Issn 1110 -6352

THE EGYPTIAN JOURNAL OF FERTILITY AND STERILITY

Volume 27 Number 5 September 2023

EFSS

The Egyptian Journal Of Fertility And Sterility

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

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Acknowledgments

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

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2- Books:

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

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Contents :

Letter from the Editor:

Dear esteemed colleagues,

Warm greetings

We welcome your comments as well as the scientific activity to be incorporated in the upcoming issues. Very important subjects are included in this issue: Planned placement of cervical cerclage in is mainly either history-indicated and/or prophylactic, especially in multifetal gestations. It appears to be effective in reducing the incidence of mid trimester miscarriage and preterm birth in high-risk cases.

MCA-PI evaluation prior to induction of labor (IOL) is a useful tool in prediction of IOL outcome. Lower PI values may predict successful outcome. CL assessment and EFW are other factors that may predict the outcome of IOL

It was found that COVID-19 has no effect on ovarian reserve.

A study compared intelligence level between breastfed and non-breastfed children, concluded that there was significant relation between high Wechsler Intelligence Scale score and breastfed.

The surgical outcome and intraoperative FIGO grading are strongly correlated with the presence of placental lacunae, loss of clear zone and myometrial thinning and moderately correlated with Placental bulge

A positive oral glucose challenge test only without gestational diabetes is a risk factor for perinatal morbidity like LGA and NICU admission, so early screening for GDM is advisable.

Best regards.

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Bilateral large ovarian lymphoma presenting by abdominal enlargement (Case Report)

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Abstract

Introduction: Primary lymphomas in the ovary are rare, and it represents less than 0.5% of primary ovarian tumors.

Case: A 22-year-old unmarried woman presented with progressive abdominal enlargement. MRI revealed bilateral suspicious adnexal masses managed by laparotomy. Histo-pathological examination revealed Bilateral Burkitt lymphoma. Conclusion: Ovarian lymphoma should be considered in the differential diagnosis of malignant ovarian masses regardless of the age of the patient.

Keywords: Bilateral ovarian lymphoma; Burkitt lymphoma; primary ovarian lymphoma.

Introduction

Primary ovarian lymphomas are one of the rare ovarian tumors which represent less than 0.5% of primary ovarian tumors [1]. Burkitt lymphoma (BL) is a type of malignant non-Hodgkin lymphoma associated with a translocation in c-MYC gene, in addition to, heavy locus immunoglobulin (which is known as IGH, it is a region on human chromosome 14 that contains a gene for the heavy chains of human antibodies or immunoglobulins), which result in the commonest variant, which is translocation t (8; 14) (q24; q32). Burkitt's lymphoma is rare in adults when compared to diffuse large B-Cell lymphoma or low-grade B-cell lymphomas [2].

The aim of the current case study is to present a rare bilateral large ovarian lymphoma in a young adult woman.

Case

A 22 years old unmarried woman presented with abdominal discomfort and progressive abdominal enlargement. By the Abdominal examination a palpable mobile pelviabdominal mass was recognized. Then office transabdominal ultrasonography showed bilateral adnexal masses. Magnetic resonance imaging (MRI) was done which showed Bilateral solid adnexal masses (the

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left adnexa 9X9.6X13.2 cm with marked diffusion restriction and internal cystic areas, while the right adnexa showed the same features but smaller in size 3.9X7.1X7.7cm), in the context of oncology workup process, tumor markers were requested (CEA, CA 19.9, CA-125, alpha feto-protein and BhCG) which were all normal except for slightly elevated CA-125.

The above collected information and evidence starting from clinical examination, imaging and lab results contributed to take the decision of exploration. The patient was informed in detail and was consented for the exploration. Exploration of the abdomen was done through a mid-line incision, which showed bilateral solid adnexal masses (video), multiple lesions in the small intestine (which wasn't detected by MRI) and some ascetic fluid. Left salpingo-oophorectomy and right ovarian biopsy was done, biopsy of small intestine lesions, in addition to, omental biopsy and cytology from the ascitic fluid were done. The patient had an uneventful recovery. Pathology revealed Burkitt's lymphoma in all tissue biopsies and ascetic fluid and the patient was referred for chemotherapy.

Discussion

Burkitt's lymphoma is defined as a type of non-Hodgkin lymphoma mainly targeting the humoral immune cells (B cells) [3]. Ovarian lymphoma may be an aggressive type of primary ovarian lesion or a secondary metastatic lesion [4].

There are very few cases of bilateral ovarian lymphoma reported in literature as that reported by Pourghasemian et al. [5] who reported isolated bilateral ovarian Burkitt lymphoma in a case presenting with an ovarian mass and right adnexal torsion, which was expected as the mass was 12x 10 cm. with a long pedicle, treated by adnexectomy and sent for histo-pathological examination which confirmed the diagnosis. Similar to the current study the tumor markers in their cases were all normal; however, their patient was a fourteen years old girl, unlike the current case which was twenty-two.

Another case of bilateral Burkitt lymphoma was reported by lee et al. [6], in a ten-year old girl presenting with abdominal pain, constipation and left ovarian torsion managed by left salpingo-oophorectomy followed by chemotherapy.

Almost like this case, a 25 old woman was represented by mass in the right ovary with a similar complaint and unilateral salpingectomy was done for her and the histo-pathological examination reveleaed the same diagnosis [8].

The above-mentioned case reports showed that primary ovarian lymphomas have no specific clinical presentation. It may be represented by abdominal discomfort, ascities, abdominal enlargement (as in the current case) and/or adnexal torsion, even with general weakness, dyspnea, fever and diaphoresis as the case presented by Briseno-Hernandez et al [7], who reported these symptoms in a thirty-one years old woman treated by bilateral removal of ovarian tumors. Such cases are usually managed surgically and discovered only when the histo-pathological examination results are revealed. The decision of unilateral adnexectomy or even bilateral removal of both ovaries based on their gross appearance is very difficult and challenging regarding the age of the patient and the possibility of management by chemotherapy. This is mainly due to their rarity.

Conclusion

Ovarian lymphoma should be considered in the differential diagnosis of malignant ovarian masses regardless of the age of the patient.

Chemotherapy is the mainstay in the management of ovarian lymphoma, so

radical surgery is not recommended in order to preserve fertility, as guided biopsy should be considered in the plan of diagnosis of solid ovarian masses since you can avoid un necessary interventions.

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Obstetric outcome of cervical cerclage among pregnant women in Mansoura University Hospital

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Abstract

Objective: To evaluate the obstetric outcome of pregnancies managed by cervical cerclage at Mansoura University Hospital (MUH).

Methods: Observational study of 50 pregnant women with cervical cerclage in the index pregnancy who attended to MUH during the period from July 2019 through December 2021.

Results: The mean gestational age at cerclage insertion was approximately 13 weeks and the mean gestational age at cerclage removal was approximately 31 weeks. Twin pregnancy was the most common indication of cerclage placement (34%), followed by previous MTM (26%), triplet pregnancy (16%), congenital malformation of uterus (14%) and previous PTB (10%). The commonest causes of cerclage removal was spontaneous PTB (38%) followed by PPROM (30%), planned removal at term (22%) and spontaneous miscarriage (10%). Twin pregnancies have more incidence of complications (40.9%) than singletons (26.3%) and triplets (11.1%). Twin gestations were found to have significant correlations with termination of pregnancy before 28 weeks (P = 0.016). Birth weight was found to have a significant relations with mode of conception (P = 0.001) and type of pregnancy (P = 0.001).

Conclusion: Planned placement of cervical cerclage in MUH is mainly either history-indicated and/or prophylactic, especially in multifetal gestations. It appears to be effective in reducing the incidence of MTM and PTB in high risk cases.

Keywords: Cervical cerclage, Preterm labor, Miscarriage.

Introduction

Cervical cerclage is an obstetric surgical procedure that involves insertion of a purse-string suture around the uterine cervix attempting to give mechanical support for the cervix in order to maintain its closure during pregnancy. It was first described by Shirodkar in 1955 and was modified by McDonald in 1957 (1, 2), and since then, this procedure has been widely used for management of women who are at high risk of midtrimester miscarriage

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(MTM) and/or spontaneous preterm birth (PTB) as a result of many factors such as cervical insufficiency, multifetal gestations, uterine anomalies, and short cervix seen on transvaginal sonography (TVS) scan (3).

Cervical cerclage is mostly inserted as a planned procedure in response to either a prior history or a short cervical length detected by TVS. Cerclage can be also inserted as an emergency procedure for women at risk of MTM (4). Prophylactic placement of cervical cerclage has been also suggested as a way to prolong pregnancy in unselected multifetal gestations (5, 6).

Controversies concerning the use of cervical cerclage include safety and efficacy as well as maternal and fetal/neonatal risks and benefits. There is no evidence of any favourable effects of history-indicated or ultrasound-indicated cerclage in women with singleton pregnancies (7, 8). Moreover, there is no evidence that cerclage is effective for preventing PTB and reduction of perinatal morbidity or mortality in multifetal gestations (9). Despite controversies, cervical cerclage remains a commonly performed prophylactic intervention used by most obstetricians (10). Consequently, the purpose of this study was to evaluate the indications and obstetric outcome of cervical cerclage among pregnant women attending to Mansoura University Hospital (MUH).

Materials and Methods

Study design:

This was an observational study of 50 pregnant women with cervical cerclage who attended to MUH during the period from July 2019 through December 2021. The study protocol was reviewed and approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. MSc.19.11.913). The main inclusion criterion was pregnant women with cervical cerclage in the index pregnancy. Women with any of the following criteria were excluded from the study: 1) age is < 18 or > 38 years; 2) major structural fetal malformations; 3) co-existing medical disorder with pregnancy; 4) obstetric problem that may affect the obstetric outcome or timing of termination of pregnancy (as placenta previa, fetal growth restriction, pregnancy induced hypertension, gestational diabetes and Rh isoimmunization); or 5) unclear details about the type, timing and indication of cervical cerclage.

Methods:

Women's clinical data was collected by reviewing their hospital and perinatal records. The following clinical characteristics were evaluated: maternal age, previous gestations, parity, indication of performing cerclage, gestational age at performing cerclage, gestational age at termination of pregnancy, mode of delivery, birth weight and Apgar score. The pregnancy and delivery complications were assessed and included premature rupture of membrane (PROM), chorioamnionitis, vaginal bleeding, cervical laceration, low birth weight (LBW) (< 2500 gm), prematurity, neonatal intensive care unit (NICU) admission and early neonatal death (END). In multifetal pregnancies, neonatal outcomes were evaluated on pregnancy level (i.e. for each multifetal gestation, the variables LBW, NICU admission, END and take home baby were considered evident when there was at least one neonate expressing the characteristic).

Statistical analysis:

Using SPSS 22.0, the data were analyzed. Data for quantitative variables were expressed as mean ± SD and median (min-max). Categorical variables were described as counts and percentage. Continuous variables were analyzed with the Student t test or the Mann Whitney U test. The categorical variables were tested using the Chi-squared or Fisher's exact tests. The logistic analysis was used to investigate the link between cerclage operations and pregnancy outcome when maternal and operation characteristics were controlled for. The statistical significance was determined using a $P \leq 0.05$ criterion.

Results

The demographic and clinical characteristics of the study cohort was shown in table 1. History of previous MTM was found in 17% of women and 11% of them had history of previous PTB. The index pregnancy was achieved naturally in 44% of women, by ovarian stimulation (OS) with timed intercourse in 24% of women, and by IVF/ICSI in 32% of women. The index pregnancy was singleton in 38% of women, twin in 44% of women and triplet in 18% of them.

Table 2 shows the cervical cerclage characteristics. The mean gestational age at cerclage insertion was approximately 13 weeks and the mean gestational age at cerclage removal was approximately 31 weeks. Twin pregnancy was the most common indication of cerclage placement (34%), followed by previous MTM (26%). Other indication included triplet pregnancy (16%), congenital malformation of uterus (14%) and previous PTB (10%). The commonest causes of cerclage removal was spontaneous PTB (38%) followed by PPROM (30%), planned removal at term (22%) and spontaneous miscarriage (10%).

Tables 3 and 4 display the pregnancy outcomes. Twin pregnancies have more incidence of complications (40.9%) than singletons (26.3%) and triplets (11.1%). Twin gestations were found to have significant correlations with termination of pregnancy before 28 weeks (P = 0.016).

Table 5 displays the neonatal outcomes of cases delivered after 24 weeks among the study cohort, excluding the 9 cases of miscarriage. Admission to NICU was evident in all triplet gestations, in 57.1% of twins and in 38.9% of singletons; however, END was more common in twins (42.9%) than in triplets (33.3%) and singletons (22.2%) and tack home baby was comparable between the 3 types of gestations. Table 6 illustrates the relation of birth weight to demographic, clinical and obstetric characteristics among cases delivered after 24 weeks. LBW was found to have a significant relations with mode of conception (P = 0.001) and type of pregnancy (P = 0.001).

Table 1: Demographic and clinical characteristics of the study cohort (n=50)

Variable	Mean ± SD	Median (Min-Max)	Number (%)
Age (years)	26.34 ± 4.88	25 (18-37)	
Occupation			
Student			11 (22%)
House wife			33 (66%)
Employee			6 (12%)
Gravidity	2.92 ± 1.95	2 (1-10)	
Parity	0.68 ± 0.82	0.5 (0-3)	
Prev MTM			17 (34%)
Previous PTB			11 (22%)
Mode of conception			
Natural			22 (44%)
OS with timed intercourse			12 (24%)
IVF/ICSI			16 (32%)
Type of pregnancy			
Singleton			19 (38%)
Twin			22 (44%)
Triplet			9 (18%)

ICSI, intracytoplasmic sperm injection; **IVF,** in vitro fertilization; **MTM,** midtrimester miscarriage; **OS,** ovarian stimulation; **PTB,** preterm birth.

Table 2: Cervical cerclage characteristics among the study cohort (n=50)

Cerclage characteristics	Mean ± SD	Median (Min Max)	Number (%)
Indication of cerclage			
Prev MTM			13 (26%)
Previous PTB			5 (10%)
Twin			17 (34%)
Triplet			8 (16%)
Congenital malformation of uterus			7 (14%)
Gestational age at performing cerclage (weeks)	13.20 ± 0.76	13 (12-16)	
Gestational age at cerclage removal (weeks)	30.71 ± 6.14	32.4 (15.6-39.0)	
Indication of cerclage removal			
Spontaneous miscarriage			5 (10%)
Spontaneous PTB			19 (38%)
PPROM			15 (30%)
Planned removal at term			11 (22%)

MTM, midtrimester miscarriage; **PPROM,** preterm premature rupture of membranes; **PTB,** preterm birth.

Table 3: Pregnancy outcomes among the study cohort according to the type of pregnancy (n=50)

Pregnancy outcomes	Singleton (n=19)	Twin (n=22)	Triplet (n=9)
Gestational age at termination of pregnancy (weeks)	34.26 ± 4.48	28.23 ± 6.81	32.00 ± 3.28
Miscarriage (at < 24 weeks)	1 (5.3%)	8 (36.4%)	0 (0%)
Delivery at < 28 weeks	2 (10.5%)	3 (13.6%)	2 (22.2%)
Delivery at < 34 weeks	6 (31.6%)	9 (40.9%)	7 (77.8%)
Delivery at < 37 weeks	11 (57.9%)	12 (54.5%)	9 (100%)
Delivery at ≥ 37 weeks	7 (36.8%)	2 (9.1%)	0 (0%)
Mode of delivery			
Vaginal delivery	5 (26.3%)	4 (18.2%)	1 (11.1%)
Caesarean section	13 (68.4)	10 (45.5%)	8 (88.9%)
Maternal complications	5 (26.3%)	9 (40.9%)	1 (11.1%)

Table 4: Relation of gestational age at termination of pregnancy to the type of pregnancy among the studied cohort (n=50)

Type of pregnancy	Gestational age at termination of pregnancy		P value
	< 28 weeks (n=16)	> 28 weeks (n=34)	
Singleton	3 (18.8%)	16 (47.1%)	0.068
Twin	11 (68.8%)	11 (32.4%)	**0.016**
Triplet	2 (7.7)	7 (24.3)	0.699

Table 5: Neonatal outcomes of cases delivered after 24 weeks among the study cohort according to the type of pregnancy (n = 41)

Neonatal outcomes	Singleton (n=18)	Twin (n=14)	Triplet (n=9)
Admission to NICU	7 (38.9%)	8 (57.1%)	9 (100.0%)
END	4 (22.2%)	6 (42.9%)	3 (33.3%)
Take home baby	14 (77.8%)	10 (71.4%)	7 (77.8%)

END, early neonatal death; **NICU,** neonatal intensive care unit.

Table 6: Relation of birth weight to demographic, clinical and obstetric characteristics among cases delivered after 24 weeks (n = 41)

Variable	Birth weight		Test of significance
	< 2500 gm (n=28)	> 2500 gm (n=13)	
Age (years)	25.36 ± 4.44	27.46 ± 5.43	t = 1.316 P = 0.196
Occupation			
Student	9 (31.1%)	1 (7.7%)	χ^2 = 3.148 P = 0.207
House wife	17 (60.7%)	10 (76.9%)	
Employee	2 (7.1%)	2 (15.4%)	
Gravidity	2 (1-7)	3 (1-10)	Z = 1.820 P = 0.075
Parity	0.5 (0-2)	1 (0-3)	Z = 1.215 P = 0.272
Mode of conception			
Natural	9 (32.1%)	12 (92.3%)	χ^2 = 13.051 P = 0.001
OS with timed intercourse	9 (31.1%)	0 (0.0%)	
IVF/ICSI	10 (35.7%)	1 (7.7%)	
Type of pregnancy			
Singleton	7 (25.0%)	11 (84.6%)	χ^2 = 13.328 P = 0.001
Twin	12 (42.9%)	2 (15.4%)	
Triplet	9 (32.1%)	0 (0.0%)	
Mode of delivery			
Vaginal delivery	9 (32.1%)	1 (7.7%)	χ^2 = 2.878 P = 0.090
Caesarean section	19 (67.9%)	12 (92.3%)	

t: Student t test , Z: Mann Whitney U test, χ^2 :Chi-Square test.

ICSI, intracytoplasmic sperm injection; **IVF,** in vitro fertilization; **OS,** ovarian stimulation.

Discussion

Cervical cerclage is a well-known surgical procedure in obstetrics and it involves insertion of a stitch around the cervix, attempting to give mechanical support for the cervix in order to maintain its closure during pregnancy. Cervical cerclage is effective in preventing cervical incompetence-related MTM and PTB, and the procedure appears to be effective in 85-90% of cases when true cervical insufficiency is present. However, cervical cerclage is not a procedure without risks because surgical cervical manipulation can initiate uterine contractions and may cause infection or bleeding which may lead to miscarriage or PTB; therefore; risks of cerclage must be carefully balanced against its benefits (11, 12).

Although cervical insufficiency has an evident role in in the etiology of PTB in singleton gestations; however, it is role remains unclear in the etiologies of PTB in multifetal gestations. The mechanism for early PTB in multifetal gestations is multifactorial and it seems that excessive mechanical stretching of the uterus is the commonest cause of PTB in multifetal pregnancies (13).

Planned placement of cervical cerclage can be either history-indicated (based on previous history of MTM and/or PRB) or ultrasound-indicated (due to short cervical length detected by TVS examination) (11). In unselected multifetal pregnancies, cervical cerclage has also been suggested to increase pregnancy duration (5, 6). Cervical cerclage placement rates are not uniform worldwide; some sources claim that they are higher in developing nations than in developed ones (14). Systemic reviews and meta-analyses on cervical cerclage placement have certainly differed conclusions on the benefits and effectiveness of this procedure in singleton and multiple gestations (11, 13).

The purpose of this study was to analyze the indications and obstetric outcomes of cervical cerclage-managed pregnancies at MUH. The median gestational age at performing cerclage was 13 weeks with a range of 12-16 weeks. This is in line with what was settled in most studies which indicated that planned cerclage tend to be performed around 14 weeks (11). In our study, the comments indications for performing cerclage were previous history of MTM and/or PTB and multifetal pregnancy. This was in line with Al-Azemi and his colleagues who analyzed 1021 women with cervical cerclage in their hospital (15).

Since PTB occurs at a different rate and is caused by different mechanisms in singleton and multifetal pregnancies, we thought it was important to assess maternal and neonatal outcomes independently. In singleton gestations in our study, the mean gestational age at termination of pregnancy was approximately 34 weeks and the rates of PTB before 34 weeks and 37 weeks were 32% and 58%, respectively. This came in line with the study by Huang et al (16) who found that history-indicated cervical cerclage had significantly prolonged gestational age of delivery to approximately 35 weeks and reduced the PTB before 34 weeks and 37 weeks to 36% (vs 59% in the non-cervical group) and 50% (71% in the non-cervical group), respectively. The rate of admission to NICU was approximately 39% in singleton gestations which is comparable to what was found by Huang et al (46%), with no significant difference with the rate in the non-cervical group in their study (16).

In twin gestations in our study, the mean gestational age at termination of pregnancy was approximately 28 weeks and the rates of PTB before 28 weeks and 34 weeks were 14% and 41%, respectively. These values were not in concordance with what was reported in the trial by Nicolaides and colleagues on unselected twin pregnancies. They reported that the median gestational age at termination of pregnancy was approximately 36.6 weeks and the rates of PTB before 28 weeks and 34 weeks were 3.2% and 16.7%, respectively.

They concluded that routine cervical cerclage for twin pregnancies do not reduce the rate of spontaneous PTB (5).

In triplet gestations in our study, the mean gestational age at termination of pregnancy was approximately 32 weeks and the rates of PTB before 28 weeks and 34 weeks were 22% and 78%, respectively. This came in agreement with other studies that reported 13% and 80% rates of PTB before 28 weeks and 34 weeks, respectively (17).

In the current study the outcome of cerclage was significantly worse among twin pregnancies than singleton and triplet pregnancies. Our twin gestations had unexplained significant relation with termination of pregnancy before 28 weeks (P = 0.016). We analyzed the relation of LBW (< 2500 gm) to demographic, clinical and obstetric characteristics among cases delivered after 24 weeks. We found that LBW had a significant relations with the mode of conception (P = 0.001) and the type of pregnancy (P = 0.001). The relation of LBW to the type of pregnancy appears logic because multifetal pregnancies have high risk for PTB and prematurity than singletons (13). The LBW were found to be more in pregnancies achieved by OS and timed intercourse, and IVF/ICI. The relation of LBW to the mode of conception may be an indirect relationship because most of pregnancies achieved by OS and timed intercourse, and IVF/ICI are multifetal pregnancies that have high risk for LBW.

A limitation of our study is the small number of participants which limits the strength of our results and another limitation lies in its observational nature with absence of a comparative group which used other interventional method. Therefore, more studies are needed, especially randomized trials, between cervical cerclage and other modalities in conditions like multifetal pregnancies and ICSI pregnancies.

In conclusion, planned placement of cervical cerclage in MUH is mainly either history-indicated and/or prophylactic, especially in multifetal gestations. It appears to be effective in reducing the incidence of MTM and PTB in high risk cases.

Acknowledgment

The authors would like to thank all participants and persons who helped them in completing this work.

Funding

The authors received no specific funding for this work.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Fetal middle cerebral artery Doppler in post term pregnancy: a predicting factor for induction of labor outcome

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Abstract

Background: Post term pregnancy necessates IOL to avoid the potential hazards on fetal and maternal outcome. Several factors affect the process of IOL, and there is often great uncertainty regarding its success. Late in pregnancy, vasodilatation of fetal brain vessels occurs as a physiological preparation for the onset of labor. MCA-PI decreases in turn as a preliminary fetal mechanism for adaptation to labor.

Objective: We assumed that evaluating MCA-PI prior to IOL may be used as a beneficial tool to predict responders to IOL.

Methodology: A prospective cohort study, which included 150 post term patients (41-42 weeks), who were admitted to Kasr Al-Ainy Hospital for IOL. Prior to induction, we performed U/S to record MCA-PI, together with CL and EFW. Patients were given 25Mcg misoprostol vaginal tab/6 hours, maximum for 24 hours. Responders were defined as those who succeeded to enter the active phase of labor, by the onset of active uterine contractions. Patients who needed CS before the onset of active labor were excluded.

