still, we believe that being aware of ultrasonographic scanning is better as it allows the surgeon to preoperatively plan the surgical steps, such as delayed dissection of the areas with high vascularity and decreasing intraoperative bleeding.

## **Conclusion**

The combined use of ultrosography and colour Doppler can predict some maternal morbidities during caesarean section for PAS. So, precise preoperative ultrasonographic evaluation of patients with PAS can help the surgeon for proper planning of the surgery and optimizing the circumstances,

thus decreasing the maternal complications related to that catastrophic condition.

**Conflict of interest:** we declare that we have no conflict of interest

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