Results: A total of 150 patients were included in the study. 133 cases (88.7%) entered the active phase of labor, while 17 (11.3%) cases failed to enter in the active phase. Both groups were comparable in the parity and BMI. MCA-PI was significantly lower in the responder group (group 1; 1.29± 0.11) compared to the non-responders (group 2;1.67± 0.13). The mean CL was 25.28± 4.25 & 33.43± 4.8 in groups 1&2 respectively. The mean EFW was 3375.47± 178 & 3722.65± 116.33 in groups 1 & 2 respectively. ROC analysis examined the ability of these parameters in predicting the response to IOL. The cutoff values, sensitivity & specificity respectively were; 1.41, 94.12% , 83.46% for MCA-PI, 26.6, 94.1%, 60% for CL, and, 3555, 94%,83.5% for EFW. WE further included all significant variables (maternal age, MCA-PI, CL, EFW) in a multivariate logistic regression analysis. MCA-PI was a statistically significant predictor for the response to IOL, even after adjustment of the other variables (P value= 0.05).

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Conclusion: MCA-PI evaluation prior to IOL is a useful tool in prediction of IOL outcome. Lower PI values may predict successful outcome. CL assessment and EFW are other factors that may predict the outcome of IOL.

KEYWORDS: post term pregnancy, MCA-PI, induction of labor, outcome

Introduction

Post term pregnancy imposes a great risk on fetal outcome, with increased perinatal morbidity and mortality. Moreover, it is associated with higher rates of cesarean sections, postpartum hemorrhage, and the need for induction of labor (IOL) (1, 2).

Taking into consideration both maternal and fetal potential risks, IOL as pregnancy advances beyond 40 weeks, seems to be the current best practice (3, 4). Still, it is quite challenging for the obstetrician to determine those who will adequately respond to IOL.

There are several factors affecting IOL, such as; parity, body mass index (BMI), fetal weight. Many parameters have been proposed by different researchers to predict the outcome of IOL; Bishop score in the 1960's (5), cervical length assessment (6, 7, 8), and more recently, posterior cervical angle measurement (9, 10, 11) and cervical elastography (12).

In the last weeks of gestation, vasodilatation of the fetal brain vessels occurs as a physiological preparation for the onset of labor. In turn, the fetal middle cerebral artery -pulstility index(MCA-PI) decreases preceding the onset of labor, as a preliminary fetal mechanism for adaptation to labor (13,14).

Since there has been an association between MCA Doppler changes and the onset of spontaneous labor (13), we assumed that evaluating MCA-PI prior to IOL may be used as a beneficial tool to predict responders to IOL.

Materials and Methods

This is a prospective cohort study, including 150 pregnant patients in late term pregnancy, who were admitted to Obstetrics and Gynaecology Department, Kasr El-Aini Hospital, Cairo University, for IOL, from March 2019 to March 2020, after approval of our ethical committee.

Before enrollment in the study, thorough history taking and clinical examination were done to verify the fulfillment of the inclusion criteria; having a singleton, living fetus, cephalic presentation, with a gestational age (GA) range; 41 to 42 weeks (as evident by reliable dating from the last menstrual period, or first trimesteric ultrasound), intact membranes and favorable cervix on examination (Bishop score >6). Cases with BMI ≥ 30, history of scarred uterus (whether CS or any uterine surgery), prior cervical procedure (cerclage,cautery),fetal macrosomia (≥ 4kg),IUGR (intrauterine growth restriction), drained liquour, placenta previa, together along cases associated with co-morbidities (such as; diabetes mellitus, hypertension, cardiac disease or any maternal medical problem), or patients in need of emergency CS (antepartum hemorrhage, prolapsed pulsating cord, fetal distress) were initially excluded.

Prior to induction, fetal MCA-PI was assessed for each enrolled case using a Voluson E10 ultrasound machine. During the ultrasound (U/S) scan, other parameters as cervical length, placental site, amniotic fluid index (AFI) and estimated fetal weight (EFW) were also documented.

In measuring the fetal MCA-PI, color flow imaging was used to locate it anatomically, being detected as a major lateral branch of the circle of Willis, anterolaterally between the anterior and middle cerebral fossae. The pulsed Doppler sample gate was adjusted on the middle part of the vessel to gain the optimal flow velocity waveforms and

calculate the PI (15). Hadlock's formula was used to calculate the EFW; utilizing biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) (16).

Transvaginal U/S was done for cervical length assessment. To ensure visualization of the entire cervical length, a sagittal plane of the cervix was obtained and once the view was optimal, the depth of the image was increased to occupy one thirds of the screen. Then the calipers were placed in a line between the internal and external cervical orifices (17).

The protocol for IOL followed our university hospital protocol (11). Patients were initially given 25 Mcg misoprostol vaginal tablet (Vagiprost, Adwia, Cairo, Egypt). The cervix was reassessed 6 hours after the initial dose to decide whether to repeat the dose or start oxytocin infusion (18). Patients who started the active phase of labor were transferred to the delivery room, and if necessary, augmentation of labor with oxytocin (Syntocinon, Novartis, Basel, Switzerland), and/or artificial rupture of membranes (ROM) were proceeded, under continuous electronic fetal monitoring.

Our primary outcome of concern was to document the onset of active labor, defined as 3 or more regular efficient uterine contractions (200 Montevideo units), lasting 40 seconds during 10 minutes, with a cervical dilatation more than 4 cm.

Failed induction was defined as; failure to establish active labor after a cycle of treatment of intravaginal misoprostol (25Mcg vaginal tab/6hours for 24 hours) or intravaginal misoprostol followed by oxytocin infusion after ROM up to 8 hours. Women who underwent CS before the onset of active labor for fetal (fetal distress, cord prolapse) or maternal (antepartum hemorrhage) indication were excluded.

The relation between pre-induction fetal MCA Doppler (MCA-PI) and the incidence of failure of IOL was assessed according to the collected data.

Statistical Analysis:

Sample size calculation of the current cross-sectional study was based on comparing MCA-PI between responders and non-responders in pregnant women undergoing induction of labor (IOL). Calculation was done based on comparing 2 proportions from independent samples using Chi test, the α-error level was fixed at 0.05, and the power was set at 80%. As previously published (19), the mean and SD of MCA-PI in responders (whether < 24h or > 24h) group was 1.45 ± 0.3, while it was 1.82 ± 0.3 in non-responders group. Assuming that IOL failure rate to be about 9% (19), we need to study 145 mothers to be able to reject the null hypothesis with the intended power. Accounting for dropout cases, we intended to include 150 mothers in the study. Sample size calculation was done using PS Power and Sample Size Calculations Software, version 3.1.2 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

Data were statistically described in terms of mean ± standard deviation (± SD), and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi-square (c2) test was performed. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. Multivariate logistic regression analysis was used to test for the significant independent predictors of success of IOL. Two-sided p values less than 0.05 was considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

Results

A total of 150 patients were included in the study. According to the response to IOL, the cases were divided into two groups: Group 1; responders (n=133, 88.7%), in whom the onset of the active phase of labor was achieved, and, Group 2; non-responders (n=17, 11.3%), who failed to enter in the active phase of labor, as shown in figure (1).

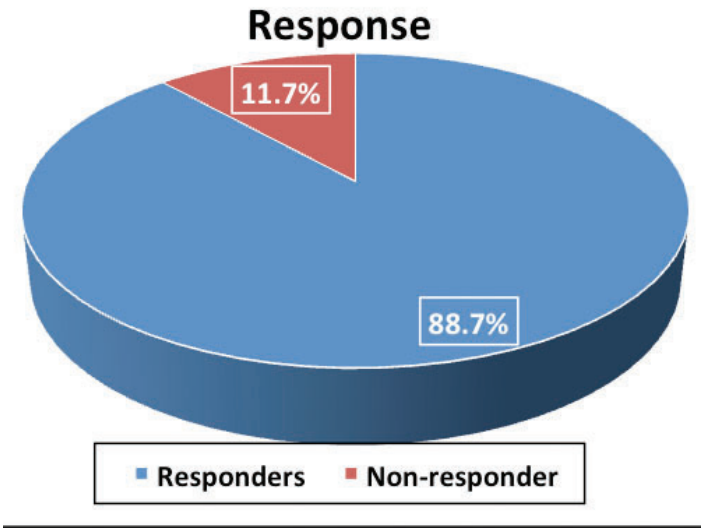

Figure (1): The distribution of response to IOL in the study sample

The baseline clinical characteristics of the enrolled cases, in either groups, as regards; maternal age, parity & BMI, are summarized in Table (1). No statistically significant difference was observed in both groups regarding the parity & BMI. However, the maternal age was significantly higher in group 1 (27.02± 4.72 years) compared to group 2 (24.06±3.45 years).

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

Characteristics	Group I Responders (n=133)	Group II Non-responder (n=17)	P value
Age (in years) Mean±SD Range	 27.02±4.72 19.00-36.00	 24.06±3.45 20.00-31.00	0.014*
BMI Mean±SD Range	 24.83±2.42 20.00-29.00	 24.24±2.17 22.00-29.00	0.333
Parity P1 P2 P3 PG	 33 24.8% 38 28.6% 22 16.5% 40 30.1%	 5 29.4% 3 17.6% 1 5.9% 8 47.1%	0.353

*statistically significant

In measuring the MCA-PI prior to IOL, a statistically significant difference was noted between both groups, with lower MCAI-PI values in group 1 (1.29± 0.11) compared to group 2 (1.67±0.13)

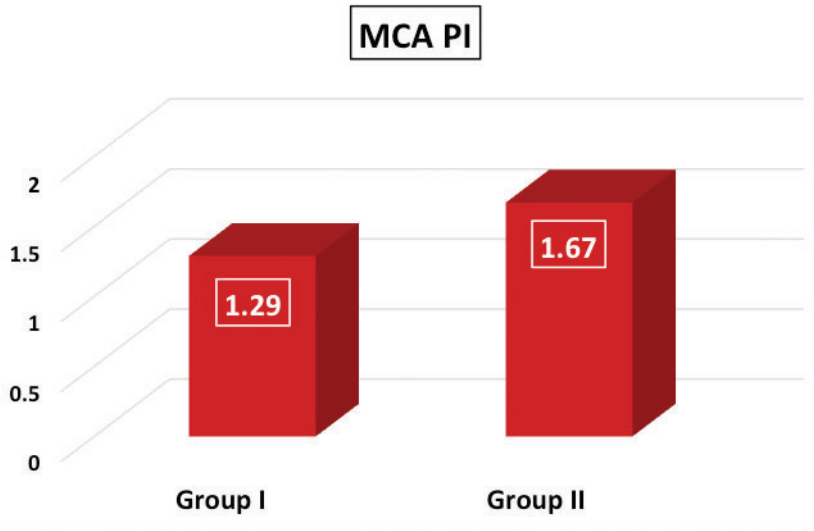

Figure (2): Fetal middle cerebral artery (MCA) pulsatility index (PI) values between the two study groups.

The other U/S parameters that were assessed prior to IOL were the cervical length (CL) and EFW. The mean of the CL was 25.28 ± 4.25 and 33.43 ± 4.80 in groups 1 and 2 respectively. The mean EFW was 3375.47 ± 178.0 and 3722.65 ± 116.33 in groups 1 and 2 respectively. There was a statistically significant difference in both variables between the two groups (P value= 0.001).

Table (2): Fetal MCA-PI values, CL, EFW between both groups.

Group	Group I Responders (n=133)	Group II Non-responder (n=17)	P
MCA-PI; Mean±s.d Range	 1.29 ± 0.11 1.07 - 1.53	 1.67 ± 0.13 1.40 - 1.92	**0.001***
Cervical length; Mean±s.d Range	 25.28 ± 4.25 16.40 - 34.10	 33.43 ± 4.80 26.40 - 41.30	**0.001***
EFW; Mean±s.d Range	 3375.47 ± 178.00 3100.0 - 3850.0	 3722.65 ± 116.33 3550.0 - 4000.0	**0.001***

*statistically significant

Receiver operating characteristics (ROC) analysis was performed to examine the ability of MCA-PI, CL and EFW in predicting the response to IOL. MCA-PI at a cutoff value 1.41 provided a sensitivity of 94.12%, and a specificity of 83.46% in predicting the outcome of IOL (in terms of the onset of the active phase of labor). The study patients were further classified according to this MCA-PI cutoff value into two groups, as shown in Table (3). In turn, the sensitivity, specificity & cutoff values of CL were 94.1%, 60.0%, 26.60, and those of EFW were 94.0%, 83.5% and 3555 respectively.

Table (3): Distribution of response according to MCA-PI cutoff value.

Characteristics		n	%
MCA PI ≤1.41	Responders	111	99.1%
	Non-responders	1	0.9%
MCA PI >1.41	Responders	22	57.9%
	Non-responders	16	42.1%

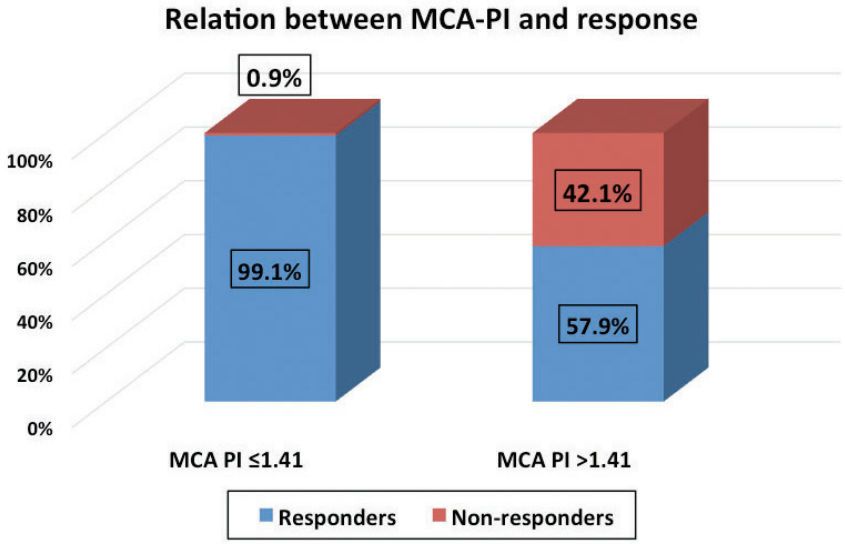

Figure (3): Distribution of response according to MCA-PI cutoff value

Variables with significant results in univariate analysis were included in multivariate logistic regression analysis. MCA PI was a significant predictor for the response even after adjustment for other variables (P=0.050).

Table (4): Multivariate logistic regression analysis for Response.

	B	SE	P value	OR	95% CI	
					LL	UL
AGE	0.545	0.482	0.258	1.724	0.671	4.430
MCA PI	25.288	12.897	0.050*	9.600	1.010	9.12
CL	0.623	0.512	0.224	1.865	0.683	5.089
EFW	0.013	0.009	0.131	1.013	0.996	1.031

B: Unstandardized Coefficients, SE: Standard Error, OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit,*: Statistically significant at $p \leq 0.05$

Discussion

In current obstetric practice, postterm pregnancy necessates IOL to avoid the potential hazardous risks on the fetomaternal outcome (3, 4). Conversely, despite the extended research for the factors that may influence the process of IOL (20,21), yet, there is often great uncertainty as regards its success(19,22).

The aim of our study was to assess the value of MCA-PI for prediction of IOL outcome.

Physiologically; the onset of labor is the product of a complex mechanism, including both maternal and fetal neuroendocrinological pathways (23). As a reflection to this mechanism, the fetal Doppler parameters (especially the cerebral indices) in turn, exhibit some changes as labor approaches (13).

Based on this hypothesis, Widschwendter et al (22), further investigated the assumption that fetal Doppler indices in late pregnancy, may provide an additional criterion to predict the success and outcome of IOL. Formerly, Severi et al (13), supporting this assumption, noted that both fetal MCA-PI and resistance decrease in late pregnancy. They even nominated these indices as a signal for the onset of labor to approach.

Thus, cerebral Doppler indices are somehow correlated to the onset of labor, but the evidences available are poor (19).

Moreover, the changes that fetal MCA exhibits in early gestation should be distinguished from those that occur at term. The well known disruption in the cerebroplacental ratio (defined as RI in UA>90th centile and RI in MCA<10%), that occurs in cases of fetal growth restriction and placental insufficiency "Brain sparing", is a pathological sequence, as a reaction of fetal circulation to hostile intrauterine environment and impending fetal hypoxia. This is totally different from the so-called "term effect" of MCA indices (fall in RI and PI of MCA), which is a physiological process, that occurs late in pregnancy, secondary to vasodilatation of fetal brain vessels preceding the onset of labor (13, 14). This physiological fall in MCA resistance will allow increased oxygenation of the brain structures (24).

Another hypothesis is that this diminished resistance may trigger fetal pituitary secretion of oxytocin, which in turn stimulates labor (22). Clifton et al (25), attributed the reduction in MCA impedance together with the initiation of labor to the release of nitric oxide (NO) in placental circulation, under the effect of corticotrophin releasing hormone (CRH).

In our study, we assessed the MCA-PI in 150 patients, in late term pregnancy (41-42 weeks), who were candidates for IOL. MCA-PI was statistically significantly lower in the responder group (1.29± 0.11) compared to the non-responder group (1.67± 0.13). Additionally, MCA-PI cutoff value 1.41 achieved 94.12% sensitivity, and 83.46% specificity in prediction of IOL outcome.

Both CL and EFW were significantly lower in the responders group. This comes in agreement with several studies which supported that shorter CL, and average EFW were in favor of successful outcome for IOL (6,7,10,11,12).

Widschwendter et al (22), correlated the MCA-PI at the start of IOL with the duration. They concluded that both MCA and Bishop score may have independent effect on the duration of IOL, especially in cases beyond 41 weeks gestation. Still, their study had low statistical power, being based on a very small number of cases (n=49), and was additionally limited by the heterogeneity of their study population.

In order to achieve good accuracy in predicting the success of IOL; Vannuccini et al (19), in a prospective cohort study, proposed an ultrasound based model, including cervical length, MCA-PI, and EFW. They concluded that there is an association between MCA-PI and failed IOL, having lowest levels in those who responded within 24 hours, and highest levels in those who did not respond. They reported that a cutoff value of MCA-PI

above 1.44, had 71.7% sensitivity, and 90.9% specificity as a predicting factor for failure of IOL. They included only nulliparous women, and set other factors together with MCA Doppler, instead of proving the valid correlation between MCA-PI and the onset of labor independently.

As regards our study, we preferred focusing on the MCA-PI as a sole factor, and thoroughly investigate its correlation with the onset of labor, to justify its validity and efficiency in predicting the outcome of IOL. That's why we further included all significant variables (maternal age, MCA-PI, CL, EFW) in a multivariate logistic regression analysis. MCA-PI was a statistically significant predictor for the response to IOL, even after adjustment of the other variables (P value= 0.05).

The strict selection criteria for the inclusion of our cases, together with the multivariate logistic regression analysis were aspects of strength in our work, aiming to nullify the other factors that may affect the response to IOL. Still, the sample size may be considered as a limitation, and the duration of induction was not documented in our data collection.

In conclusion; there is no doubt that vaginal delivery following IOL is the end-stay outcome of several factors, functioning in harmony together. MCA-PI evaluation prior to IOL is a useful tool in prediction of IOL outcome. Further studies on larger population are needed.

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COVID-19 disease effect on ovarian reserve in women of reproductive age: an analytical before-and-after COVID-19 study

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Abstract

Background: COVID-19 is a serious pandemic that affected multiple systems in the human body. Its effect on female fertility is not widely evaluated.

Objective: to evaluate the effect of COVID-19 infection on the ovarian reserve and menstrual cycle in infertile women undergoing an assisted reproductive technology protocol.

Study design: A cross-sectional analytical study was conducted on 120 infertile (primary or secondary infertility) women attending the Gynecology and Obstetrics Department at Fayoum University Hospital with confirmed previous COVID-19 disease. The ovarian reserve in this group was studied using AMH, AFC, and serum FSH, LH. The menstrual cycle length was evaluated before and after infection.

Results: We studied 120 infertile women with confirmed COVID-19 infection. The average age was 26.96 ±5.68 years. Out of the 120 cases, 86 cases (71.7%) were diagnosed as mild COVID-19 infection, while severe cases were reported in 30 (25%), and only four women (3.3%) reported a moderate form of the infection. AMH, AFC, FSH and LH mean serum levels tested post-COVID-19 showed non-statistically significant difference in pre and post covid with infection (p-values > 0.05). A great proportion of the patients reported no change in the cycle length (63.3%) with insignificant difference reported between patients with mild, moderate, and severe infection (P value 0.874).

Conclusion: It was found that COVID-19 has no effect on ovarian reserve.

Keywords: COVID-19; Ovarian Reserve; AMH; AFC; FSH; LH.

Introduction

There has been a global pandemic of COVID-19 since December 2019. Concerns about the short- and long-term repercussions of COVID-19 infection extend beyond the virus's impact on mortality rates. Many different organs may be involved in the wide variety of clinical symptoms caused by SARS - COVID-19 (1).

Human fertility and the effects of the COVID-19 virus were at the center of a heated discussion during the pandemic. Studies have suggested that higher serum luteinizing hormone (LH) level is linked to changes in semen parameters in infected males (2, 3). Others have investigated the potential effect of SARS-CoV-2 infection on sperm and oocyte function (4, 5, 6). By directly interacting with surface angiotensin-converting enzyme 2 (ACE2) receptors, the SARS-CoV-2 virus is able to infect human cells (7). Both ovarian (6,7,8) and testicular tissues have ACE2 receptors (9-11); therefore, follicle growth, angiogenesis, and degeneration, as well as the reaction to gonadotrophins, would be impacted by ACE2 (7, 8, 11).

In addition to influencing the formation of endometrial tissue, ACE2, Angiopoietin II (Ang II), and Angiopoietin 1-7 (Ang 1-7) may control the angiogenesis and degeneration of the corpus luteum and the follicular and ovarian follicles, as well as the timing of ovulation. The ovarian reserve of a woman is a major factor in her ability to have children. Fecundity may be negatively impacted by diminished ovarian reserve due to decreased egg quality (11). More importantly, ACE2 is abundantly expressed in the ovary (12). Additionally, there has been concerns about the menstrual changes that were reported by some patients as change in duration, change in menstrual bleeding pattern, and altered pain which indicated further evaluation (13).

Alterations in ovarian function, the biological process of oocyte formation and maturation, oocyte quality, and fertility function may result from a decrease in ACE2 activity caused by SARS-CoV-2 infection, which can increase circulating Ang II (14). Also, the recruitment of Ang II promotes oxidative stress (6), causes inflammation, which might hamper ovarian function and fertility (15).

Therefore, indicators of the effect of COVID-19 on female fertility should focus primarily on the ovarian reserve function. Ovarian reserve is often measured by measuring a patient's basal FSH or LH concentration, as well as E2, AMH, and an assessment of ovarian function capacity. Accordingly, the primary objective of this study was to evaluate the effect of COVID-19 infection on ovarian reserve among infertile women. A secondary objective was to evaluate the effect of infection on the menstrual cycle length.

Methods

This was a cross-sectional study conducted on infertile (primary or secondary infertility) women attending the Gynecology and Obstetrics Department at Fayoum University Hospital (from March 2022 to September 2022). According to findings from a previous study (16), the global prevalence of infertility is estimated to be around 9%. Using Power Analysis and Sample Size Software (PASS 2020) "NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass", we estimated that 120 participants are needed in order to achieve 85% power, - error probability 0.05, and a 10% dropout rate during follow up.

Women aged from 18 to 35 years old, with history of confirmed COVID-19 infection by PCR and / CT, with no coexisting medical disorders were included in this study. While those with PCOS or border line ovarian insufficiency (premature ovarian failure), and associated medical conditions (hypothyroidism or hyperthyroidism, auto immune disease, chronic diseases such as DM and those with previous pelvic surgery

potentially affecting ovarian vasculature) were excluded.

The diagnosis of SARS-CoV-2 infection was done using a real-time reverse-transcriptase polymerase chain reaction (PCR) assay of throat swabs (17). SARS-CoV-2 cases were classified as either "mild," "moderate," or "severe" according to criteria established by the American Thoracic Society and the Infectious Diseases Society of America (18). All positive PCR test dates of the participants were noted. Information on ovarian function (AMH, FSH, LH and AFC), prior to COVID-19 infection was obtained from hospital records between January 2019 and April 2021.

At study entry, baseline demographic was recorded, including age, body mass index (BMI) (kg/m^2), tobacco smoking, as well as type and duration of infertility. Past obstetric and medical histories were collected first from all patients included in the study. Time from SARS-CoV-2 infection was recorded.

Ultrasound assessment of ovarian reserve:

Qualified gynecological sonographers performed pelvic ultrasound assessments between days 3 and 5 of the menstrual cycle, using a transvaginal 9-MHz ultrasound probe (Voluson S10, GE). The recorded antral follicle count (AFC) represents the combined total antral follicles between 2 and 10 mm from the left and right ovaries.

Laboratory tests: Serum samples were taken for the measurement of AMH, basal follicle-stimulating hormone (FSH), and basal luteinizing hormone (LH). All samples and ultrasound evaluations were done 3- 6 months after cured infection.

The patients were asked to report their menstrual cycle length (average length of 24-38 days) (19) before and after infection.

The primary outcome of the current study was the proportion of women with decreased fertility post SARS-CoV-2 infection according to the following indicators of ovarian reserve function (AMH, basal FSH, basal (LH) and AFC). A secondary outcome measure was to evaluate the effect of COVID-19 infection on the menstrual cycle length.

Ethical approval: The ethical committee of Fayoum University's Faculty of Medicine approved the current study on 13/2/2021, approval number: (M 575). Before enrolling in the study, all women gave a written informed consent after clarifying the study's goals. The confidentiality of the data base was ensured.

Statistical Data Analysis:

Data were collected, reviewed, coded, and entered into IBM version 21 of SPSS (Statistical Package for the Social Sciences). Quantitative data were presented as means, standard deviations, and ranges when their distribution was found to be parametric, while qualitative data were shown as counts and percentages. The Chi-square test was used to compare two groups based on qualitative data, whereas the Fisher exact test was used in place of the Chi-square test whenever the predicted count in any given cell was less than 5. Independent sample t-test was used to evaluate differences between the two groups, both of which had quantitative data with a parametric distribution. The Mann-Whitney U test was used to compare two unrelated groups based on quantitative data with a non-parametric distribution. The margin of error was approved at 5%, and the confidence interval was set to 95%. P> 0.05 was considered not significant, P 0.05 or less was thought to be significant, and P 0.001 was deemed to be highly significant. Basic graphs were used to present some data.

Results

One hundred thirty- three women were eligible for the study. Upon evaluation of the hospital records, laboratory results were not available for 13 patients, leaving 120 patients for the final analysis.

Table (1) presents the baseline data of the 120 women included in the current study. Their ages ranged from 18 to 38 with an average age of 26.96 ±5.68years, their BMI ranged from 19.8 to 23.4 with an average BMI of 21.8 ±7.62kg/m2. The infertility duration ranged from 2 to 8 years with an average of (3.78 ± 2.32) years. The time frame of COVID-19 infection ranged from 2 to 8 months with an average duration of 3.95 ± 1.16 months. Regarding COVID-19 severity, most women reported a mild form of the disease (86 71.7%), while severe cases were reported by 30 (25%), and only four women (3.3%) reported a moderate form of the disease.

Figure (1) shows the change in menstrual cycle post-COVID-19 according to disease severity. Most of the women reported no changes in menstrual cycle length (63.3%), 25.8% reported an increased cycle length, and 10.3% reported a decreased cycle length. There was no significant difference in menstrual cycle length change among women with mild, moderate, and severe infection (P value 0.874). A comparison of menstrual cycle regularity pre- and post-COVID-19 infection, according to disease severity, revealed non-statistically significant changes in menstrual regularity in the three studied women groups (p-values <0.05).

According to SARS-CoV-2 severity, Table (2) shows a comparison of the reproductive function and ovarian reserve between the studied population. The mean concentration of AMH tested during ART treatment post-COVID-19 infection was slightly decreased but not significantly different as compared with the mean concentration of AMH tested before COVID-19 infection in the three groups. Similarly, FSH and LH mean serum levels tested post-COVID-19 showed non-statistically significant difference as compared with the mean serum levels tested before COVID-19 infection in the three groups according to disease severity: (p-values >0.05). The basal antral follicle count (AFC) showed non-statistically significant difference in the three studied groups according to SARS-CoV-2 severity: (p>0.05).

Discussion

The inflammatory effects of COVID19 infection, known as chronic COVID syndrome, can linger for months after the initial infection. It is hypothesized that COVID19 exerts its effects on the ovary because of this prolonged COVID condition characterized by persistent inflammation and also by the direct binding of SARSCoV2 to the ovary.

The ACE2 system, the main component of the renin-angiotensin-aldosterone pathway, is the primary host receptor for the SARS-CoV-2 virus. By binding to ACE2 and altering ACE2 expression in host cells, the virus can infect its intended host cell. Since it is expressed and has a regulatory influence on follicle formation and ovulation, there is concern that the virus may hinder female reproductive activities by modulating ACE2. This has been investigated by numerous studies.

After analyzing the effect of COVID-19 on fertility, Li et al. noted that the virus's potential pathogenicity on testicular and ovarian tissues and on granulosa cells could affect testicular and ovarian functions, spermatozoa, oocyte quality, and pregnancy outcomes (20). For this reason, they stressed the importance of future fertility assessments for persons with COVID-19 infections. Jing et al., showed that in SARS-CoV-2, the expression of ACE2 allows the virus to infect the placenta as well as the uterine lining, which can lead to infertility, monthly abnormalities, and fetal discomfort in pregnant women (6).

Several studies have shed light on the effects of COVID19 on fertility and menstrual cycles, however, there is no clear evidence. This cross-sectional study of 120 infertile women (those with primary or secondary

infertility who were participating in an assisted reproductive technology (ART) regimen) investigated the impact of SARS-CoV-2 on ovarian reserve.

In the current investigation, although there was a trend toward lower AMH levels between the pre- and post-COVID-19 periods, the difference was not statistically significant. Similarly, there was a trend toward lower FSH and LH levels, but the difference was not statistically significant. There was also no statistically significant difference between the three groups tested according to COVID-19 severity.

In line with these findings, a study of 132 young women aged 18 to 40 years, found no statistically significant variation in the blood concentrations of AMH between pre- and post-illness (P = 0.097), suggesting that reproductive function in the early follicular phase was not affected by COVID-19 disease (21, 22). Comparing the levels of sex hormones like FSH, LH, oestradiol, progesterone, and testosterone in 91 women with COVID-19 who were of reproductive age and 91 healthy women, the lack of an effect on ovarian reserve or sex hormone concentrations by SARS-CoV-2 was also confirmed by Li et al. (20). Similar to the present study, previous research has shown no difference between patients' pre- and post-COVID-19 illness blood FSH and LH concentrations.

Wang et al. also reported no changes in FSH, AMH, and the number of antral follicles (AFC) between women who had SARS-CoV-2 Ig-G and those who did not. Their study comprised 65 women with positive SARS-CoV-2 Ig-G and 195 women as the control group (-ve Ig-G) (23).

In a study by Kolanska et al., the AMH levels of the 14 women who tested positive for SARS-CoV-2 (all with moderate disease) were comparable to those of negative SARS-CoV-2 in the control (24). Similar results were obtained in a study that compared AMH levels in hospitalized women with and without COVID-19 (20).

Contrary to our findings, among 1132 individuals who underwent IVF between April and September 2020 (compared to a pre-pandemic study), FSH levels were considerably higher at the beginning of the cycle than before the pandemic, a finding associated with decreased pregnancy rates (25).

Contradictory findings regarding ovarian hormone levels were reported by Ding et al., who found that serum AMH concentrations of 78 COVID-19 patients (17 of whom had severe illness) were significantly lower than the serum AMH concentrations of 51 healthy women, leading them to conclude that COVID had a potentially detrimental impact on ovarian reserve and endocrine function (26, 27). This disagreement in findings between these different studies could be due to several factors, including the use of different groups, the use of different study methods, or the use of a relatively small sample size.

In the process of embryo implantation, the endometrium plays a crucial function. Based on their findings, Henarejos et al., in a meta-analysis of COVID-19 effects on the uterine lining, established that the endometrium is protected from SARS-CoV-2 infection via TMPRSS2 due to its low ACE2 and medium TMPRSS2 levels. However, towards the middle of the secretory process, upregulation of TMPRSS4 was found to be linked to that of Cathepsin L (CTSL), CTSB, FURIN, and MX1. Consequently, during the early and middle secretory phases, the endometrium may be vulnerable to SARS-CoV-2 infection via TMPRSS4. BSG (potential additional host receptor for viral entry) was an alternative receptor whose expression, like that of ACE2 (a protein on the surface of many cells, it is an enzyme that generates small proteins) and TMPRSS2 (a cell service protein primarily expressed by endothelial cells across the respiratory and digestive tracts), changed over the menstrual cycle. It

was discovered that the S protein cleavage factor FURIN strongly activates BSG. In addition to ACE2, increased BSG expression may explain SARS-CoV-2 infection (28, 29).

A cross-sectional online questionnaire study by Malloy et al. (12,302 women) found that 87% of the women had experienced disruptions in their menstrual cycle pattern, 29% had experienced more severe menstrual symptoms (abdominal pain, back pain, discharge changes), and 27% had experienced heavier menstrual bleeding (30).

In the cross-sectional study by Li et al., 25% of infected women experienced altered menstrual flow (most commonly lower flow), and 28% experienced changes in their menstrual cycle pattern after contracting COVID-19 (mainly longer cycle). In patients with systemic problems, menstrual irregularities were most common. Longer menstrual cycles were observed in women with severe illnesses (20).

Conclusion

SARS-CoV-2 virus have no effect on ovarian reserve; however, menstrual changes were found.

Conflict of interest

The authors report no conflicts of interest..

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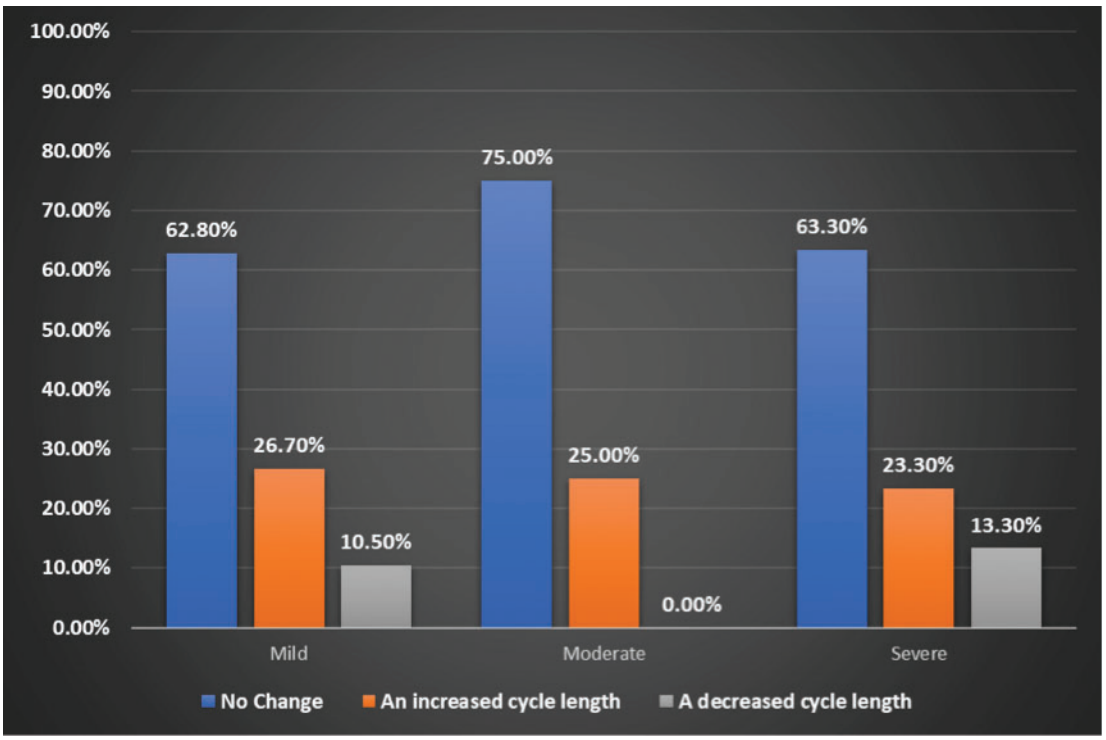
Table (1): Baseline data of the studied women; (N= 120):

		Descriptive statistics
Age	Range (Min – Max)	18.0 - 38.0
	Mean ±SD	26.96 ±5.68
BMI (kg/m²)	Range (Min – Max)	21.8 ±7.62
	Mean ±SD	19.8 - 23.4
Infertility Type; N (%)	Primary	58 (48.3%)
	Secondary	62 (51.7%)
Duration of infertility	Range (Min – Max)	1.0 - 12.0
	Mean ±SD	3.78 ±2.32
Duration since COVID-19 infection	Range (Min – Max)	2.0 - 8.0
	Mean ±SD	3.95 ±1.16
COVID-19 Severity	Mild	86 (71.7%)
	Moderate	4 (3.3%)
	Sever	30 (25.0%)

Table (2): Comparison of the reproductive function and ovarian reserve between the studied population according to COVID-19 severity; (N= 120):

	Mild N= 86	p-value	Moderate N= 4	p-value	Severe N= 30	p-value
AMH ng/ml (before)	2.11 ±1.11	0.071	1.99 ±0.43	0.999	1.82 ±0.84	0.081
AMH ng/ml (after)	2.07 ±1.10		1.99 ±0.45		1.74 ±0.84	
FSH IU/L (before)	5.67 ±2.33	0.063	6.65 ±0.95	0.817	6.50 ±2.26	0.659
FSH IU/L (after)	6.65 ±2.18		6.56 ±1.38		6.61 ±1.66	
LH IU/L (before)	5.55 ±2.74	0.551	5.05 ±2.72	0.693	5.78 ±2.07	0.576
LH IU/L (after)	5.36 ±1.94		4.64 ±1.76		5.88 ±1.83	
AFC (before)	7.85 ±2.03	0.587	8.75 ±4.11	0.769	10.03 ±1.69	0.821
AFC (after)	7.78 ±2.14		8.25 ±1.50		9.97 ±2.62	

Figure 1: Change in menstrual cycle post-COVID-19 according to disease severity.



Breastfed Impact on Intelligence Quotient in Children Attended To Pediatric Clinic in Al-Hussien Hospital at Cairo, Egypt

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Abstract

Background: Both genetic background and environmental factors have an impact on children's intellectual development. One of the initial postpartum experiences is breastfeeding.

Aim and objectives: The main goal of this research was to compare the level of intelligence between breastfed children and non-breastfed and find if there is an impact of breastfed on IQ.

Subjects & methods: This cross-sectional research was conducted in **pediatric clinics at Al-Azhar University Hospitals**. Research was showed on 50 children.

Results: regarding Full-Scale Intelligence Quotient of Wechsler Intelligence Scale of studied children. Full-Scale Intelligence in breastfed group ranged from 75 to 99 with mean ± SD = 88.39 ± 6.42 while in non-breastfed group the Full-Scale Intelligence ranged from 64 to 92 with mean ± SD = 82.63 ± 7.15.

Conclusion: The present study compare intelligence level between breastfed and non-breastfed children. We concluded that there was significant relation between high Wechsler Intelligence Scale score and breastfed.

Key words: Breastfed; IQ.

INTRODUCTION

Both genetic inheritance and environmental factors have an impact on children's intellectual development. One of the early postnatal experiences of this kind is breastfeeding.

The Academy of Nutrition and Dietetics contends that for the first six months of life, breastfeeding exclusively offers the best nutrition and health protection and that from six months of age until at least 12 months of age, breastfeeding with complementary food is considered to provide the best nutrition for infants. [1]

In studies of young children, the advantages of breastfeeding seem to be the greatest. It has a wide range of anti-inflammatory, immunomodulatory, and antibacterial

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compounds that benefit children's cognitive and psychomotor development. [2]

A worldwide increase in Intelligence has been linked to improvements in nutritional policy. The brain's shape, behavior, and IQ are all correlated with prenatal and early nutrition. There is evidence that giving very preterm babies, especially boys, a high-nutrient diet will assist to lessen the loss of brain growth and IQ these babies frequently face. Low IQ can also be brought on by deficiencies in protein, iron, zinc, folate, iodine, and B12. [3]

It is now clear that the gut microbiome is important for a baby's growth and that the way a baby is fed can affect the microbial communities in their gastrointestinal tract. [4]

Little doses of formula milk can alter the composition and relative abundance of the bacterial communities that are typically present in a breastfed infant's gastrointestinal tract. By interfering with the colonisation and growth of the neonatal gut microbiome, formula feeding has the potential to lessen the advantages of feeding infants just human milk. [5]

Patients and methods

Children attending pediatric clinics at Al-Azhar University Hospitals in the period of 1st of October 2021 to 31st of March 2022. Inclusion criteria: children ranging from 6 to 14 years old and accepted to participate in this study, from both sex (male and female), the children who don't have no mental disorder or any syndrome or organic disease affecting the IQ level.

Exclusion criteria: children with any medical syndrome, children who have been injured during birth, children who had admitted to Neonatal ICU for any reason, children who have any psychiatric disorder affecting the mental function and the children who have any other organic disorder.

Statistical Analysis: SPSS 26.0 for Windows was used to gather, tabulate, and statistically analyse all of the data (SPSS Inc., Chicago, IL, USA).Chi-square (X2)

test of significance: was used to relate proportions among qualitative parameters.

Independent T-test: was used it in order to compare between two independent groups with parametric quantitative data.

To identify the relationship between an exposure and an outcome, odds ratios (OR) interpreted with 95% confidence intervals are used. These odds ratios show the likelihood that an outcome occurred given a specific exposure in comparison to the likelihood that the outcome would not have occurred without that exposure.

RESULTS

Table (1): Demographic & Clinical characteristics.

	Breastfed (n=23)	Non-breastfed (n=27)	P
Age (years)			.219
Mean ± SD	7.96 ± 1.55	8.56 ± 1.81	
Range	6 – 12	6 – 13	
Sex, n (%)			.845
Male	13 (56.5%)	16 (59.3%)	
Female	10 (43.5%)	11 (40.7%)	
Mother age (years)			.326
Mean ± SD	30.57 ± 1.81	31.11 ± 2.04	
Range	27 – 34	26 – 36	

Mother education, n (%)			
Not educated	0	2 (7.4%)	.369
Elementary	2 (6.7%)	5 (18.5%)	
Intermediate	4 (17.4%)	5 (18.5%)	
Secondary	5 (21.7%)	8 (29.6%)	
University	9 (39.1%)	6 (22.2%)	
Postgraduate	3 (13.1%)	1 (3.7%)	
Economic status, n (%)			
Low	5 (21.7%)	4 (14.8%)	.252
Moderate	11 (47.8%)	19 (70.4%)	
High	7 (30.4%)	4 (14.8%)	
Residence			
Rural	10 (43.5%)	11 (40.7%)	.845
Urban	13 (56.5%)	16 (59.3%)	

This table showed that basic characteristics were comparable in both group but without statistically significant difference (P>0.05)

Table (2): Wechsler Intelligence Scale for children and Full-Scale Intelligence Quotient of Wechsler Intelligence Scale of studied children.

	Breastfed (n=23)	**Non-breastfed (n=27)**	**P**
Verbal Comprehension Index			**.044**
Mean ± SD	94.96 ± 6.68	90.74 ± 7.56	
Range	86 – 110	77 – 104	
Perceptual Reasoning Index			.151
Mean ± SD	83.26 ± 8.51	79.78 ± 8.35	
Range	69 – 100	64 – 96	
Working Memory Index			.319
Mean ± SD	91.7 ± 8.61	89.67 ± 5.51	
Range	76 – 106	74 – 101	
Processing Speed Index			.153
Mean ± SD	79.3 ± 8.82	76.1 ± 7.29	
Range	65 – 96	62 – 90	
Full-Scale IQ			**.005**
Mean ± SD	88.39 ± 6.42	82.63 ± 7.15	
Range	75 – 99	64 – 92	

Table (2) showed Verbal Comprehension Index and Full-Scale Intelligence were significantly higher among breastfed children (P<0.05). However, perceptual reasoning index, working memory index, and processing speed index were higher among breastfed children but without statistically significant difference (P>0.05)

Table (3): Association between breastfed and Wechsler Intelligence Scale score

	OR	S.E.	Sig.	95% C.I.	
				Lower	Upper
Verbal Comprehension Index	.913	.058	**.031***	.815	1.023
Perceptual Reasoning Index	.902	.048	.118	.821	.991
Working Memory Index	1.021	.058	.722	.911	1.145
Processing Speed Index	.911	.048	.053	.828	1.001
Full Scale IQ	.840	.066	**.008***	.738	.956

OR: Odd Ratio. CI: Confidence interval. SE: standard error.

This table showed breastfeeding is significantly associated with higher Verbal Comprehension Index and full-scale IQ.

Discussion

This cross-sectional study was conducted in pediatric clinics at Al-Azhar University Hospitals. This study was conducted on 50 children. All patients were divided into 2 groups: Breastfed group (n=23) and non-breastfed group (n=27).

All children in breastfed group have been got exclusive breast milk for 6 months with adding complementary food from 6 months until at least 12 months of age

All the 50 children participate in our study going to national schools in Cairo, Egypt and they are either at primary or secondary school according to their age

About the study's breastfed children's demographics. 13 cases, or 56.5% of the total population, were men. Children in the study cohort varied in age from 6 to 12, with a mean age and standard deviation of 7.96 1.55. Mothers' ages in the research population varied from 27 to 34, with a mean and SD of 30.57 and 1.81, respectively. There were 5 patients (21.7%) in the study population with low income.

As well as the demographic details of the research non-breastfed children. 16 patients, or 59.3% of the study group, were men. The study cohort included children aged 6 to 13; the mean age standard deviation was 8.56 1.81. Mothers' ages in the research population varied from 26 to 36, with a mean and SD of 31.11 and 2.04, respectively. In the study population, there were 4 patients with low income levels (14.8%).

Verbal Comprehension in the breastfeeding group varied from 86 to 110, with a mean and standard deviation of 94.96 and 6.68 respectively. The range of Perceptual Reasoning in the sample population was 69–100, with a mean and standard deviation of 83.26–8.51. With a mean and standard deviation of 91.7 and 8.61, working memory in the study sample varied from 76 to 106. Processing Speed in the study population was 65–96, with a mean and standard deviation of 79.3–8.82. With a mean and standard deviation of 88.39 and 6.42, full-scale intelligence in the research population varied from 75 to 99.

In the non-breastfed group we found that Verbal Comprehension in the study population ranged from 77 to 104 with mean ± SD = 90.74 ± 7.56. Perceptual Reasoning in the study population ranged from 64 to 96 with mean ± SD = 79.78 ± 8.35. Working Memory in the study population ranged from 74 to 101 with mean ± SD = 89.67 ± 5.51. Processing Speed in the study population ranged from 62 to 90 with mean ± SD = 76.1 ± 7.29 .Full-Scale IQ in the research sample varied from 64 to 92, with a mean and SD of 82.63 and 7.15, respectively.

(Lopez et al., 2021) argued that conflicting research on both positive and insignificant

impacts of breastfeeding on children's cognitive development. Factors related to breastfeeding, particularly the socioeconomic status and intelligence of the mother, may complicate a relationship. [6]

(Mychaleckyj et al., 2018) was that the hypothesised interaction effect of FADS2 and breastfeeding on IQ was not supported and that the reported benefits of breastfeeding on IQ represent differential likelihood of breastfeeding as a function of parental education. Current understanding of genotype-phenotype interactions generally suggests that, if there is a genetic propensity for some infants to benefit more from breastfeeding, it is likely polygenic, but additional research would be required to validate this. So, it may be inferred that breastfeeding may have a marginal impact on IQ, but that impact may be mitigated by confounding variables such as maternal intellect. [7]

However, a meta-analysis of prospective studies looking into the relationship between breastfeeding and IQ in 2006 found 431 references and a combined sample size of 5,475 kids. The research group concluded that breastfed had no significant effect on intelligence. [8]

However, a recent systematic review and meta-analysis that included 17 trials and a total of 17,046 healthy breastfed infants was published in 2015. Of these infants, 13,889 (81.5%) participated for 6.5 years. In both children and adolescents, IQ performance was favourably correlated with breastfeeding. Average participants who were breastfed had more high IQ participants than non-breastfed participants. [9] And these results line up with the conclusions of our investigation.

Conclusion

This is comparative study compare the intelligence quotient between breastfed and non-breastfed children. We concluded that there was significant relation between high IQ on Wechsler Intelligence Scale and breastfed children.

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Cairo, Egypt

2022

The Correlation between Duration of Fetal Extraction during Cesarean Section and Development of Transient Tachypnea of Newborn

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Abstract

Background: Pregnancy and delivery are considered as normal in women. Some of the deliveries put the mother and baby's life at risk requiring caesarean section but sometimes it is also performed on request. Negative obstetric and perinatal outcomes are more likely after a cesarean section.

Objectives: Our research was done to demonstrate how operating time affects the immediate neonatal outcome.

Methodology: The study included 200 women having a singleton pregnancy, a full term cesarean delivery, and no underlying medical conditions (uncomplicated pregnancy), fetal distress or neonatal congenital anomalies. The neonates were assessed and evaluated through Apgar score.

Results: : the duration from incision of the skin till clamping the cord was ranged between 3 and 22 minutes, and the duration from incision of the uterus till clamping of the cord was ranged between .5 to 4 minutes. No significant correlation between Apgar score of the neonates, either after 1 minute or 5 minutes, and the U-C interval. 13 neonates developed Transient Tachypnea of Newborn (TTN) and transferred to NICU. Gestational age ranged between 38 and 40 weeks, with mean of 38.740± 0.753 weeks. TTN was developed in 7 males and 6 females. no significant relation between BMI and development of TTN. no significant correlation between the S-C interval and the development of TTN. No statically significant correlation between development of TTN and U-C interval.

Conclusion: Gestational Age is a predictor for the development of TTN; CS is preferred to be done at 39 weeks. Increase the duration from the uterine incision till the cord clamp increase the probability of TTN occurrence.

Key words: Caesarean section; uncomplicated pregnancy; Apgar score; Transient Tachypnea of Newborn

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Introduction

The traditional definition of a cesarean birth is the delivery of a fetus via an anterior uterine wall incision made during surgery [1].

Cesarean deliveries are now the most common surgery in obstetrics. The emergence of newborn respiratory diseases, particularly the incidence of Transient Tachypnea of the Newborn, have been mirrored by this circumstance. A cesarean section is often carried out when a vaginal delivery might endanger the life or health of the mother or the infant, however in more recent years it has also been requested for deliveries that would have otherwise been natural [2].

CS has more postoperative problems, such as hemorrhage and a lengthier recovery period. Even though they may have been done at full term, CS conducted without antecedent labor is linked to a greater risk of respiratory distress than those performed after the beginning of labor [4, 5].

Understanding the impact of operating duration on perinatal morbidity is crucial given the rising prevalence of cesarean sections worldwide, since operative time may be one of the variables contributing to a poor neonatal outcome during cesarean surgery [6].

Infants born by cesarean section are more likely than infants born vaginally to experience negative respiratory outcomes like respiratory distress syndrome, transient tachypnea of the newborn, higher neonatal morbidity, admission to the NICU, especially if delivery occurs before the start of labor, and maternal pain in the puerperium [7,8].

An increased risk of newborn encephalopathy, future cerebral palsy (cp), and learning challenges is substantially correlated with a critically low Apgar score at 5 minutes [9].

The purpose of this research was to evaluate the relationship between the length of fetal extraction after cesarean delivery and the likelihood that the baby may have brief tachypnea.

Patients and methods

The present study was carried out in Beni-Suef University Hospital and Nasser central Hospital during the period from May 2020 to December 2020, Two Hundred (200) pregnant women were included in the study fulfilling the inclusion and exclusion criteria.

Inclusion criteria included: Elective cesarean section, Primary and repeat Cesarean section, No history of medical disorders, Gestational age between 38 weeks to 40 weeks

Exclusion criteria included: Cesarean section due to fetal distress, Fetal congenital anomalies, Multiple pregnancies, Gestational age below 38 weeks and above 40 weeks, IUGR, General anesthesia, Maternal drug intake before C.S which may affect the neonatal wellbeing e.g. “narcotics”, Antepartum hemorrhage, Maternal medical disorders e.g. DM, hypertension, anti-phospholipid syndrome, Premature rupture of membrane.

Patients included in the study were subjected to the following:

Full History Including: Maternal age, Gestational Age, Obstetric history, Mode of delivery in the previous pregnancy/ pregnancies if present, Exclusion of any medical disorder, or any drug intake which may affect neonatal wellbeing. Clinical Examination Including: Vital signs, systematic and obstetric Examination. Laboratory Investigations Including: Fasting and 2h PP Blood Sugar, Albumin in Urine, CBC, coagulation profile, liver & kidney function tests.

Ultrasound: To asses Biophysical Profile (BPP), which include: Amniotic Fluid Index (AFI), Fetal Movement, Fetal tone, Fetal Breathing, and Non stress test using CTG, to assess fetal wellbeing and to confirm the Gestational Age.

Operative assesment including: Time from initiation of anesthesia till clamping of the

cord and time from incision of the uterus till clamping of the cord were recorded.

Neonatal assessment Including: Follow up the neonate for Apgar score at 5 min then follow up after 6-24 hours by trained pediatrician and neonatal weight. Apgar score at 1minute and 5 minutes, respiratory rate and weight of neonate were reported by the pediatric team, and then occurrence of Transient Tachypnea of Newborn (TTN) among the studied neonates (which was followed up for 6-24 hours) was observed.

Ethical statement:

In accordance with its guidelines, the ethical research council of the faculty of medicine at Beni-Suef University accepted this study. All of the pregnant participants gave their written permission after receiving full disclosure.

Statistical analysis

SPSS version 25 was used for data analysis. Description of variables was presented as mean, standard deviation (SD), median, range, numbers (No.) and percent's (%); Using kolomogrove, ANOVA, T-test test, Pearson and spearman. The significant results were when P-value $\leq$ 0.05

Results

The mean age of the studied women was 27.3±5.5 years. The mean gestational age was 38.7±0.75 weeks. The mean BMI of the studied women was 29.2±3.5. Most of fetal presentations were cephalic 92.5% and least of them were breach 7% and only one case 0.5% had transverse presentation.39.5% of the studied cases were the third time to pass section, 36.5% were the second time and 24% were the 1st time. The mean time from initiation to cord clamping was 17.5±4.6 minutes while the Time from uterine incision till cord clamping was 2.4±1.1 minutes. The mean weight of the studied neonates was 3298±346 grams. The Apgar score after 1 minute and after 5 minutes was 5.6±1.5 and 8.2±1.3 and the respiratory rate was 51±7/ minute. The sex distribution of the neonates was almost equal as males were 45.5% and females were 54.5% (Table 1).

There were 6.5% of the studied neonates had transient tachypnea of neonates (Table 2).

Babies who had TTN had statistically significant lower gestational age 38.1±0.3 weeks versus38.8±0.8 weeks of who passed without TTN and also had statistically significant longer duration from uterine incision till cord clamping 3.4±0.9 minutes versus 2.3±1.1 minutes of who passed without TTN (P-value=0.001) (Table 3).

There was a statistically significant weak negative correlation between the respiratory rate and gestational age, maternal BMI and neonatal weight. Also, there was a statistically significant weak positive correlation between the Apgar score at 5 minutes and the gestational age (Table 4).

Babies with transverse position had a significant higher respiratory rate and lower Apgar score at 1 and five minutes (Table 5).

There was no significant difference between male and female babies regarding their respiratory rate and Apgar score at 1 and five minutes (Table 6).

There was no significant difference between mothers who were passing 1st, 2nd or 3rd section regarding their babies' respiratory rate and Apgar score at 1 and five minutes (Table 7).

The cut off was 2.9 (minutes) of the duration from the uterine incision till the cord clamp, it is predicted the occurrence of TTN by sensitivity 84.6% and exclude its absence with specificity 55%. Increase the duration from the uterine incision till the cord clamp increase the probability of TTN occurrence and decreases the probability of its exclusion or absence (Figure 1).

Discussion

TTN, being the most common cause of neonatal respiratory distress, is closely related to Cesarean section. This association is more pronounced when the cesarean delivery is scheduled before initiation of labor [10].

On the other hand, spinal anesthesia has become the default anesthetic procedure offered in everyday obstetric practice, except when general anesthesia is necessary in certain indications. The goal of the current study was to investigate the relationship between the length of the fetal extraction procedure during a cesarean section, measured as the development of TTN and the Apgar score recorded after five minutes (I-C interval) or as the time from the beginning of anesthesia to clamping the cord (U-C interval). According to the study's findings, which included 200 women, there was no statistically significant link between the I-C interval and the Apgar score recorded after five minutes (P-value = 0.95) and between the U-C interval and the Apgar score reported after five minutes (P-value = 0.22).

The current study is supported by a study by Maayan-Metzger and colleagues [11] that found no significant correlations between the majority of the major neonatal short-term clinical outcomes and the length of the three main stages of an elective cesarean delivery at term (from induction of anesthesia to delivery (I-D), from incision of the skin to delivery (S-D), and from incision of the uterus to delivery (U-D). The findings suggest that obstetricians conducting regional anesthetic-assisted elective cesareans for term pregnancies have a reasonably long timeframe to complete the procedure without compromising infant health.

The study agrees also with a study done by ZAHER and colleagues [12] and demonstrated no correlation between the time between the start of anesthetic and the time the cord was clamped (up to 25.5 minutes for uterine incision and 4.5 minutes for cord clamping) and the Apgar score at 1 and 5 minutes. However, Doherty and colleagues found in their research A longer operating duration was directly correlated with low five-minute Apgar scores. They divide the cesarean section time intervals into three categories: 30 min, 30–60 min, and > 60 min. Apgar 5 min < 7 was significant with the duration between 30-60 min and >60 min. These findings persisted even after the underlying maternal conditions and the reason for the cesarean had been taken into consideration. This suggests that the surgical technique from incision to delivery is an important consideration in neonatal outcome [13].

The current results showed no significant correlation between multiple cesarean section and Apgar score recorded after 5 minutes (P-value = 0.256). The present study agrees with a study done by Qublan and Tahat [14] ,in Jordon, and showed no significant correlation between multiple cesarean section and Apgar score recorded after 1 minute and 5 minutes, where Apgar score >7 at one and 5 minutes were similar in the 3 groups; Group 1 = with 1 previous C.S (n=1183); Group 2 = 2 previous C.S (n=781); and Group 3 = >3 previous C.S (n=312). However, it differs with different research conducted by Gedikbasi et al. [15] that shown that having several, consecutive cesarean procedures raise the chances for operating complications and unfavorable neonatal outcomes.

Unexpectedly, in the current study also, there was no significant correlation between the gestational age and Apgar score 5 min (P-value=0.09), this can be explained as all the cases in the study were between 38 to 40 weeks.

However, Li et al. [16] demonstrated that gestational age had an effect on Apgar score. The gestational age was closely correlated with the 1- and 5-minute Apgar scores. The main factors that contributed to a falling Apgar score as gestational age decreased were respiratory efforts, muscular tone, and

reflex.

Another American research revealed that gestational age affected the distribution of Apgar scores, with the lowest gestational ages having larger proportions of low Apgar scores [17].

More analysis for the results in the present study, showed that pregnant women with history of previous cesarean section increased the duration of the I-C interval, with highly significant correlation (P-value = 0.01).

According to research conducted in Mississippi, the length of prior cesarean sections had a substantial impact on the length of the cesarean operating time [13].

It agrees with another study done by Wilson et al. [18] who concluded that in women with previous cesarean deliveries, operative times become longer. It was noticed, in the present study, the absence of significant correlation between the I-C interval and the neonatal respiratory rate (P-value = 0.817), or the occurrence of TTN (P-value = 0.437). A thesis done in 2013, by OYEYEMI [19], on 200 pregnant women, showed that the duration of fetal extraction from initiation of anesthesia until extraction of fetus during cesarean section has no effect on incidence of Transient Tachypnea of The Newborn; While the increase in duration of fetal extraction during cesarean section is associated with increase in neonatal respiratory rate.

The current study show that U-C interval increased in the duration, with the increase of the duration of I-C interval with a significant correlation (P-value = 0.001). It agrees with in a study done by Maayan-Metzger and colleagues [11] where longer I-C interval among women with longer U–C intervals (P-value = 0.04).

History of doing Previous cesarean section before showed no significant correlation with the U-C interval (P-value = 0.829).

It agrees with Maayan-Metzger and colleagues [11] study where no significant correlation between those with previous cesarean section and U-C interval.

In the present study also, birth weight of the neonates showed no significant correlation with the I-C interval and U-C interval (P-value = 0.3, P-value = 0.883, respectively).

It agrees with Doherty and co-workers study [13], while in Maayan-Metzger and colleagues study [11] , there was a significant correlation between birth weight of the neonates and U-C interval, but no significant correlation with I-C interval.

Further analysis in the results of the present study showed that the gestational age was statistically significant with Transient Tachypnea of Newborn (TTN), as gestational increase the incidence of TTN decrease (P-value= 0.002).

The findings supports a study by Riskin and colleagues that revealed that GA before 38 weeks was linked to a higher risk of TTN in babies delivered through elective CS. Longer hospital stays and substantial morbidities were linked to TTN. Younger GA and CS delivery are risk factors for TTN. Even though TTN is a self-limiting condition, it is still accompanied by serious morbidities. Scheduling elective CS at a gestational age of at least 38 weeks may reduce the incidence of TTN [20].

According to the research done by Tita and colleagues, if an elective cesarean birth is postponed until the fetal gestational age is between 39 and 41 weeks, minimal complications arise. If an elective cesarean birth was carried out in the 37th through 38th week of pregnancy, complications, especially those involving the neonatal respiratory system, were more likely to occur. Before 39 weeks of pregnancy, elective recurrent cesarean birth is prevalent and is linked to poor respiratory and other newborn outcomes [21].

When compared to intended vaginal delivery, Tita and colleagues [21] found that elective cesarean delivery was generally

associated with a worse neonatal outcome. Delivery by elective cesarean before 39 weeks also increased the incidence of serious neonatal respiratory morbidity, which is defined as requiring continuous oxygen supplementation, continuous positive airway pressure, or mechanical ventilation for any length of time. Compared to babies born by elective cesarean at 39 weeks or those delivered vaginally at any gestational age, infants delivered by elective cesarean at 37 weeks were 2- and 4-times more likely to develop significant respiratory morbidity.

According to Robinson et al., [22] there are advantages to delaying an intentional repeat cesarean birth until 39 weeks of gestation. The model showed rising costs via an increase in unfavorable outcomes among elective repeat cesarean births carried out before 39 weeks of pregnancy.

With a P-value of 0.707, the present investigation found no statistically significant relationship between newborn gender and TTN. According to research by Derbent and colleagues [23], lower gestational age, cesarean birth, and male sex are all independent risk factors for TTN.

Conclusion

Babies with transverse position had a significant higher respiratory rate and lower Apgar score at 1 and five minutes. Increase the duration from the uterine incision till the cord clamp increase the probability of TTN occurrence and decreases the probability of its exclusion or absence.

Conflict of interest

None

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Table (1) Basic operative characteristics of the studied cases:

Characteristics	Number No=200(%)
Presentation:	
Cephalic	185(92.5%)
Breach	14(7%)
Transverse	1(0.5%)
C/S code:	
1st	48(24%)
2nd	73(36.5%)
3rd	79(39.5%)
Maternal age (years):	27.3±5.5
Gestational age (weeks):	38.7±0.75
Maternal BMI	29.2±3.5
SC Duration	12.8±3.9
Neonatal weight(gm):	3298±346
Neonatal sex:	
Males	91(45.5%)
Females	109(54.5%)
Apgar score after 1 min:	5.6±1.5
Apgar score after 5 mins:	8.2±1.3
Respiratory rate:	51±7

Table (2) Incidence of transient tachypnea of the studied neonates

TTN	no=200 (%)
Yes	13(6.5%)
No	187(93.5%)

Table (3) Relation between TTN and different maternal characteristics

Maternal and fetal	TTN	Mean±SD	P-value
Maternal age	**Yes**	27.9±3.5	0.664
	No	27.2±5.6	
GA	**Yes**	**38.1±0.3**	0.001**
	No	38.8±0.8	
Maternal BMI	**Yes**	28.4±4	0.384
	No	29.3±3.4	
Neonatal Weight	**Yes**	3185.4±402.4	0.224
	No	3306.3±341.6	
Duration from initiation to cord clamping	**Yes**	18±2.9	0.695
	No	17.5±4.7	
Duration from Skin incision to Cord clamping	**Yes**	13.5±2.8	0.447
	No	12.7±3.9	
Duration from uterine incision till cord clamping	**Yes**	**3.4±0.9**	0.001**
	No	2.3±1.1	

**P-value is highly significant at ≤0.001

Table (4) Correlation between fetal Respiratory rate and Apgar score at 1 minute and 5 minutes and different maternal and neonatal characteristics

Maternal and fetal characteristics		RR	Apgar after 1 min	Apgar after 5min
Maternal age	Pearson Correlation (r)	0.052	0.043	-0.092
	P-value	0.467	0.548	0.196
GA	Pearson Correlation (r)	**-0.215****	0.125	**0.151***
	P-value	**0.002**	0.078	**0.033**
Maternal BMI	Pearson Correlation (r)	**-0.174***	-0.009	0.004
	P-value	**0.014**	0.896	0.953
Neonatal Weight	Pearson Correlation (r)	**-0.154***	0.091	0.120
	P-value	**0.029**	0.200	0.092

Duration from initiation to cord clamping	Pearson Correlation (r)	-0.032	0.033	-0.068
	P-value	0.656	0.646	0.340
SC Duration	Pearson Correlation (r)	0.036	0.047	-0.075
	P-value	0.616	0.511	0.291
Duration from the uterine incision till the cord clamp	Pearson Correlation (r)	0.121	-0.021	-0.055
	P-value	0.089	0.772	0.442
Ops Code	Pearson Correlation (r)	0.028	0.043	-0.098
	P-value	0.694	0.543	0.166

Table (5) Comparison between different fetal presentation regarding fetal Respiratory rate and Apgar score at 1 minute and 5 minutes

Dependent factors		Mean±SD	
RR	cephalic	50.79±7.029	
	breach	54.71±10.373	<0.001**
	transverse	77.00±0	
Apgar after 1 min	cephalic	5.70±1.469	
	breach	5.07±1.940	0.019*
	transverse	2.00±0	
Apgar after 5min	cephalic	8.27±1.235	
	breach	8.07±1.492	0.031*
	transverse	5.00±0	

Table (6) Comparison between males and females regarding fetal Respiratory rate and Apgar score at 1 minute and 5 minutes

Dependent factors		Mean±SD	P-value
RR	Male	52.01±8.088	0.163
	female	50.51±7.046	
Apgar after 1 min	Male	5.51±1.649	0.374
	female	5.74±1.417	
Apgar after 5min	Male	8.23±1.359	0.925
	female	8.25±1.195	

Table (7) Comparison between women with different counting of the current section regarding fetal Respiratory rate and Apgar score at 1 minute and 5 minutes

Dependent factors		Mean±SD	P-value
RR	1st	49.90±6.957	
	2nd	52.45±7.984	0.162
	3rd	50.82±7.414	
Apgar after 1 min	1st	5.58±1.471	
	2nd	5.56±1.581	0.759
	3rd	5.73±1.525	
Apgar after 5min	1st	8.44±1.147	
	2nd	8.25±1.382	0.380
	3rd	8.11±1.230	

Figures

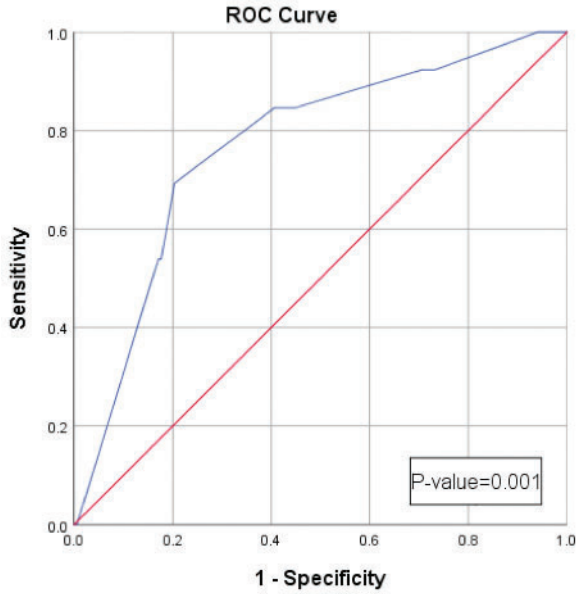

Figure (1) Receiver operating characteristic curve for prediction of the occurrence of TTN from the duration from the uterine incision till the cord clamping

Trans Obturator Tape (TOT) Procedure in cases of Stress Urinary Incontinence: Patients' Satisfaction and Cure Rates (Retrospective Analysis)

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Abstract

Background: Stress urinary incontinence (SUI) is the involuntary escape of urine on exertion or physical effort, including sports activities, or on coughing or sneezing, affecting the women's health-related quality of life, either the psychological well-being or physical activity.

Aim of the Work: To assess the rates of cure, complications, and patient's satisfaction after doing a Trans-obturator tape (TOT) procedure in patients with stress urinary incontinence (SUI).

Patients and Methods: This retrospective study was conducted at at the Urogynecology Department, Ain Shams University Maternity Hospital from June 2022 till January 2023 and performed on a total of 79 women who underwent trans-obturator tape (TOT) procedure for treatment of female urinary incontinence in the last four years in urogynecology department.

Results: As regards Follow-up postoperatively, our study results revealed that cure rate and satisfaction rate were 55.7% and leak and Unsatisfaction were reported in 44.3% of cases and the cases with urine leak and unsatisfaction significantly had higher age as well as more frequent hypertension, pelvic prolapse and urinary positive culture as well as longer hospital stay. In addition, diabetes mellitus is significantly associated with leak. The total ICIQ-SF scores and IIQ-7 were 0 in all patients after the surgery while before the surgery, the ICIQ-SF scores and IIQ-7 were missed which is the disadvantage the retrospective study design of the current study.

Conclusion: Our study showed that the TOT procedure is effective in the treatment of pure SI and Mixed incontinence with high success rates, high patient satisfaction and the least complications.

Keywords: Trans Obturator Tape - Stress Urinary Incontinence - Tension Free Vaginal Tape.

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Introduction

Stress urinary incontinence is a gynecological condition that negatively affects the woman life either psychologically, and quality of life. however, it is more prevalent in older women, particularly amongst those in institutionalized care. [1]

The predisposing factors include multiple vaginal deliveries, constipation, increased BMI, chronic cough, old age, menopause. 2 The Diagnosis depends on the clinical assessment, symptoms (frequency and triggering factors) and to assess the effect of SI by QOL (quality of life) questionnaire. Different urodynamics studies confirm the diagnosis and help in assessing degree of incontinence [3]

Modification of lifestyle is a crucial step in the treatment of SUI and includes diet modifications, weight reduction, cessation or decrease smoking , regular pelvic floor muscle training for at least 3 month. [4]

When conservative treatment fails, the surgical treatment is resorted in the form of mid urethral slings. [5]

The most common performed procedures now for treating SUI are the mid urethral slings are currently TOT and tension free vaginal tape (TVT) on top of these procedures. [6]

The common point of mid urethral sling operations is the use of mesh material passed under the urethra. [7]

Based on the "Integral Theory" by Petros and Ulmsten 8, the retro pubic tapes (TVT) were released and introduced in 1996. Their role was to imitate the pubo urethral ligament and became widely adopted. [9]

Taking into consideration the complications associated with the retro pubic approach (Bladder injury, Injury of the major vessels, Bowel Injury, Postoperative Voiding difficulties and low patients' satisfaction) Delorme et al. 10 promoted the TOT outside and de Leval 11-12 the TOT inside out approach based on the "Hammock Hypothesis". [9]

Aim of the Work: To assess the rates of cure, complications, and patients' satisfaction after doing a Trans-obturator tape (TOT) procedure in patients with stress urinary incontinence (SUI).

Patients and Methods

After ethical committee approval and informed consent from the patients, this retrospective study was conducted at tertiary care hospital at Urogynecology Department, Ain Shams University Maternity Hospital from June 2022 till January 2023 and performed on a total of 79 women who underwent trans-obturator tape (TOT) procedure for treatment of female urinary incontinence in the last 4 years in urogynecology department.

Study population:

All women who undergone transobturator tape (TOT) procedure for treatment of female urinary incontinence in the last 4 years in urogynecology department, Ain Shams University Maternity hospital.

Inclusion criteria:

Being aged above 18 years, and patient with stress urinary incontinence (SUI) and stress predominant mixed urinary incontinence (MUI).

Stress Urinary Incontinence (SUI) diagnosed by urodynamic study was defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction (Detrusor Overactivity Incontinence "DOI"). 13

Exclusion criteria:

Having a neurogenic bladder, history of urethral reconstruction, history of anti-incontinence surgery, and being aged below 18 years.

Sample size:

Şik et al. 14 reported proportion of objective

cure rate after TOT of 88.5%. A sample size of at least 79 cases produces a two-sided 95% confidence interval with a width equal to 0.200 when the sample proportion is 0.880. Sample size calculation produced a sample size of a minimum of 79 patients achieving 80% power and x error at 0.05.

Study procedure:

The patient files in the urogynecology unit as well as other units in the hospital were reviewed & the following data were collected: Age, Parity, & BMI, associated medical conditions like Diabetes Mellitus, Hypertension, Chronic Obstructive Pulmonary Disease, Chronic Kidney Disease, Chronic Lung Disease, Chronic Constipation, Abdominal Ascites and Swellings, pre operative preparation, urine analysis, urine culture, results of urodynamic study, and associated prolapse assessed by POPQ system.

Primary outcome

1. Cure rate:

Defined as a self-reported absence of symptoms, no treatment over two years. We used the Arabic version of the International Consultation of Incontinence Questionnaire Short Form (ICIQ-UI-SF) to assess urinary incontinence before surgery and at two years postoperatively. 15

Its validation revealed that the assessment of the internal consistency was excellent, with the Cronbach's alpha coefficient of 0.97 (95% CI: 0.88-0.98). 16-17

2. Patient satisfaction "satisfaction rate"

We used the Arabic version of the IIQ-7 (Incontinence Impact Questionnaire) to evaluate generalized health-related quality of life (physical activity, social relationships, travel, and emotional health). 18-19

The IIQ (incontinence impact questionnaire) was used in this study for QOL assessment 20. It was composed of 30 questions. 21

3.Recurrence rate at 2 years

Secondary outcome:

Injury to (bladder, urethra, obturator vessels), post-operative retention of urine & intermittent self-catheterization, duration of hospital stay, vaginal erosion, and female sexual dysfunction (dyspareunia).

Statistical analysis:

The Statistical Package for Social Sciences (SPSS, V. 22) was used for coding, tabulation, and analysis of study data. Quantitative data were expressed by mean and SD, while qualitative data were described by number and percentage.

Shapiro-Wilk test was used to check normal distribution. We used Chi-Square and Fisher's Exact test to compare different groups. P value < 0.050 was considered significant.

Results

I) Descriptive statistics of the studied cases

Table (1): Baseline demographic characteristics and comorbidities among the studied cases

Characteristics	Mean±SD	Range
Age (years)	46.3±10.0	27.0–70.0
BMI (kg/m^2)	32.4±4.7	20.5–48.9
Parity	4.0 (3.0–5.0)	0.0–8.0
	n	**%**
Diabetes mellitus	17	21.5%
Hypertension	18	22.8%

Constipation	50	63.3%
Chronic liver disease	13	16.5%
Asictes	4	5.1%
Chronic kidney disease	1	1.3%
Chronic obstructive pulmonary diseases	0	0.0%
Pelvic prolapse	57	72.2%

Total=79

Table (1) showed that: among the studied cases; pelvic prolapse & constipation were the most frequent comorbidities (72.2% and 63.3% respectively).

Table (2): Baseline urine analysis among the studied cases

Characteristics	n	%
Red blood cells	3	3.8%
Pus cells	46	58.2%
Epithelial cells	15	19.0%
Red cells	6	7.6%
Calcium oxalate	17	21.5%
Uric acid	2	2.5%
Amporphus	9	11.4%
Positive culture	21	26.6%

Total=79

Table (2) showed that: among the studied cases; pus cells were detected in 58.2% of the studied cases, 26.0% had positive culture.

Table (3): Operative findings among the studied cases

Characteristics	n	%
Visceral injury	2	2.5%
Vaginal erosions	1	1.3%
	Median (1st - 3rd IQ)	**Range**
Hospital stay (days)	2.0 (1.0–3.0)	1.0−14

Total=79. IQ: Interquartiles.

Table (3) showed that: among the studied cases; visceral injury and vaginal erosions were uncommon (2.5% and 1.3% respectively).

Table (4): Postoperative complications among the studied cases

Complications		n	%
Urine retention		4	5.1%
Dyspareunia		27	34.2%
Recurrence		13	16.5%
Time to recurrence (Total=13)	**1-6 months**	7	53.8%
	7-12 months	4	30.8%
	13-18 months	2	15.4%

Total=79

Table (4) showed that: among the studied cases; dyspareunia was the most frequent complication (34.2%), while recurrence and urine retention were (16.5% and 5.1% respectively).

Majority of recurrence occurred in the 1st 6-months (53.0%), followed by 2nd 6-months (30.8%), then 3rd 6-months (15.4%).

Table (5): International Consultation of Incontinence Questionnaire Short Form (ICIQ UI SF) findings among the studied cases

Characteristics		n	%
Leak		35	44.3%
How often	Never	44	55.7%
	About once a week or less often	3	3.8%
	2 or 3 times a week	5	6.3%
	About once a day	14	17.7%
	Several times a day	12	15.2%
	All the time	1	1.3%
How much urine	None	44	55.7%
	A small amount	21	26.6%
	A moderate amount	8	10.1%
	A large amount	6	7.6%
When	Never	44	55.7%
	Before you can get to the toilet	7	8.9%
	When you cough or sneeze	7	8.9%
	When you are asleep	8	10.1%
	When you are physically active/exercising	6	7.6%
	When you have ¢nished urinating and are dressed	3	3.8%
	For no obvious reason	2	2.5%
	All the time	2	2.5%
		Median (1st -3rd IQ)	Range
Interfere with activity		0.0 (0.0–3.0)	0.0–10.0
Total ICIQ score		0.0 (0.0–8.0)	0.0–20.0

Total=79. IQ: Interquartiles.

Table (5) showed that: among the studied cases; leak was reported in less than half of cases (44.3%).

Table (6): Incontinence Impact Questionnaire-Short Form (IIQ-7) findings among the studied cases

Characteristics		n	%
Affect household activities	Not at all	55	69.6%
	Slightly	13	16.5%
	Moderate	7	8.9%
	Greatly	4	5.1%

Affect physical recreational activities	**Not at all**	52	65.8%
	Slightly	17	21.5%
	Moderate	4	5.1%
	Greatly	6	7.6%
Disrupt your prayer schedule	**Not at all**	57	72.2%
	Slightly	10	12.7%
	Moderate	10	12.7%
	Greatly	2	2.5%
Affect ability to do social activities	**Not at all**	52	65.8%
	Slightly	17	21.5%
	Moderate	5	6.3%
	Greatly	5	6.3%
Affect ability to travel	**Not at all**	59	74.7%
	Slightly	10	12.7%
	Moderate	3	3.8%
	Greatly	7	8.9%
Experience frustration	**Not at all**	49	62.0%
	Slightly	18	22.8%
	Moderate	8	10.1%
	Greatly	4	5.1%
Affect emotional health	**Not at all**	53	67.1%
	Slightly	15	19.0%
	Moderate	4	5.1%
	Greatly	7	8.9%
Unsatisfaction		35	44.3%
		Median (1st - 3rd IQ)	**Range**
Total score		0.0 (0.0–19.0)	0.0–95.2

Total=79. IQ: Interquartiles.

Table (6) showed that: among the studied cases; unsatisfaction was reported in less than half of cases (44.3%).

Table (7): Comparison according to recurrence

Characteristics	Recurrence (Total=13)	No recurrence (Total=66)	p-value
Age (years)	54.5±6.9	44.7±9.8	**^0.001***
BMI (kg/m²)	34.2±5.8	32.0±4.5	^0.129
Parity	4.0 (3.0–5.0)	4.0 (3.0–5.0)	⌂0.634
Diabetes mellitus	7 (53.8%)	10 (15.2%)	**§0.005***
Hypertension	4 (30.8%)	14 (21.2%)	§0.479
Constipation	7 (53.8%)	43 (65.2%)	§0.533
Chronic liver disease	2 (15.4%)	11 (16.7%)	§0.999
Asictes	0 (0.0%)	4 (6.1%)	§0.999

Chronic kidney disease	0 (0.0%)	1 (1.5%)	§0.999
Pelvic prolapse	11 (84.6%)	46 (69.7%)	§0.334
Red blood cells	2 (15.4%)	1 (1.5%)	§0.069
Pus cells	11 (84.6%)	35 (53.0%)	**#0.035***
Epithelial cells	4 (30.8%)	11 (16.7%)	§0.256
Red cells	0 (0.0%)	6 (9.1%)	§0.582
Calcium oxalate	8 (61.5%)	9 (13.6%)	**§0.001***
Uric acid	0 (0.0%)	2 (3.0%)	§0.999
Amporphus	3 (23.1%)	6 (9.1%)	§0.162
Positive culture	7 (53.8%)	14 (21.2%)	**§0.034***
Visceral injury	1 (7.7%)	1 (1.5%)	§0.304
Vaginal erosions	0 (0.0%)	1 (1.5%)	§0.999
Hospital stay (days)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	⌂0.827

^Indepednent t-test. ⌂Mann Whitney. §Fisher's Exact test. *Significant.

Table (7) showed that: Cases with rescurrence significantly had higher age and more frequent diabetes mellitus, pus cells, calcium oxalate and positive culture.

Table (8): Comparison according to urine retention

Characteristics	Retention (Total=4)	No retention (Total=65)	p-value
Age (years)	47.8±14.2	46.2±9.9	^0.765
BMI (kg/m^2)	30.4±5.1	32.5±4.7	^0.380
Parity	5.0 (4.0–5.0)	4.0 (3.0–5.0)	⌂0.538
Diabetes mellitus	1 (25.0%)	16 (21.3%)	§0.999
Hypertension	1 (25.0%)	17 (22.7%)	§0.999
Constipation	4 (100.0%)	46 (61.3%)	§0.291
Chronic liver disease	0 (0.0%)	13 (17.3%)	§0.999
Asictes	1 (25.0%)	3 (4.0%)	§0.191
Chronic kidney disease	0 (0.0%)	1 (1.3%)	§0.999
Pelvic prolapse	4 (100.0%)	53 (70.7%)	§0.572
Red blood cells	0 (0.0%)	3 (4.0%)	§0.999
Pus cells	2 (50.0%)	44 (58.7%)	§0.999
Epithelial cells	1 (25.0%)	14 (18.7%)	§0.577
Red cells	1 (25.0%)	5 (6.7%)	§0.276
Calcium oxalate	1 (25.0%)	16 (21.3%)	§0.999
Uric acid	0 (0.0%)	2 (2.7%)	§0.999
Amporphus	1 (25.0%)	8 (10.7%)	§0.390
Positive culture	1 (25.0%)	20 (26.7%)	§0.999
Visceral injury	2 (50.0%)	0 (0.0%)	**§0.002***
Vaginal erosions	1 (25.0%)	0 (0.0%)	§0.051
Hospital stay (days)	1.5 (1.0–4.5)	2.0 (1.0–3.0)	⌂0.674

^Indepednent t-test. ⌂Mann Whitney. §Fisher's Exact test. *Significant.

Table (8) showed that: Cases with urine retention significantly had more frequent visceral injury.

Table (9): Comparison according to dyspareunia

Characteristics	Dyspareunia (Total=27)	No dyspareunia (Total=52)	
Age (years)	43.2±8.6	47.9±10.4	**^0.047***
BMI (kg/m²)	32.1±5.9	32.5±4.1	^0.722
Parity	4.0 (3.0–5.0)	4.0 (3.0–5.0)	⌂0.398
Diabetes mellitus	5 (18.5%)	12 (23.1%)	#0.640
Hypertension	2 (7.4%)	16 (30.8%)	**#0.019***
Constipation	22 (81.5%)	28 (53.8%)	**#0.016***
Chronic liver disease	6 (22.2%)	7 (13.5%)	§0.350
Asictes	2 (7.4%)	2 (3.8%)	§0.603
Chronic kidney disease	0 (0.0%)	1 (1.9%)	§0.999
Pelvic prolapse	20 (74.1%)	37 (71.2%)	#0.784
Red blood cells	1 (3.7%)	2 (3.8%)	§0.999
Pus cells	16 (59.3%)	30 (57.7%)	#0.983
Epithelial cells	3 (11.1%)	12 (23.1%)	#0.198
Red cells	2 (7.4%)	4 (7.7%)	§0.999
Calcium oxalate	10 (37.0%)	7 (13.5%)	**#0.016***
Uric acid	0 (0.0%)	2 (3.8%)	§0.056
Amporphus	6 (22.2%)	3 (5.8%)	§0.999
Positive culture	7 (25.9%)	14 (26.9%)	#0.924
Visceral injury	2 (7.4%)	0 (0.0%)	§0.114
Vaginal erosions	1 (3.7%)	0 (0.0%)	§0.342
Hospital stay (days)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	⌂0.137

^Indepednent t-test. ⌂Mann Whitney. #Chi square test. §Fisher's Exact test. *Significant.

Table (9) showed that: Cases with dyspareunia significantly had lower age as well as more frequent constipation and urinary calcium oxalate, while less frequent hypertention.

Table (10): Comparison according to cure

Characteristics	Leak (Total=35)	Cure (Total=44)	p-value
Age (years)	50.7±9.8	42.8±8.8	**^<0.001***
BMI (kg/m²)	33.4±6.0	31.6±3.3	^0.110
Parity	5.0 (3.0–5.0)	4.0 (3.0–5.0)	⌂0.152
Diabetes mellitus	12 (34.3%)	5 (11.4%)	**#0.014***
Hypertension	14 (40.0%)	4 (9.1%)	**#0.001***
Constipation	25 (71.4%)	25 (56.8%)	#0.181
Chronic liver disease	5 (14.3%)	8 (18.2%)	#0.643
Asictes	2 (5.7%)	2 (4.5%)	§0.999
Chronic kidney disease	0 (0.0%)	1 (2.3%)	§0.999
Pelvic prolapse	30 (85.7%)	27 (61.4%)	**#0.016***
Red blood cells	2 (5.7%)	1 (2.3%)	§0.581
Pus cells	23 (65.7%)	23 (52.3%)	#0.229

Epithelial cells	9 (25.7%)	6 (13.6%)	#0.174
Red cells	4 (11.4%)	2 (4.5%)	§0.398
Calcium oxalate	11 (31.4%)	6 (13.6%)	#0.056
Uric acid	1 (2.9%)	1 (2.3%)	§0.999
Amporphus	3 (8.6%)	6 (13.6%)	§0.724
Positive culture	15 (42.9%)	6 (13.6%)	**#0.003***
Visceral injury	2 (5.7%)	0 (0.0%)	§0.193
Vaginal erosions	1 (2.9%)	0 (0.0%)	§0.443
Hospital stay (days)	3.0 (2.0–3.0)	2.0 (1.0–3.0)	⌂**0.006***

^Indepednent t-test. ⌂Mann Whitney. #Chi square test. §Fisher's Exact test. *Significant.

Table (10) showed that: cases with urine leak significantly had higher age as well as more frequent hypertention, diabetes mellitus, pelvic prolapse and urinary positive culture as well as longer hospital stay.

Table (11): Comparison according to satisfaction

Characteristics	Unsatisfied (Total=35)	Satisfied (Total=34)	p-value
Age (years)	49.7±9.5	43.5±9.7	**^0.006***
BMI (kg/m²)	33.1±6.2	31.8±3.2	^0.272
Parity	5.0 (3.0–5.0)	4.0 (3.0–5.0)	⌂0.152
Diabetes mellitus	11 (31.4%)	6 (13.6%)	#0.056
Hypertension	13 (37.1%)	5 (11.4%)	**#0.007***
Constipation	25 (71.4%)	25 (56.8%)	#0.181
Chronic liver disease	5 (14.3%)	8 (18.2%)	#0.643
Asictes	3 (8.6%)	1 (2.3%)	§0.317
Chronic kidney disease	0 (0.0%)	1 (2.3%)	§0.999
Pelvic prolapse	30 (85.7%)	27 (61.4%)	**#0.016***
Red blood cells	2 (5.7%)	1 (2.3%)	§0.581
Pus cells	24 (68.6%)	22 (50.0%)	#0.096
Epithelial cells	8 (22.9%)	7 (15.9%)	#0.434
Red cells	3 (8.6%)	3 (6.8%)	§0.999
Calcium oxalate	11 (31.4%)	6 (13.6%)	#0.596
Uric acid	1 (2.9%)	1 (2.3%)	§0.999
Amporphus	4 (11.4%)	5 (11.4%)	§0.999
Positive culture	15 (42.9%)	6 (13.6%)	**#0.003***
Visceral injury	2 (5.7%)	0 (0.0%)	§0.193
Vaginal erosions	1 (2.9%)	0 (0.0%)	§0.443
Hospital stay (days)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	⌂**0.018***

^Indepednent t-test. ⌂Mann Whitney. #Chi square test. §Fisher's Exact test. *Significant.

Table (11) showed that cases with unsatisfaction significantly had higher age and more frequent hypertension, red blood cells and urinary positive culture as well as longer hospital stay.

Discussion

The estimated prevalence of female stress urinary incontinence is nearly 16 % in women aged 30–60. 22 Lifestyle modifications, bladder training, and pelvic floor exercises are considered initial conservative management. If failed to improve the QOL, the role of surgery is to treat the SI. [23]

Synthetic mid-urethral sling techniques have minimized operative times and complication rates for treating female urinary incontinence. The safety and efficacy of TOT (trans-obturator tape procedure) in treating SUI has been proven since 2001. [24]

Since Stress urinary incontinence in women's lives represents major conflict and may be associated with impaired quality of life and satisfaction, evaluating the effectiveness of trans-obturator tape (TOT) in treating female SUI was highlighted as a main point of interest. [23]

Our analysis was based on the data of 79 women who underwent the trans-obturator tape (TOT) procedure for treating female urinary incontinence in the last four years in the urogynecology department.

As regards the demographic characteristics, the current study results revealed that the mean age of the patients was 46.3±10.0 years, BMI was 32.4±4.7 kg/m2 and the parity was 4.0 (3.0–5.0) which were multiparous. The Pelvic prolapse & constipation were the most frequent associated comorbidities (72.2% and 63.3% respectively). Pus cells were detected in 58.2% of the studied cases. However, 26.0% had positive culture.

To the best of our knowledge, there is a paucity of studies in literature in Egypt evaluating the rates of cure, complications and patients' satisfaction after doing a trans-obturator tape (TOT) procedure in patients with stress urinary incontinence, and that represents a strong point of our study.

Magon and Chopra [22] conducted a prospective experimental study that enrolled 59 patients who applied TOT in treating female SI. Their study revealed that the mean age was 46.2 years and 84.7% were multiparous women. This is consistent with Taweel and Rabah 25 who reported that the mean age of patients was 52 ± 9 years (range 34–70 years). Moore and Miklos 26 in their study had patients with an average age of 56.8±11.7. Kaelin-Gambirasio et al. 27 in their study of 233 patients, the average age was 57.9 ±13.2 years.

Natale et al. [23] conducted a single-center prospective study that enrolled 136 patients and revealed that a mean age of 59 years, BMI was 27.22±2.8 kg/m^2 and the parity was 2.0 (0.0–6.0).

As regards the operative complications, our study results revealed that visceral injury (2 cases) and vaginal erosions (1 case) were uncommon (2.5% and 1.3% respectively). Furthermore, Dyspareunia was the most frequent complication (34.2%), while recurrence and urine retention were (16.5% and 5.1% respectively). The majority of recurrence occurred in the 1st 6-months (53.0%), followed by 2nd 6-months (30.8%), then 3rd 6-months (15.4%). The patients' average hospital stay after the operation was two days (range=1.0–3.0).

Our study results reported that Cases with dyspareunia significantly had lower age and more frequent constipation and urinary calcium oxalate, while less frequent hypertension (p value= 0.047, 0.019, 0.016, 0.016), respectively.

In concordance with our results, Magon and Chopra [22] revealed intraoperative injury of the bladder in 1 case and intraoperative injury of the urethra in 1 patient. Twenty-seven patients (45.8%) were discharged within the first day of surgery, Thirty patients (50.8%) were discharged within third day of surgery, and only two patients (3.4%) had to

stay hospitalized for more than three days due to bladder/ urethral injury. The average stay was 1.6 days in this study.

The average stay in the study of Purnichescu et al. 28 was 1.6 days and was 2.2 days in study of Kaelin-Gambirasio et al. [27]

Yonguc et al. [24] conducted a retrospective study that enrolled 126 women who underwent TOT to evaluate long-term cure rates and late complication rates after treatment for female stress urinary incontinence (SUI) with trans-obturator tape (TOT) procedure and reported an overall complication rate was 11.1%. Vaginal erosion was recorded in 2 patients (1.6%), one treated by local estrogen cream and the other by mesh removal. Two patients had dyspareunia and two cases of urinary retention (one treated by prolonged urethral catheterization and the other by tape incision).

Our study results reported that Cases with recurrence significantly had higher age and more frequent diabetes mellitus, pus cells, calcium oxalate, and positive culture (p value= 0.001, 0.005, 0.035, 0.001, 0.034), respectively. In contrast, Cases with urine retention significantly had more frequent visceral injury (p value= 0.002).

In line with our results, Natale et al. [23] suggested that elderly cases developed more storage symptoms. Detrousal instability (due to DM or UTI) was significantly associated with recurrent SI (P = 0.038), and parity of more than two was significantly associated with recurrent SI (P = 0.023).

Our results agree with the study of Gleason et al. [29], who demonstrated significantly lower success rates in Mixed Urinary Incontinence patients compared to those with Stress Urinary Incontinence (64% vs 85%, P <.001) proofing the association of DM and UTI risk factors for the recurrence and the failure of the operation.

On the contrary, Ayhan et al. [30] showed that patients with low parities, especially those with less deliveries, had significantly a higher success rates following SI surgery.

As regards Follow-up postoperatively, our study results revealed that the cure rate and satisfaction rate were 55.7% and leak and Unsatisfaction were reported in 44.3% of cases and the cases with urine leak and unsatisfaction significantly had higher age as well as more frequent hypertension, pelvic prolapse and urinary positive culture as well as longer hospital stay. In addition, diabetes mellitus is significantly associated with leak. The total ICIQ-SF scores and IIQ-7 were 0 in all patients after the surgery while before the surgery, the ICIQ-SF scores and IIQ-7 were missed which is the disadvantage the retrospective study design of the current study.

Patient satisfaction is a very important issue in incontinence surgery, since it quantitates the effect of the treatment on the patient's QoL. [24]

In agreement with our findings, Magon and Chopra [22] revealed that total success rate of trans-obturator sling fixation in the study was 93.2% (95% CI: 86.4–99.5). A total of 51 patients which constituted 86.4% of patients were completely satisfied with the surgical outcome, whereas 4 patients (6.8%) were partially satisfied and an equal number of patients, i.e., 4 were unsatisfied with the surgical outcome, the same patients in whom the surgery was not successful. Yonguc et al. [24] reported that the aging process brought about more UUI symptoms during 5 years compared to baseline.

Natale et al. [23] reported that the objective cure rate was 87.1% (97 patients). In 2017, Serati et al. 31 reported the objective cure rates of TOT, in a group of 160 women with uro-dynamically proven pure SUI with a follow-up of 10 years and showed an objective outcome of 92%. In 2019, Zhang et al. [32] published data on a group of 73 uncomplicated SUI patients who underwent TOT with a follow-up of 12 years and

reported an objective cure rate of 82.2% and a subjective satisfaction rate of 80.8%. These cure rates are higher than in our study due to the larger sample size and prospective study design which are different from our study.

Yonguc et al. [24] revealed that the cure rate and satisfaction rate were 89.6% and 92% respectively and reported that the mean ICIQ-SF scores of the 126 patients before surgery were 15.7 (SD ± 3.1). At first year, of the 126 patients, 109 patients had 0 score that were accepted as subjective cure and the remaining 17 patients had a mean score of 10.1 (SD ± 4.6) from ICIQ-SF.

Also, Cheng and Liu [33] reported patient satisfaction rates at 1 and 5 years as 78 and 69%, respectively, whereas Richter et al. 34 reported a 90% patient satisfaction rate for 12-month follow-up.

One of the most important and not well recognized advantages of the TOT as compared with other mid-urethral sling procedures is the lower rate of de novo urge/urge incontinence. In the trans-obturator approach, the path of the tape, crossing the obturator foramen, muscle, and fascia, reproduces the natural sub-urethral suspension by reinforcing the rotational pivot point, restoring continence while sparing the retropubic space. Sparing the retropubic space may preserve any periurethral nerve fibers that may be associated with urethral function and stability. 35 Second, the TOT is associated with a lower risk of urethral obstruction as compared with other mid-urethral sling procedures. The trans-obturator sling procedure spares the retropubic space and thus also eliminates the risk of major bowel, neural, and vascular complications which have been reported with the TVT. 24 In our study, there was no incidence of de novo urgency/urge incontinence, while Natale et al. 23 observed de novo urgency in 7.3% and de novo Urge urinary incontinence (UUI) in 4.1% of the studied patients. Also, Yonguc et al. 24 reported that two patients (1.6%) had de novo urge symptoms confirmed with urodynamic studies (UDS). Forty-one patients (32.5%) whose UUI symptoms continued after surgery and 2 patients who had de novo urgency were treated with antimuscarinic agents.

Another important advantage of TOT is that since it is not possible anatomically to over tighten the tape, there is hardly any reported incidence of urinary retention because of mechanical obstruction, whereas obstructive voiding dysfunction is the most commonly reported complication of some other mid urethral sling placements like TVT. 23 In the present study, no patient developed urethral obstruction while Yonguc et al. 24 reported that five patients (3.9%) were diagnosed with recurrent SUI and had obstructive urinary symptoms with increased residual urine.

The strength points of this study:

The strength points of this study are that its setting at a single tertiary care center and it is the first study in Ain Shams Maternity Hospital to assess the rates of cure, complications and patients' satisfaction after doing trans obturator tape (TOT) procedure in patients with stress urinary incontinence (SUI). The postoperative complications, satisfaction, and objective cure rates were comprehensively evaluated with standardized methods; we used questionnaires, that were validated in our language.

The limitations of the study:

The limitations of the study are worthy of mention, firstly by its retrospective nature which can be associated with missed clinical information of patients. Secondly, relatively smaller sample size relative to the previous studies, not being a multicentric study and this represents a significant risk of publication bias. Thirdly, the relatively short-term follow-up of patients postoperatively as most of the previous studies tracked outcomes for 3 years postoperatively, which may underestimate the incidence of recurrence of de novo SUI, or mesh erosion.

Although there have been studies quoted in the literature which have followed up patients for almost up to 3 years after TOT application, it is still felt desirable that larger trials with bigger sample size and with a longer duration of follow-up for evaluating long-term success of TOT are required.

Further, comparative trials comparing TOT with other surgical options available for treatment of SUI shall be able to give it its right place of honor in the treatment of SUI. It has all the potential to be the new Gold Standard in the treatment of female SUI.

Conclusion

As evident from the current study, TOT procedure is one of the effective minimally invasive alternatives for the treatment of pure SUI and MUI in long term with low complication rates, high cure rates, fast recovery and good patient satisfaction for SUI in short term in a retrospective point of view, although our study has limitations about the time period in which the patients were followed.

The present study can burden the knowledge and shed some light on future prospective studies with larger sample sizes demonstrating the long-term outcomes of TOT.

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THIRD TRIMESTRIC ULTRASOUND DIAGNOSIS OF PLACENTA ACCRETA SPECTRUM AND CORRELATION OF THE FINDING WITH FIGO GRADING SYSTEM

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Short Running Header: Ultrasound Diagnosis of PAS

All Authors reported no conflict of interest.

No funding received.

Abstract

Objective: This study aimed to evaluate the correlation between ultrasound criteria for diagnosis of Placenta Accreta Spectrum (PAS) with intra-operative FIGO grading to ensure accurate prenatal US diagnosis.

Design: Descriptive Prospective cohort study.

Setting: Kasr Al-Ainy maternity Hospital - Fetal Medicine Unit.

Subjects and methods: Sixty-four women in 3rd trimester of pregnancy diagnosed with low lying anterior placenta and had previous one or more cesarean deliveries were included. All patients were examined by ultrasound for criteria of abnormal placental implantation according to standardized description proposed by European Working group on PAS few days before the scheduled elective C.S. Then FIGO grading was done intra-operative followed by pathological confirmation of hysterectomy specimen. The main outcome was the correlation between prenatal ultrasound criteria of PAS and intra-operative FIGO grading of PAS are then histopathological confirmation was done.

Results: A strong correlation was found between the presence of ultrasound placental lacunae (CC 0.429, P<0.001), loss of clear zone (CC 0.652, P <0.001) and myometrial thinning (CC 0.498, P <0.001) with intra-operative FIGO grading. While ultrasound Placental bulge (CC 0.265, P = 0.034) and Bladder wall interruption (CC 0.367, P 0.003) were moderately correlated with intra-operative FIGO grading.

Conclusion: The surgical outcome and intraoperative FIGO grading are strongly correlated with the presence of placental lacunae, loss of clear zone and myometrial thinning and moderately correlated with Placental bulge

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and Bladder wall interruption ultrasound criteria.

Funding: Self-Funded.

Keywords: Abnormal placental implantation; European Working Group of AIP; FIGO.

Synopsis: The surgical outcome and intraoperative FIGO grading are strongly correlated with the presence of placental lacunae, loss of clear zone and myometrial thinning and moderately correlated with placental bulge and bladder wall interruption in prenatal ultrasound.

Introduction

Placenta accreta spectrum (PAS) -previously named morbidly adherent placenta- is a serious condition caused by the presence of abnormal placental adhesion and invasion of the myometrium because of defective fibrinoid or Nitabuch layer [1].

The frequency of PAS is progressively increasing over time. It was reported as 1 in 20,000 births in 1951, 1 in 2500 births in the 1980s [2]. and reached 1 in 533 between1982 to 2002 [3].

The presence of low-lying placenta and prior cesarean delivery are considered the main risk factors for PAS [4]. The risk of development of PAS in women with low lying placenta is 3%, 11%, 40%, 61%, and 67%, after 1,2,3,4 and 5 or more cesarean deliveries, respectively [5].

FIGO classified PAS into 3 grades according to the presence of clinical criteria at vaginal delivery and at laparotomy and microscopic examination of placental bed into grade 1 (placenta adherenta or creta), grade 2 (Increta) and grade 3 (Percreta) which is further subdivided into 3a,3b and 3c categories [6].

PAS is associated with life-threatening bleeding (both intra- and post-operative) that usually requires additional surgical interventions including hysterectomy or vascular ligation. PAS is associated with high risk of maternal morbidity and mortality, massive blood transfusion, maternal ICU admission and prolonged hospital costs and stay [7]

The reduction of maternal morbidity and mortality is dependent on antenatal diagnosis of PAS and arrangement the management carried by a multidisciplinary team (MDT) at level III/IV maternal care facility [8,9]

The antenatal diagnosis of PAS is usually carried though ultrasonography combined with Doppler color mapping and if needed through MRI [10]

Ultrasonographic criteria include the presence of placental lacunae, the loss of retroplacental clear zone, serosa–bladder interface interruption, myometrial thinning (< 1 mm), bridging vessels, uterovesical vascularity, and the presence of exophytic placental extension [11].

The overall accuracy of ultrasound and individual ultrasonographic criteria varies among different studies. Some reported high accuracy reaching 100 % [12] while other studies reported a much lower accuracy [9].

Aim of the work

The aim of this study is to evaluate the accuracy of 3rd trimester ultrasound in diagnosis of PAS.

Material and methods

This is a prospective cohort study conducted between June 2020 and June 2021 at Cairo University Maternal-Fetal Medicine Unit (CAIMFM) - Kasr Al-Ainy Teaching Hospital. The Study included 64 Pregnant women, in the third trimester, with history of one or more previous cesarean sections, low lying placenta or placenta previa, who were admitted to the Obstetrics and Gynecology department-Kasr El- Aini yospital-Cairo University. The diagnosis of placenta previa was based on the presence of placental tissue covering the internal os and low lying placenta was diagnosed when placenta was

< 2cm from the internal os but did not cover it. Exclusion criteria were multiple pregnancy, posterior placenta and those who refused to participate in the clinical research. All participating women signed an informed written consents after explanation of the study aim, design, risks, and benefits.

All participants were subjected to evaluation through comprehensive history, general and abdominal examination followed by routine laboratory investigations.

A very precise ultrasound was done to all participants few days prior to CS. The following ultrasound items were examined: fetal viability, amniotic fluid assessment, fetal biometrics, fetal presentation, expected fetal weight & location of placenta. Next step was looking for Ultrasound criteria of placenta accreta according to EW group on PAS which include:

1. Loss of retroplacental clear zone (The hypoechoic plane in the myometrium behind the placental bed is lost).
2. Abnormal placenta lacunae (Presence of multiple variable sized lacunae with irregular wall and turbulent flow in grey-scale imaging).
3. Myometrial thinning (Decreased thickness of myometrium overlying the placenta to <1 mm or undetectable).
4. Bladder wall interruption (Loss of all or part of the hyperechoic band between the uterine serosa and the bladder lumen).
5. Placental bulge (Abnormal bulge of the placenta into neighbouring organ usually the bladder with intact serosa).
6. Focal exophytic mass (Placental tissue is seen usually inside the urinary bladder with interrupted uterine serosa).

Both ultrasound and Doppler examinations were done using Voluson E 10 GE (Korea) equipped with a 4–7 MHz curvilinear transabdominal probe with the mother in slight left tilted supine position to avoid supine hypotension with partially full bladder to allow optimum uterine serosa and bladder wall visualization.

FIGO grading was done to assess and categorizes placental adherence or invasion at delivery. Intraoperative finding according to FIGO grading system include:1-Placental tissue seen, 2- Placental separation with uterotonics, 3- Manual removal of placenta, 4- Clear surgical plane between the bladder and the uterus and 5-Involvement of parametrium.

Finally, diagnosis was confirmed by histopathologic examination of hysterectomy specimen.

The main outcome was the correlation between prenatal ultrasound criteria of AIP and intra-operative FIGO grading of AIP then histopathological confirmation was done.

Statistical analysis

Data were statistically described in terms of mean + standard deviation (+SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test.

Comparison of numerical variables between the study groups was done using Kruskal Wallis test. For comparing categorical data, Chi-square (X^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Spearman rank correlation. Two-sided p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

The Correlation Coefficient used to measure the strength of association between two variables; above 0.4 consider strong, 0.2-0.4 moderate and below 0.2 weak.

Sample size calculation was based on correlation between ultrasound criteria of abnormal placental implantation according to standardized description proposed by EW group and intraoperative FIGO grading of AIP. According to the individual data extracted from a prior publication [13], the coefficient of determination between ultrasonographic criteria and FIGO clinical staging of placenta accreta to be able to detect a correlation coefficient of 0.4 with 80 % power setting type 1 error probability to 0.05. Sample size calculation was done using G*Power software version 3.1.2 for MS Windows, Franz Faul, Kiel University, Germany. If you changed the detected correlation coefficient to 0.3, the sample will be 64 cases.

Results

The mean maternal age at diagnosis was 32.92+/-4.172 and the mean gestational age at delivery was 35+/-1.7.

Nine patients (14.1%) showed no ultrasound criteria of PAS, 7 of them were found to be FIGO grade1 and 2 were FIGO grade 2. All the nine patients were treated conservatively and didn't need hysterectomy nor blood transfusion. 55 patients (85.9 %) showed one or more ultrasound criteria of PAS. 49 (89 %) of them managed by hysterectomy; 14 (28.5 %) had 2 Ultrasound criteria, 30(61.2 %) had 3 ultrasound criteria, 3 (6.1 %) had 4 Ultrasound criteria and 2(4 %) had 5 Ultrasound criteria. (10.9 %) patients showed only 1 ultrasound criterion of PAS; 4 of them were found to be FIGO grade 1 and 2 were FIGO Grade 2. All of them were managed conservatively with no need for hysterectomy.

Ultrasound loss of retroplacental clear zone was found in 51 patients (79.7%), 1 of them was FIGO grade 1(2%), 6 were grade 2(11.8%), 37 were FIGO grade 3(72.5%), 3 were FIGO grade 4(5.9%) and 4were FIGO grade 5(7.8%). Ultrasound preserved retroplacental clear zone was found in13 patients (20.3%); 10 of them were FIGO grade 1(76.9%), 1was FIGO grade 2(7.7%) and 2 were FIGO grade 3(5.1%), Non were FIGO grade4 or 5.

Ultrasound placental lacunae was found in 44 patients (68.8%), 4 of them were FIGO grade 1 (9.1%), 3 were FIGO grade 2 (6.8%), 30 were FIGO grade 3 (68.2%), 3 were FIGO grade 4 (608%) and 4 were FIGO grade 5 (9.1%). Ultrasound placental lacunae was not found in 20 patients (31.3%), 7 of them were FIGO grade 1(35.0%), 4 were FIGO grade 2 (20.0%), 9 were FIGO grade 3 (45.0%), Non were FIGO grade 4 or 5.

Ultrasound bladder wall interruption was found in 4 patients, 1 was FIGO grade 3(25.0%), 1was FIGO grade 4(25.0%) and 2 were FIGO grade 5(50.0%). Non were FIGO grade 1 or 2. Ultrasound bladder wall interruption was not found in 60 patients (93.0%), 11 were FIGO grade 1(18.3%), 7 were FIGO grade 2 (11.7%), 38 were FIGO grade 3 (63.3%), 2 were FIGO grade 4 (3.3%) and 2 were FIGO grade 5 (3.3%).

Ultrasound myometrial thinning was found in 51 patients (79.7%), 3 were FIGO grade 1(5.9%), 6 were FIGO grade 2(11.8%), 35 were FIGO grade 3(68.6%), 3were FIGO grade 4(5.9%) and 4were FIGO grade 5(7.8%). Ultrasound myometrial thinning was not found in 13 patients (20.3%), 8 were FIGO grade 1(61.5%), 1 was FIGO grade 2(7.7%), 4were FIGO grade 3(30.8%).Non were FIGO grade 4 or 5.

Ultrasound placental bulge was found in 6 patients (9.4%), 1 was FIGO grade 2(16.7%), 2 were FIGO grade 3 (33.3%), 1was FIGOgrade 4(16.7%) and 2 were FIGO grade 5(33.3%). Non were FIGO grade 1. Ultrasound placental bulge was not found in 58 patients (90.6), 11 were FIGO grade 1(19.0%), 6 were FIGO grade 2(10.3%), 37 were FIGO grade 3(63.8%), 2 were FIGO grade 4(3.4%) and 2 were FIGO grade 5(3.4%).

Non of the studied patients showed focal exophytic mass and so correlation with FIGO grading could not be done.

When correlating ultrasound finding with intraoperative FIGO grading (Table:1) strong correlation was found with loss of clear zone, ultrasound placental lacunae and myometrial thinning; correlation coefficient was 0.652, 0.429 and 0.498 respectively. While moderate correlation was found with ultrasound bladder wall interruption and placental bulge; correlation coefficient was 0.367 and 0.265 respectively. Correlation couldn't be assessed for ultrasound focal exophytic mass as none of our patients showed this finding.

Table (1): Correlation Coefficient calculation using Spearman rank correlation

			FIGO Grading
Spearman's rho	US-loss of clear zone	Correlation Coefficient	0.652
		p value	0.000
		N	64
	US-placental lacunae	Correlation Coefficient	0.429
		p value	0.000
		N	64
	US-bladder wall interruption	Correlation Coefficient	0.367
		p value	0.003
		N	64
	US-myometrial thining	Correlation Coefficient	0.498
		p value	0.000
		N	64
	US-placental bulge	Correlation Coefficient	0.265
		p value	0.034
		N	64

Discssion

Main Findings:

64 women with placenta previa or low lying anterior placenta and previous 1 or more CS scar were included in this study, 55 (85.9%) of them were diagnosed as having PAS by US criteria proposed by EW group. 51 (92.7%) patients showed loss of ultrasound clear zone, 44(80%) showed placental lacunae, 4 (7.2%) showed bladder wall interruption, 51 (92.7%) showed myometrial thinning and 6 (10.9%) showed ultrasound placental bulge. Non showed ultrasound focalexophytic mass.

When correlating ultrasound finding with intraoperative FIGO grading strong correlation was found with loss of clear zone, ultrasound placental lacunae and myometrial thinning; correlation coefficient was 0.652, 0.429 and 0.498 respectively. While moderate correlation was found with ultrasound bladder wall interruption and placental bulge; correlation coefficient was 0.367 and 0.265 respectively. Correlation couldn't be assessed for ultrasound focal exophytic mass as none of our patients showed this finding.

Ultrasound diagnosis of PAS according to the criteria proposed by the EW- group have good -ve predictive value as all patients who had no or only one ultrasound criteria were treated conservatively and didn't need hysterectomy nor blood transfusion. While those with 2 or more ultrasound findings were found to be FIGO 3 or more and did hysterectomy which means that the number

of ultrasound findings correlates with the severity of invasion.

PAS ultrasound signs are due to destruction of the uterine wall till the serosa because of the placental tissue reaching the deep uterine circulation. Adherent and invasive placentation may coexist in the same placental bed. This is why it's difficult to differentiate between adherent and invasive placenta using ultrasound signs. Correlation of operative finding (FIGO grading) with prenatal ultrasound finding is essential to improvescreening, diagnosis and management of PAS [14].

Only a few studies have attempted to explore the feasibility and diagnostic performance of ultrasound in assessing the presence and severity of PAS disorders in correlation with the intraoperative clinical staging suggested by FIGO.

Cali G.et al., 2019 studied 259 women with placenta previa and reported that the ultrasound scoring system including clear zone loss, interrupted bladder wall, placental lacunae, increased vascularity of both uterovesical zone and the parametrium correlated with the clinical staging suggested by FIGO. They found that increased severity of the ultrasound stage of PAS disorders was associated with increased blood loss, need for blood transfusion, operative time and post operative hospital stay[15].

Cali G. et al., 2018 studied 210 women with placenta previa and previous CS scar and aimed to confirm the accuracy of Ultrasound in diagnosing myometrial invasion in PAS disorders. They found that Ultrasound is highly accurate in diagnosing placental invasion when applied to a population with

high risk for PAS. The use of three ultrasound signs was associated with a better specificity for placenta percreta [16].

Tovbin J. et al., 2016 reported that a scoring system including the number of placental lacunae and the presence of bladder wall interruption had a high diagnostic performance for PAS disorders allowing for adequate antenatal assessment. Its helpful for patients counseling and delivery planning with multidisciplinary team approach [17].

Eric J. et al., 2021 found that proper prenatal diagnosis, especially accurate differentiation between abnormal placental adherence & invasion is mandatory for proper management. Histopathologic confirmation of diagnosis is the golden standard for PAS. This system may also improve management outcome data by allowing the development of targeted screening protocols for women at high risk of PAS [18].

Zachry B. et al., 2019 discussed the ultrasound appearance and sensitivity in evaluating cases of suspected PAS. Ultrasound was found to be very sensitive and specific with several sonographic features that when present, raise the diagnosis of PAS. Ultrasound remains the best imaging tool for the assessment of PAS with MRI shown to have a complementary role when used appropriately [19].

Strength and limitations:

The prospective data collection, large sample size and confirmation of diagnosis by histopathological examinations represent the major strengths of this study. Finally, all cases affected by PAS were managed by the same multidisciplinary team and treated with hysterectomy, thus reducingbias related to the operator's experience and type of surgical approach adopted.

The main limitation of the study is some patients who were diagnosed as focal accreta by ultrasound (1 or 2 ultrasound criteria) did not do hysterectomy and thus there was no pathological confirmation of the diagnosis.

Another limitation was the inability to estimate the correlation of ultrasound focal exophytic mass and FIGO grading as none of our patients showed ultrasound focal exophytic mass.

Conclusion

In this study we conclude that the ultrasound finding of PAS as proposed by the EW-group correlates with the intraoperative FIGO clinical grading system and surgical outcome. Antenatal ultrasound diagnosis of PASshows both good positive and negative predictive values.

We recommend using ultrasound for prenatal assessment of women who are at high risk of having PAS disorders being accurate, relatively inexpensive and widely available imaging modality and therefore should be the first line for the diagnosis of PAS disorder.

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The impact of self-administered vaginal isonicotinic acid hydrazide (INH) administration 12 hours prior to levonorgestrel-releasing intrauterine system in women delivered only by elective cesarean section: A randomized double blinded clinical trial

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Abstract

Objective: To evaluate if self-administered 900 mg Isonicotinic Acid Hydrazide (INH) vaginally reduced pain during the insertion of the Levonorgestrel releasing intrauterine system (52 mg LNG-IUS) among women with elective caesarean section (CS).

Methods: This was a double-blinded, single-center, randomized controlled trial. 12 hours before 52 mg LNG-IUS insertion, 220 women were randomly allocated to receive INH 900mg vaginaly or placebo. The mean pain score during 52 mg LNG-IUS insertion was our primary endpoint. Mean pain scores during tenaculum application, uterine sounding, and 10 minutes after insertion were our secondary outcomes, as were ease of insertion, satisfaction score, need for further analgesics, and side effects. On a 10-cm VAS scale, IUD insertion ease was assessed from 0 to 10, with 0 signifying very easy insertion and 10 denoting extremely difficult insertion. Fisher 's exact test and Chi square test were used for comparison between groups, as appropriate. The student t test was used to compare quantitative data between the two groups.

Results: When compared to the placebo group, the INH group experienced significantly less pain during IUD insertion (4.13± 0.98 vs. 6.22± 0.895; P<0.001) and 10 minutes after insertion (2.63 ± 0.82 vs. 4.52 ± 0.79), easier IUD insertion (2.67 0.83 vs. 5.56 0.87; p0.01), and higher satisfaction (7.25 ± 0.77 vs. 4.74 ± 0.87). When compared to the placebo group, the INH group required fewer extra analgesics (P<0.001). The two groups had similar side effects.

Conclusions: In women who had solely delivered via elective CS, self-administered 900 mg INH vaginally before 52 mg LNG-IUS insertion reduces pain scores during LNG-IUS insertion, making insertion easier and increasing women's satisfaction, with tolerable side-effects.

Key words: Cesarean delivery; intrauterine device; Isonicotinic Acid Hydrazide; pain

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Clinical trial registration number: NCT04500028

key message

- **What is already known on this topic**: Seeking for alternatives to improve the patients' experience at intrauterine device insertion is an important topic, since the fear of pain during intrauterine device insertion can discourage some potential users.
- **What this study adds:** In women who delivered only by elective cesarean section, vaginal INH self-administered12 hours prior to 52 mg LNG-IUS placement has the ability to reduce the amount of pain women experience throughout the procedure. Furthermore, it may increase the ease of insertion.
- **How this study might affect research, practice or policy:** INH can simply be utilised to aid in the insertion of 52 mg LNG-IUS. One disadvantage of an intervention that must be provided 12 hours before to 52 mg LNG-IUS placement is that it is ineffective for same-day IUD insertion. However, INH was not used on the same day of the 52 mg LNG-IUS placement in our trial, needs to be addressed in future research.

Introduction

Levonorgestrel releasing intrauterine system (52 mg LNG-IUS) has shown to be a highly effective method of decreasing unplanned births across the world. 52 mg LNG-IUS is a procedure that provides long-term, reliable contraception to many women (1).

The use of LNG-IUS varies by country, although it is used by anywhere from 2% to 75% of contraceptive users worldwide. (2).The insertion procedure, however, is associated with a great deal of pain, which may discourage some women from using it (3).

When compared to placebo, oral and local analgesics, as well as cervical priming, can reduce 52 mg LNG-IUS placement-related discomfort, although their routine usage is still debatable. Predictive indicators may aid healthcare providers in identifying women who are at risk of discomfort(4).

Women who have never given birth vaginally are considered to have more discomfort following 52 mg LNG-IUS insertion (5). Two possible barriers to IUD use include expected pain during insertion and provider concerns about problematic insertion. Finding effective techniques to make IUD insertion less difficult might result in more 52 mg LNG-IUS insertions.(6)

Isonicotinic acid hydrazide (INH) is an anti-tuberculosis medication that helps the cervical ripening process. In term pregnancies, it may be just as effective as misoprostol (7) . Although misoprostol is effective for cervical ripening, it does not reduce pain related to IUD insertion (8). According to some study, the effect of INH on cervical ripening may be due in part to nitric oxide (NO) production in the cervix (9,10).

We conducted this study to evaluate if 900 mg of vaginal INH given 12 hours before insertion of a 52 mg LNG-IUS was more effective than placebo for decrease pain scores and increase the ease of insertion among women with elective caesarean section (CS).

Materials and methods

Study design

From August 2021 to December 2022, we conducted a randomized, double-blinded, placebo-controlled trial in a family planning clinic of a tertiary referral hospital in Aswan, Egypt. After receiving protocol approval from the institutional ethical review board (ASWU/202/7/20), we prospectively registered the study in the clinicaltrials.gov registry (number NCT04500028). Every

participant signed a written informed consent form.

study population

We clinically assessed all women who requested 52 mg LNG-IUS insertion at the Family Planning Clinic throughout the research period and offered them to participate if they did not have any contraindications for insertion based on WHO eligibility criteria and were solely delivered by elective CS.

All the women in the study were non-pregnant, between the ages of 18 and 45, and had not taken any analgesics in the 48 hours before to the 52 mg LNG-IUS insertion.

The study excluded women with uterine anomalies such as congenital deformities, endometrial lesions, adenomyosis, fibroids, or intrauterine adhesions. The study excluded women who had Chronic pelvic pain including dysmenorrhea, irregular uterine bleeding, or a history of cervical surgery, and active vaginitis, cervicitis, or pelvic inflammatory disease within the past 3 months. Women who had an allergy to INH, had a medical condition that prevented them from using it, or women with known psychiatric disorders and chronic use of antidepressants or anticonvulsants were also ruled out, as were those who refused to take part in the study.

Recruitment

Following an explanation of the conventional 10-cm visual analogue scale, one investigator from our research team recorded the participants' baseline characteristics. To establish eligibility and rule out any contraindications, we performed a history taking, abdominal and pelvic examinations, and transvaginal ultrasonography (TVS) using the Sonoace R5 apparatus (Samsung Medison). To rule out pregnancy, the clinic nurse administered a urine pregnancy test to all participants.

LNG-IUS insertion procedure

For insertion, each woman was given LNG-IUS (Mirena®, Bayer HealthCare, Berlin, Germany). The IUD was inserted during menstruation, on days ranging from the third to the fifth of the menstrual cycle.

Before starting the procedure, we reported all drug-related side symptoms such as nausea, vomiting, stomach cramps, diarrhea, fever (oral temperature 38 °C), and shivering

LNG-IUS insertion was performed by two of the research investigators who was familiar with IUD insertion using the manufacturer's recommended procedure of 52 mg LNG-IUS (Mirena®, Bayer HealthCare, Berlin, Germany).

The providers inserted a speculum into the vagina and used povidone-iodine to clean the cervix. Then, using a single toothed tenaculum, they grabbed the anterior lip of the cervix for fixation of the uterus and inserted uterine sound for uterine length measurement, followed by 52 mg LNG-IUS placement.

Randomization and interventions

The participants were randomly assigned to one of two groups: the INH group, which received 900-mg INH tablets vaginally, or the placebo group, which received placebo tablets that were identical in form, color, and consistency to the INH tablets. A statistician who was not involved in the study generated a random numbers table using computer randomizer software (http://www.graphpad.com/quickcalcs/index. cfm), and the allocation was hidden in sequentially numbered sealed opaque envelopes. Until the trial was over, the statistician maintained the key to the randomization method and allocation.

According to the randomization procedure, a single pharmacist made the placebo tablets and packed both INH and placebo tablets into boxes that were then placed in sequentially numbered opaque sealed envelopes. The only person who knew what was in the envelopes was the pharmacist, and neither

the clinicians nor the women knew what kind of medication was inside. The clinic nurse opened the envelopes in the order in which the women arrived at the clinic and dispensed the pills in the sealed boxes. The clinic nurse taught how to store the research medications properly and made sure that all patients had refrigerators.

All patients were given a second appointment for IUD placement and directed to insert the study medicines vaginally 12 hours before to the planned appointment, according to the clinic nurse. One day before IUD installation, an investigator called all participants to remind them to take their medication.

Patients in Group I received a placebo to INH (placebo group)12 hours prior to the insertion of the 52 mg LNG-IUS, whereas those in Group II received 900 mg vaginal INH (INH group).

All women reported their perceived level of pain at different time points: during tenaculum placement, during sounding of the uterus, during IUD insertion, and 10 minutes after the procedure with the use of the 10-cm VAS (in which 0 corresponds to no pain and 10 to the worst possible pain imaginable).

The duration of IUD insertion as well as immediate problems such as uterine perforation, failure of insertion, and vasovagal response were documented. The providers reported the ease of IUD placement using the ease of insertion score after the procedure was completed (ES). The ES was determined using a graded VAS-like scale ranging from zero to ten, with ten indicating extremely difficult insertion and zero indicating very simple insertion.

All women rated their pain severity on a 10-cm VAS scale after 10 minutes of the procedure and expressed their satisfaction with IUD placement on a 10-cm VAS scale (with 0 = no satisfaction and 10 = maximum satisfaction). We also inquired about post-operative bleeding or spotting, as well as the need for further analgesics. Ibuprofen 400 mg orally was given if needed, as it is a safe and effective medication that is readily available in our clinic.

The participants also mentioned the medication's side effects. Headache, nausea/vomiting, stomach cramps, chills, fever, and diarrhea.

We requested all participants to return to the clinic in one month for a string check and to complete a final questionnaire about patient satisfaction; during that time, we also did a pelvic examination and TVS to rule out pelvic infection and 52 mg LNG-IUS expulsion. We reminded them by phone prior to the appointment, and we scheduled home visits for those who were unable or unwilling to return for follow-up.

Study outcomes

The difference in pain VAS ratings during IUD insertion was the main result. The VAS scale is graded from 0 to 10 on a 10 cm horizontal straight line, with 0 representing no pain and 10 indicating the worst imaginable pain. On a VAS sheet, the participant was asked to select the point that corresponded to the level of pain she had experienced.

The difference in IUD insertion ease ratings across study groups was the secondary end measure (as reported by physicians responsible for IUD insertion). On a 10-cm VAS scale, this score ranges from 0 to 10, with 0 indicating very simple insertion and 10 indicating exceedingly difficult insertion.

The difference in pain VAS scores during tenaculum application, at the placement of uterine sound, 10 minutes after IUD placement, the women's level of satisfaction at the end of insertion, the number of women who require additional analgesics after insertion, and the medication's side effects were among the secondary outcomes.

Sample size

The sample size was calculated using the Open Epi software program, version 2.3.1(11). Based on earlier research (12, 13),

we assumed a minimum clinically important difference (MCID) in VAS pain score to be 1.5 cm and based on Samy et al. (14) trial which reported the mean VAS with LNG-IUS insertion in placebo group (6.4cm); we needed a sample size of 100 women in each group with 90% power and an α error of 0.05 to detect this MCID with INH use. To account for attrition and missing data, we raised the sample size by 10%, resulting in a total of 220 cases (110 patients per group).

Statistical Analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences ((SPSS Inc., Chicago, IL).) version 23. Qualitative data were described as numbers and percentages. Fisher 's exact test and Chi square test were used for comparison between groups, as appropriate. Quantitative data were described as means (SD) or medians, after testing for normality by Kolmogorov-Smirnov test. In normally distributed variables, independent samples t-test was used for comparison between groups, while in the non-normally distributed variables, Mann-Whitney U test was used for comparison between groups. Because this study used a within-subjects design, linear mixed model (LMM) was used. Odds ratios and their 95% confidence interval were calculated. "p value ≤0.05" was considered to be statistically significant.

Patient and public involvement

There was no direct patient and public involvement in the design of the study.

Results

We screened 250 individuals requesting 52 mg LNG-IUS placement for study eligibility; 30 patients were excluded, 25 patients did not fulfil the inclusion criteria, and 5 patients refused to participate. As a result, the remaining 220 patients were divided into two groups, each with 110 patients. Patients in Group I received a placebo to INH (placebo group), whereas those in Group II received vaginal INH prior to the insertion of the 52 mg LNG-IUS (INH group). (See Figure 1).

Table 1 shows that the baseline characteristics of the study participants were similar in both groups. The two groups revealed no significant differences in terms of age, weight, height, body mass index (BMI), gravidity, location, education, previous IUD insertion history, time since last birth, and uterine position. The uterine position was anteverted in most cases in both groups

Table 2 shows in addition, there was no statistically significant difference in the mean duration of IUD placement between the two groups (p=0.934).

women in the INH group had significantly lower pain scores during the LNG-IUD insertion process than the placebo group, as determined by the visual analogue scale (VAS) during tenaculum placement, sound insertion, IUD insertion, and 10 minutes after the procedure. women in the INH group had significantly higher satisfaction scores compared with those in the placebo group.

Providers reported significantly more ease of insertion in the INH group compared with the placebo group.

In addition, as compared to placebo group, the requirement for additional analgesic was significantly reduced in INH group. ($p<0.001$). (Table 2)

Table 3 shows there were no significant differences related to the complication of the insertion procedure as tenaculum site bleeding, abdominal cramps, fever, headache, headache, vomiting, and failure of insertion. No reported cases of diarrhea or chills. (Table 3).

Discussion

Self-administering INH vaginally 12 hours before LNG-IUS insertion reduces pain at all stages of 52 mg LNG-IUS insertion, with no significant difference in procedure time and

greater women's satisfaction, according to the current study. It also makes IUD placement easier for women who have previously just had a CS.

This is the first randomized, double-blind, placebo-controlled study to assess the efficacy of vaginal INH 900 mg against placebo in decreasing insertion pain and enhancing 52 mg LNG-IUS insertion ease in women who only had a CS.

Because the CS rate has been steadily increasing in our country in recent years, and the IUD is the most popular contraceptive method among Egyptian women, it was necessary to investigate ways to reduce pain and make IUD insertion easier for those who only delivered by elective CS to avoid unintended pregnancies (15, 16). Due to the existence of a scar at the internal os impairing softening of the cervix, previous CD resulted in higher pain levels after IUD insertion and more insertion failures (13).

In our study, the difference in pain scores between the INH and placebo groups was more than 1.6, which was clinically significant.

Even when the cervical width is less than 4 mm, the force required to expand the cervix prior to a first trimester abortion is decreased in several randomized studies using NO donors (17-20).

Two investigations looked at the effect of nitric oxide donors on the ease of insertion and the need for further insertion procedures. (21,22) and both show that, there were no significant differences in pain scores between the nitroprusside gel and the control groups. There may be a difference between these studies and our experiment. It's conceivable that the period between nitroglycerin and IUD insertion was too short in their trials, or that our drug dose was high enough, to allow for cervical remodeling. Furthermore, the authors of these studies indicate that a bigger sample size may have shown significantly different results as the number of participants only 12 in each group.

The ease of insertion score in the INH group was lower than in the placebo group, indicating that insertion was easier for providers in the INH group

Initial cervical dilatation and dilatation length were longer with vaginal misoprostol than with Foley catheter with vaginal isosorbide mononitrate, according to El-Khayat et al. (23), but there was no significant difference in the procedure duration or difficulty in dilation between the two groups. It's conceivable that their lack of statistical significance is attributable to different sample sizes or methods than those used in the current study.

Women who underwent INH insertion were more satisfied than women in the placebo group when questioned about their satisfaction with 52 mg LNG-IUS insertion. There were no significant differences in side effects or procedure-related problems between the two groups. In our trial, there were four unsuccessful insertions (three in the placebo group and one in the INH group), all of which were caused by a very tight cervical os. After the operation, women in the placebo group needed more analgesics than women in the INH group, and this proves the clinical value and implications of INH administration.

The requirement for cervical dilatation was reduced in the INH group than in the placebo group, implying that insertion was easier for doctors in the INH group.

In a recent study (24), 315 doctors who had inserted the LNG-IUS in nulligravida's reported a relative risk of 2.0 (95 percent confidence range, 1.2–3.2) for a problematic insertion when compared to parous women. The degree of difficulty, on the other hand, was inversely linked to the number of insertions conducted by each professional, with doctors who had performed less than 10 insertions having a higher risk of difficulty (relative risk, 2.2; 95 percent confidence range, 1.6–3.1).

Strengths and limitations

This research provides several advantages. This is the first experiment to explicitly examine the effect of INH on pain at the time of 52 mg LNG-IUS implantation in women delivered only by cesarean section, as previously mentioned. We were able to reduce possible biases that an unblinded or observational study would have introduced by using a prospective, double-blinded, randomized control trial to compare the two treatment arms. We were also able to examine the effect of INH on pain at the time of 52 mg LNG-IUS insertion since we excluded women who had taken other pain medicines on the day of insertion. Finally, an adequate sample size with sufficient power to detect any significant differences between groups using CONSORT guidelines for clinical trials.

The study's main limitation was the requirement for two visits for IUD placement. In addition, the need to be administered 12 hours prior 52 mg LNG-IUS placement is that it not useful for same-day 52 mg LNG-IUS. Patients need two visits: one to pick the medication and another to insert the IUD. This is, however, typical procedure for our family planning clinic, and it allows us to provide better counselling and patient decision-making on the 52 mg LNG-IUD contraception. However, INH was not used on the same day of the 52 mg LNG-IUS placement in our trial, which is one of the study flaws that needs to be addressed in future research.

The subjective evaluation of pain in our study was restricted by the fact that it might be influenced by patient characteristics or anxiety levels. Randomization and adequate research design, however, were able to overcome this issue.

Women in the vaginal INH group were more likely to report clinically significant lower pain scores during vulsellum application which may not explained. The variations in pain perception between the two groups during tenaculum application may be attributed to the effect of INH on cervical ripening and the effect of No on cervical tissue perception of pain. Another drawback was that we did not measure discomfort at different time periods following the operation. Some baseline factors, such as provider experience and time since the previous birth, may have influenced pain and ease of insertion results. However, due to the strong resemblance of these features in the two groups, this hypothesis was ruled out.

INH can simply be used to facilitate IUCD implantation. However, the basic mechanism of cervical ripening is unknown. More study is needed to identify the mechanisms of action and clinical effectiveness of INH in comparison to alternative therapies for cervix softening prior to IUCD implantation, as well as the optimal dosage and timing of INH for cervix softening before to IUCD implantation.

Research implications

To corroborate our findings, more well-designed RCTs on this topic are needed. Future RCTs should compare INH to other drugs for pain alleviation during LNG-IUS insertion, with women who have other risk factors for greater pain scores during LNG-IUS insertion, such as nulliparity, included. However, in the future, more investigation into the efficacy of INH given on the same day as the 52 mg LNG-IUS insertion is needed.

Conclusions

In women who had solely delivered via elective CS, self-administered 900 mg INH vaginally before LNG-IUS insertion reduces pain scores during 52 mg LNG-IUS insertion, making insertion easier and increasing women's satisfaction, with tolerable side-effects.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (Aswu/202/7/20). ClinicalTrials.gov identifier: NCT04500028

The study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Authors contribution:

NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation. AT: literature review, manuscript preparation.

No funding

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Figure legends

Figure 1: Consort flowchart showing enrollment of participants

Impact Of Positive GCT With Negative Oral GTT On Perinatal Morbidity: Prospective Cohort Study

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Abstract

Background: Abnormalities in glucose metabolism during pregnancy can lead to significant adverse perinatal outcomes, while the effect of minor glucose metabolism abnormalities is poorly understood.

Objectives: This study was designed to investigate the impact of a +ve glucose challenge test on perinatal morbidity.

Patients and methods: This is a prospective cohort study at Ain Shams University Maternity Hospital that included 200 pregnant women with singleton pregnancies at 24-28 weeks of gestation. These patients were at high risk of developing GDM. A glucose challenge test (GCT) was done on all patients. It was divided according to results into two groups of 100 patients each, a group with positive (GCT) and negative 100 gm glucose tolerance test, and a group 2 patients with negative (GCT) All patients were followed till delivery, documenting adverse maternal or perinatal outcomes. The primary outcome was fetal macrosomia, while secondary outcomes were shoulder dystocia, preterm labor, pregnancy-induced hypertension, NICU admission, and neonatal death.

Results: Among 200 patients included in the study, BMI was 30.17±4.48 in the study group vs 28.31±4.5 in the control group with a P value of 0.004, macrosomia was in 22 (22%) in the study group vs 7 (7%) in the control group. And 19 (19%) cases in the study group need NICU admission vs. 10 (10%) cases in the control group with a P value of 0.032. No significant differences were observed between study groups as regards age, GA, parity, APGAR score at 5 min, shoulder dystocia, PTL, PIH, and neonatal death.

Conclusion: A positive oral glucose challenge test only without gestational diabetes is a risk factor for perinatal morbidity like LGA and NICU admission, so early screening for GDM is advisable.

Key words: glucose challenge test, glucose tolerance test, pregnancy, gestational diabetes, macrosomia, perinatal morbidity.

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BACKGROUND

Carbohydrate metabolism undergoes significant changes during pregnancy especially in the second half leading to a state of glucose intolerance and physiological insulin resistance (1). Gestational diabetes is defined as carbohydrate intolerance first diagnosed during pregnancy (2). It is commonly affecting about 2% -5% of pregnant ladies.

Due to well-known adverse pregnancy outcomes caused by diabetes and affecting both mother and newborn as fetal growth abnormalities mainly macrosomia ,birth traumas and neonatal chemical imbalances such as hypoglycaemia which in turn increases incidence of NICU admission (3),screening for gestational diabetes is recommended by ACOG to be done between 24-28 wks gestation.

They recommend two-step screening and diagnostic procedure, 1st step screening using 50-g glucose challenge test (GCT) then if positive test result(blood sugar ;130-140mg/dl), diagnostic 100 gm, 3-hour glucose tolerance test (OGTT)should be done.

All previously mentioned adverse outcomes are directly related to blood sugar control ,blood sugar adjustment should be the goal during antenatal care.

Adverse effect of minor abnormalities in glucose tolerance such as women with single high reading on OGTT or with +ve screening by GCT and -ve confirmatory test is not well understood but supposed to be increased (4).

So our study aimed to investigate the impact of positive glucose challenge test and negative OGTT on perinatal morbidity.

PATIENTS AND METHODS

This is a prospective cohort study . It was conducted at Ain Shams University Maternity Hospital from January 2022 to September 2022. Study included 200 Pregnant women at 24-28 weeks of gestation, having singleton pregnancy ,Who has high risk of developing GDM such as maternal age>35, Previous polycystic ovarian syndrome, Long-term corticosteroid use, BMI > 30 kg/m2, Previous gestational diabetes, while patients known to be diabetic, women having GCT result >200 mg/dL ,women who had abnormal OGTT during follow up , with Fetal malformations or hydrops were excluded from the study . The study was conducted after approval of Research Ethical Committee, faculty of medicine of Ain Shams University.

After detailed discussion with patients, all were accurately informed about the steps of the study and a written informed consent was taken from each patient after full explanation of the study procedure . All patient participated in this study were undergone the following procedures: full history taking include detailed obstetric history ,family history especially for DM ,general examination ,BMI calculation ,abdominal examination and symphysiofundal height measurement ,obstetric ultrasound to assess fetal biometry and exclude anomalies.

300 pregnant women were recruited for the study after matching inclusion criteria for all of them GCT was done using 50 gm glucose (without fasting) , positive test if blood sugar more than or equal 140mg/dl (5), then patients were divided according to results into +ve screening group(study group) and -ve screening group(control group) .

Patients were advised to a full carbohydrate diet for three days before the test. They were instructed to come on the fourth day with at least fasting for 8 hours; the first sample was taken as a fasting sample; they were given a standard 100 gm juice and instructed to drink it slowly. After they finished by 1 hour the second sample was withdrawn then 2 hour and 3rd hour samples. (Carpenter & Coustan criteria Table 1).

Negative patients were taken if zero or one abnormal values oly was present . Patients

with positive test were excluded from the study (n=50) remaining patients from both groups (n=250) were followed regularly every month till delivery if patient developed of PIH (defined as new-onset hypertension with systolic blood pressure >140 mm Hg or diastolic > 90 mm Hg on two occasions at least 6 hours apart,with or without proteinuria based on 2002 ACOG diagnostic criteria, status of the liquor ,any preterm labour before 37 wks gestation was recorded and perinatal outcomes was followed up in terms of macrosomia (birth weight>4000 gm), hypoglycemia, hyperbilirubinemia, shoulder dystocia, birth weight, Apgar score at 5 minutes of life of < 7, admission to the neonatal intensive care unit (NICU), stillbirth or neonatal death, , and respiratory distress syndrome. 50 patients were also dropped out during follow up so 200 pregnant women were only finally analysed.

Induction protocol

Patients underwent controlled ovarian stimulation using the long GnRH agonist protocol for pituitary down-regulation. Ovarian stimulation was done by human menopausal gonadotropin (HMG)(Merional IBSA,Swittzerland). The initial dose of HMG was individualized for each patient according to age, FSH level, antral follicle count (AFC) and BMI. Dose adjustments was performed according to ovarian response, which was monitored according to TVS and E2 levels. Serum progesterone was performed on the day of hCG administration (Chorioumon ,IBSA,Swittzerland)which was given if 3 or more follicles reached 18 mm.

Blood sample	National Diabetes Data Group Criteria	Carpenter and Coustan Criteria
Fasting	105 mg/dL (5.8 mmol/L)	95 mg/dL (5.3 mmol/L)
1-hour	190 mg/dL (10.5 mmol/L)	180 mg/dL (10.0 mmol/L)
2-hour	165 mg/dL (9.2 mmol/L)	155 mg/dL (8.6 mmol/L)
3-hour	145 mg/dL (8.0 mmol/L)	140 mg/dL (7.8 mmol/L)

Table (1): Criteria for Abnormal Result of 100 g,Three-Hour Oral Glucose Tolerance Tests in Pregnant Women

Sample size calculation: was done using the rate of fetal macrosomia in pregnant women with high risk for diabetes. As reported in previous publication(6) ,the proportion of fetal macrosomia in pregnant women with positive glucose challenge test was approximately 20%, while in pregnant women with negative glucose challenge test it was approximately 5%, both groups had normal 3h oral glucose tolerance test Accordingly, we calculated that the minimum proper sample size was 100 participants in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.025$ level using Chi-square test for independent samples. Sample size calculation was done using MedCalc® Statistical Software version 19.5.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

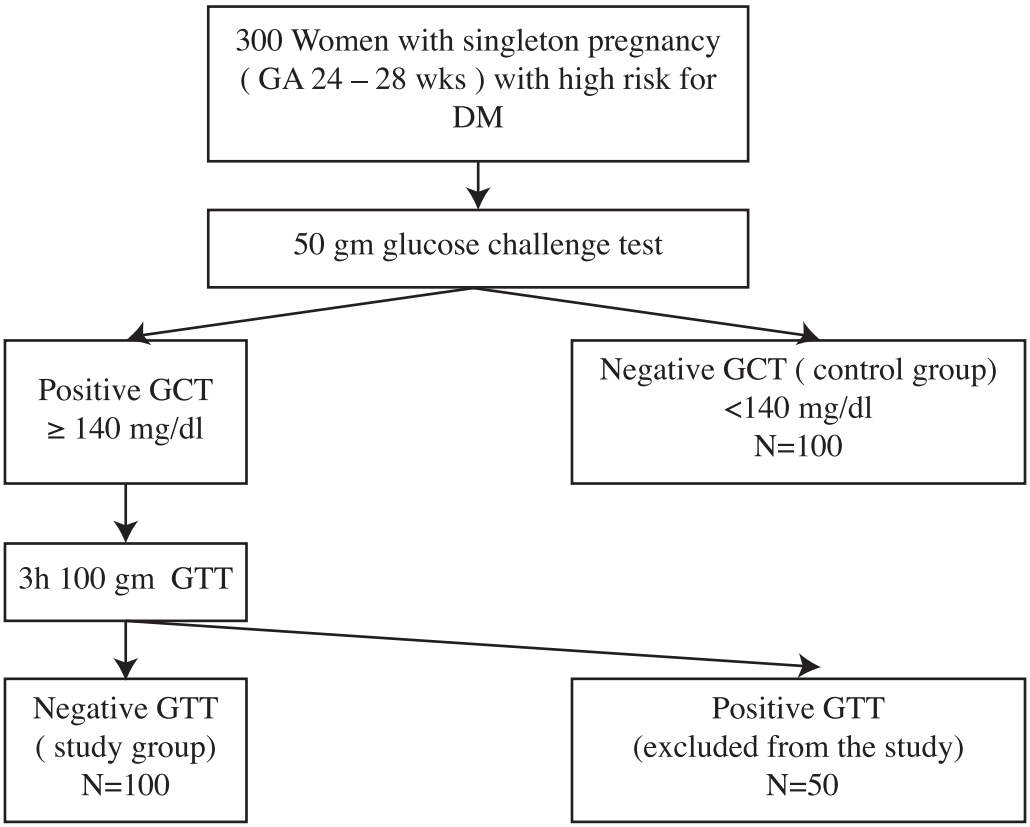
Statistical analysis:

The Social Package of Statistical Analysis ver. 24 was used for data collection, tabulation, and analysis (IBMCorp., Armonk, New York). Kolmogorov–Smirnov test test was used to check the normal distribution. We used the mean and SD to express the normal distributed numerical data, and we used median and interquartile range for the numerical skewed data. The numbers and percentages were used for expressing the qualitative data. We used the unpaired t-test to

compare the normally distributed numerical data. Mann-Whitney test was used for comparing the skewed numerical data. If appropriate, the chi-squared test or Fisher's exact test was used for qualitative categorical data. P less than 0.05 was considered significant.

RESULTS

Figure 1:Flow chart for study participants



NB: 50 patients also were dropped out from the study during follow up from both groups.

Demographic characteristics of study participants :

Table (2) showed that there was no statistically significant difference between study groups as regard age, GA and parity while there was statistically significant difference between study groups as regard BMI which being higher in positive GCT (study group) than negative GCT (control group).

Table (2): Demographic characteristics of study participants

variable	Control group	Study group	P Value
Age[1]	28.82±6.16	29.47±5.98	0.449* NS
BMI[2]	28.31±4.5	30.17±4.48	0.004* HS
GA[3]	38.20±1.10	37.94±1.2	0.111* NS
Parity[4] • **PG** • **P1-3** • **P≥4**	 25 (25%) 58 (58%) 17 (17%)	 21 (21%) 63 (63%) 16 (16%)	0.746# NS

[1,2,3]Values (continuous quantitative data) are given as mean±SD, while 4Values (numerical data) are given as numbers (percentage)Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of age, BMI, GA of all study cases.

*t-test test for normally distributed data.

Chi-Square Testsused to determine P value

P value <0.05 significant so P value of study groups is not significant.

NS: non-significant, HS: highly signific

Maternal and neonatal outcomes are tabulated in **table (3)** showed that there was no statistically significant difference between study groups as regard birth weight, APGAR score at 5 min, shoulder dystocia, PTL, PIH and neonatal death while there was statistically significant difference between study groups as regard macrosomia as 22% of positive GCT cases had macrosomia compared to 7% of negative cases. Similarly, NICU admission was higher among positive cases compared to negative cases (19% vs. 10%). While table (4) showed that using logistic regression and after adjustment to all relevant factors, it was found that Positive GCT (study group) have higher risk for NICU admission compared to negative GCT (control group) (AOR=2.30, CI: 1.01-5.2).

Table (3):Comparison between study groups as regard pregnancy outcome

Variable	Control group	Study group	95% CI	P value
Birth weight	3189.5±408.02	3315.5±621	---	0.092* NS
APGAR score 5 min	8.56±0.84	8.37±1.09	---	0.17* NS
Macrosomia **No** **Yes**	 93 (93%) 7 (7.0%)	 78 (78%) 22 (22%)	3.74(1.5-9.2)	0.003# HS
Shoulder dystocia **No** **Yes**	 98 (98%) 2 (2.0%)	 96 (96%) 4 (4.0%)	2.04 (0.36-11.4)	0.683** NS
PIH **No** **Yes**	 86 (86%) 14 (14%)	 82 (82%) 18 (18%)	1.34(0.63-2.88)	0.440# NS
PTL **No** **Yes**	 93 (93%) 7 (7.0%)	 90 (90%) 10 (10%)	1.46(0.53-4.04)	0.447# NS
NICU **No** **Yes**	 90 (90%) 10 (10%)	 81 (81%) 19 (19%)	2.32 (1.06-5.3)	0.032# HS
Neonatal Death **No** **Yes**	 100 (100%) 0 (0.0%)	 100 (100%) 0 (0.0%)	-----	-----

*t-test test for normally distributed data.

Chi-Square Tests used to determine P value

**fisher exact test used to determine P value

P value <0.05 is significant so P value of study groups is not significant.

NS: non-significant, HS: highly significant

Table (4):Logistic Regression model to study independent factors affecting NICU admission.

	AOR*	P value	Sig.	95% Confidence interval for AOR	
				Lower	Upper
Age	.976	.588	NS	.895	1.065
GA	.728	.214	NS	.441	1.202
Parity	1.279	.193	NS	.883	1.851
Birth weight	1.000	.732	NS	.999	1.001
PIH	.663	.490	NS	.206	2.132
PTL	.697	.670	NS	.132	3.666
Positive GCT	**2.308**	**.045**	**S**	**1.018**	**5.234**

*Adjusted odds ratio

**Reference group Gravidity (one)

DISCUSSION

Main finding

In our study, there were no statistically significant differences between negative GCT and positive GCT regarding the sociodemographic data regarding age, GA, and parity. Still, BMI was higher in the positive group. Also, the present study showed no statistically significant difference between study groups regarding birth weight, APGAR score at 5 min, shoulder dystocia, PTL, PIH, and neonatal death. At the same time, there was a statistically significant difference between study groups regarding macrosomia, as 22% of positive GCT cases had macrosomia babies compared to 7% of negative points. Similarly, NICU admission was higher among positive patients than negative cases (19% vs. 10%).

Interpretation

In our study, there were no statistically significant differences between negative GCT and positive GCT regarding the sociodemographic data regarding age, GA, and parity. These results agreed with the study of Temming, et al. (6), who found no statistically significant differences between the normal GCT group and elevated GCT group regarding age and gestational age at delivery. The present study also showed that there was no statistically significant difference between study groups as regards birth weight, APGAR score at 5 min, shoulder dystocia, PTL, PIH, and neonatal death. At the same time, there was a statistically significant difference between study groups regarding macrosomia, as 22% of positive GCT cases had macrosomia babies compared to 7% of negative cases. Similarly, NICU admission was higher among positive and negative cases (19% vs. 10%). The study by Temming et al,2016, proved that women with elevated 1-hour GCT (normal GTT) had s an increased risk of CS, macrosomia, shoulder dystocia, preterm labor and difficult labor t among women. These findings suggest that patients with abnormal glucose testing below the threshold of GDM diagnosis are at risk of adverse obstetric outcomes (6). Similar to our study is that of Shinohara et al. on 2248 pregnant Japanese women at 24-28 GA; the primary outcome was the incidence of LGA. They performed a 1-hour glucose challenge test and OGTT. The incidence of LGA was 9.4% (211/2248), and the women with false +ve GCT results were 11.4% (257/2248). After adjusting the different variables (age, weight before pregnancy, parity, and weight gain during pregnancy, the False +ve Glucose challenge test results were significantly

associated with an increased risk of LGA (OR, 1.51; 95% CI, 1.02 to 2.23). [7-8]

Also, our study analyzed more risk factors for NICU admission with a relatively large sample size in Egyptian women. It showed that using logistic regression and after adjustment to all relevant aspects, it was found that case groups (Positive GCT) have a higher risk for NICU admission compared to (negative GCT) groups (AOR=2.30, CI: 1.01-5.2).

In the retrospective cohort study of Ankumah et al. 2016, 602 women with GDM were members of the study of singleton pregnancies complicated by GDM. They studied different maternal and neonatal outcomes; the maternal outcomes were CS rates, Type 2 DM, PET, and failed TOLAC. The neonatal outcomes were SGA, LGA, difficult labor, and shoulder dystocia. Their results showed that Shoulder dystocia (3.1 vs. 1.0%) and PET(16.4 vs. 10.6%) were increased significantly in the group of women diagnosed with GDM using 1-hour GCT ≥ 200 mg/dL than those with women diagnosed by GDM using a +ve OGTT following a 1-hour GCT of 135-199 mg/dL with adjusted odds ratio and 95% confidence interval were 1.80 (1.10-2.94) and 5.10 (1.25-20.76), respectively (9).

Conversely, Freidman et al performed a retrospective study chart review that included 387 black pregnant patients to assess the incidence of GDM(between 24 and 28 weeks) according to various 1-hour GCT different cut-off values (they used 130 mg/dL or above and 100 gm 3H GTT). They found that the incidence of GDM was 31.2 by using 1-hour GCT(130 mg/dL or higher) and was 10.7 using -hour GCT(130-140) and the incidence reached 72.0% by using 1-hour GCT(180 mg/dL or higher). They recommended using 130 mg/dL as the threshold for a +ve GCT and suggested using a GTT to confirm the diagnosis of gestational diabetes for screening values up to 200 mg/dL.

Korucuoglu et al also found a +ve correlation between increasing glucose challenge tests with adverse neonatal outcomes. 152 Women with glucose challenge test≥180 mg/dL had an increased incidence of macrosomia and Large for Gestational age neonates and higher rates of NICU admission for hypoglycemia and hyperbilirubinemia than women with glucose challenge test <180 mg/dL. (11) .

Strengths and limitations

Strengths of this study include the sample size. This study confirmed the findings of adverse outcomes in those with an elevated 1-hour GCT without GDM, in the Egyptian population. In addition, it is a prospective cohort study that allow evaluation of both maternal and neonatal outcomes. it also allowed analyzing more risk factors for NICU admission than previous studies. Our study has some limitations. First, it was conducted at a single center so extrapolation of our results to the general population might be difficult. Therefore, a large-scale, multicenter, cohort study is needed to confirm these results in the general population. second, the generalizability of our findings may be limited by the homogeneity of this cohort, which contained only Egyptian patients.

CONCLUSION

Our study confirms that +ve oral glucose challenge test only without gestational diabetes is a risk factor for perinatal morbidity like LGA and NICU admission.

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Patient satisfaction and Quality of life after dienogest treatment versus surgical excision of ovarian endometrioma

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Abstract

Background: Endometriosis is a chronic condition affecting females in the reproductive period. Variable medical treatment options have been provided with comparable results to surgery.

Objective: Comparing dienogest treatment and surgical excision of endometrioma regarding patients' satisfaction and Quality of life.

Study design: This randomized clinical trial was conducted at a tertiary hospital from Nov 1, 2020, to Jul 31, 2022. We recruited patients according to specific inclusion and exclusion criteria. The study population was randomly allocated into two groups; group one received Dienogest, and group two had laparoscopic cystectomy. Group one patients received medical treatment with Dienogest (2mg/day) starting on the first day of the first menstrual cycle for three months. After three months, patients were subjected to clinical evaluation, including cyst diameter, recurrence after surgical excision, evaluation of patient satisfaction using the endometriosis treatment satisfaction questionnaire (ETSQ), and Quality of life using the SF-36 questionnaire.

Results: The recurrence rate after excision was 12/60 (20%). There was a significant difference in patient satisfaction after medical treatment rather than surgical excision. This was noted in each item of the satisfaction questionnaire and the total score (p-value <0.05). There was a significant improvement in all aspects of the Quality of life with dienogest therapy rather than surgical treatment (p-value <0.05).

Conclusion: Dienogest greatly improved patients' Quality of life and satisfaction rather than surgical intervention.

Keywords: Endometrioma; Dienogest; Surgical excision; Satisfaction; Quality of life.

Trial registration number: PACTR202010622528145

Date of registration: 15/10/2020

Date of first patient enrollment: 1/11/2020

URL:https://trialsearch.who.int/Trial2.aspx?TrialID=PACTR202010622528145

Name of the registry: Pan African clinical trial registry

Introduction

Endometriosis is a benign chronic condition affecting females with variable presentations such as infertility and chronic pelvic pain (1). When it affects the ovary, an endometrioma develops that requires surgical intervention (2). Laparoscopic excision of endometrioma is the mainstay treatment; however, concerns regarding decreased ovarian reserve due to accidental removal of healthy ovarian tissue or impaired vascularity due to electrocoagulation are paramount (3). Also, recurrence after surgery represents a significant challenge (4). Non-surgical options have proved effective in the management of endometriosis (3). These include non-steroidal anti-inflammatory drugs, combined hormonal contraception, gonadotropin-releasing hormone agonists, and progestogens. They were effective in reducing pain and endometrioma size (5). Dienogest is a synthetic progestogen with moderate anti-gonadotropic properties and no androgenic activity (6, 7). It also has anti-inflammatory and anti-proliferative activities (8). Studies have focused on the effectiveness of dienogest in reducing pain compared to other medical options (9, 10). A study reported a 20-37% dissatisfaction rate after norethisterone acetate treatment (11). Few studies reported patient satisfaction after dienogest therapy compared to surgical intervention (12, 13). This study evaluated patient satisfaction after dienogest versus surgical excision of endometrioma.

Methods

This randomized clinical trial was conducted at the obstetrics and gynecology department at Suez Canal university hospital from Nov 1, 2020, to Jul 31, 2022, after approval of the research ethics committee. We recruited patients according to specific inclusion and exclusion criteria. Inclusion criteria: a) unilateral endometrioma, b) size of 2-8 cm, c) age 18-45 years, d) regular cycles, and e) no previous ovarian operations in the last three months. Exclusion criteria: a) suspected or confirmed malignancy, b) women within two years of menarche, and c) women on progesterone or combined hormonal contraception.

After a detailed explanation of the study procedure, informed consent was obtained from all eligible patients accepting participation in the study. The study population was randomly allocated into two groups using the random generation of numbers through computer software in a 1: 1 manner. Group one received Dienogest, and group two had laparoscopic cystectomy. Randomization was done after evaluating the participants for eligibility. The allocation sequence was concealed from the researcher, enrolling and assessing participants using opaque sealed envelopes. Patients and researchers were aware of group allocation, but outcome assessors and data analysts were kept blinded.

Eligible patients were subjected to the following:

1. Complete personal and medical history.
2. Complete physical examination and local examination to evaluate pelvic pain.
3. Ultrasound examination, either transabdominal for virgins or transvaginal for sexually active women, to diagnose ovarian endometrioma. This was done after demonstrating a unilocular cystic lesion with a ground glass echogenicity of the fluid and a regular thick wall (14).
4. Group one patients received medical treatment with Dienogest (Visanne VR, Bayer AG, Soficopharm) (2mg/day) starting on the first day of the first

menstrual cycle for three months.

5. Group two patients had laparoscopic ovarian cystectomy.
6. After three months, patients were subjected to clinical evaluation, including cyst diameter, recurrence after surgical excision, and evaluation of patient satisfaction using the endometriosis treatment satisfaction questionnaire (ETSQ). 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 (15).
7. Quality of life was evaluated using the SF-36 questionnaire. It included 36 questions addressing the following eight scales: physical function, role limitation due to physical health, body pain, general health, vitality, social functioning, role limitation due to emotional problems, and emotional well-being. Each item was scored, and the average was obtained according to the instructions of the RAND corporation website. A higher score represented better Quality of life (16, 17).

This study represents the secondary outcome measure of a clinical trial that evaluated both groups' ovarian reserve before and after the intervention.

Sample size: - The sample size was calculated using the following formula (18):

$$n = 2\left[\frac{(Z_{\alpha/2} + Z_{\beta}) * \sigma}{\mu 1 - \mu 2}\right]^2$$

n = Sample size in each group.

$Z_{\alpha/2}$ = 1.96 (The critical Value corresponds to a 95% confidence level).

Z_{β} = 0.84 (The critical value corresponding to 80% power of the study).

$\mu 1$ = Percentage of change of AMH in the Dienogest group (10.1±3.1) (19)

$\mu 2$ = Percentage of change of AMH in laparoscopic cystectomy group (11±6) (20)

σ = estimate of pooled standard deviation [=2.5].

Dropout = 12% [Sampling error].

According to the previous equation, the sample size was 120 patients, with 60 patients in each group.

Ethical approval: this study was conducted after approval of the Scientific Research Ethics Committee on 27/7/2020 with a reference number of 4255#.

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. The Chi-square test was used for categorical variables and the (t) test for continuous variables with normally distributed data. Non-normally distributed data were tested using Fisher's exact for categorical variables and Mann-Whitney U tests for continuous variables.

Results

One hundred twenty-five women were eligible for the study, three declined to participate, and one refused medical treatment. Another one was lost for follow-up, leaving 120

women divided into two groups for the final analysis **(Figure 1)**.

There was no difference in the primary demographic data of the studied population, as demonstrated in **table 1**.

The recurrence rate after excision was 12/60 (20%). There was a significant difference in the endometrioma size with dienogest therapy from 5.42 ± 1.47 cm to 1.99 ± 0.54 cm (p-value **<0.001**).

There was a significant difference in patient satisfaction after medical treatment rather than surgical excision. This was noted in each item of the satisfaction questionnaire as well as the total score (p-value <0.05) **(Table 2)**. This was evidenced in each group before and after the intervention, also.

There was a significant improvement in all aspects of the Quality of life with dienogest therapy rather than surgical treatment (p-value <0.05) **(Table 3)**. Both interventions resulted in a significant improvement in the patient's Quality of life.

Discussion

The recurrence rate was 20% in the surgical excision group. A high recurrence rate was reported previously, ranging from 29-56% after two years and 43% after five years (21). A low recurrence rate of 6.4% was also documented (22). The current study provided no medical treatment after surgery, while the follow-up period was only three months. Recurrent endometriosis was rendered to the effects of immune cells and extracellular matrix metalloproteinase leading to the proliferation and survival of endometriotic cells (23). The variability in recurrence rates was rendered to the different factors attributing to its recurrence as the definition of recurrence, whether depended on subjective pain sensation or imaging diagnosis, the type of endometriosis, disease severity, method of excision, surgical skills, and time to recurrence reported (4). When accounting for symptoms, higher recurrence rates are reported, with a poor correlation between pain and actual recurrence (24)—the current study evaluated recurrence using ultrasound after three months of excision.

There was a significant improvement in the satisfaction scores between both groups. Dienogest provided a better satisfaction score than surgical excision. Surgical excision was associated with improved patient satisfaction as 43.8%- 45.2% were very satisfied at 3-12 months after ablative surgery for endometriosis and endometrioma (25). In a study comparing dienogest and norethisterone acetate, dienogest was associated with better satisfaction (50% and 26%, respectively). The overall satisfaction was insignificant between both groups, despite better tolerability of dienogest (26). A study evaluating patients' satisfaction after surgical treatment and progestin (norethisterone acetate) therapy reported that 43% of patients were satisfied after surgical treatment versus 59% after progestin therapy. This showed varied rates as time elapsed from 3- 12 months after intervention (13). Higher satisfaction rates were reported by Cho et al. (75.5%) (27). Tolerability is an essential factor in determining patients' satisfaction. It represents the ability to tolerate the medication's side effects, making it suitable for long-term treatment (28). Of note, no patient discontinued dienogest therapy in the current study. Satisfaction with the treatment option was rendered to improve dysmenorrhea, dyspareunia, and overall pelvic pain. Greater satisfaction after medical treatment was explained by its long-lasting effect, while surgery was associated with recurrences that resulted in pain occurring six months after the operation (13).

The Quality of life was improved significantly after both interventions. When the groups were compared, a significant improvement was in favor of dienogest therapy. An earlier study reported a significant improvement in the Quality of life after dienogest therapy with remarkable improvement in the

dysmenorrhea score (26). Another reported improved endometriosis health profile after undergoing dienogest therapy for six months (12). This was rendered to the fact that dienogest is effective in pain control with few side effects increasing its tolerability (29). The current study recruited women who had endometrioma excision only without any additional procedures. Dienogest has potential benefits, such as being progesterone receptor selective with anti-inflammatory properties that decrease cytokine production by the endometriotic implants (30). In addition, it affects pain modulation and transmission, even in the absence of significant changes in endometriotic spots (12), explaining the significant difference between the study groups.

Strength and limitations: Few studies evaluated patient satisfaction after dienogest therapy compared to surgical excision of endometrioma. The evaluation was limited to 3 months only. Patient satisfaction was represented as the mean score; the percentage of satisfied and dissatisfied patients was not presented. There was no evaluation of the stage of endometriosis for the recruited patients. The evaluation was based on validated scales; however, the SF-36 questionnaire failed to assess dyspareunia.

Conclusion

Dienogest therapy is an excellent alternative to surgical intervention for women with declining endometriosis surgery with long-lasting effects and few tolerable side effects. This significantly impacted the patient's Quality of life and satisfaction after dienogest therapy than after surgical intervention.

Conflict of interest: None

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Tables:

Table 1: Basic demographic data of the studied population

Group		Medication (60)	Operation (60)	p-value
Age (years) (Mean ± SD)		32.77 ± 8.09	30.33 ± 7.95	0.099[a]
Occupation N (%)	Not working	37 (61.67%)	29 (48.33%)	0.142[b]
	Working	23 (38.33%)	31 (51.67%)	
Residence N (%)	Urban	30 (50%)	28 (46.67%)	0.715[b]
	Rural	30 (50%)	32 (53.33%)	
Marital status N (%)	Virgin	27 (45%)	30 (50%)	0.583[b]
	Married/Divorced/Widowed	33 (55%)	30 (50%)	
Parity (Mean ± SD)		1.09 ± 0.68	1.27 ± 0.69	0.297[c]

[a] Independent samples t-test, [b] Chi-squared test, [c] Mann-Whitney U test

Table 2: Patient satisfaction after both modalities of treatment

Group	Medication	Surgery	P value
Endometriosis-related pain before or during periods	4.38 ± 1.06	3.43 ± 1.13	**≤0.001**[a]
Endometriosis-related pain during or after sexual activity	4.58 ± 1.05	3.43 ± 1.2	**≤0.001**[a]
Endometriosis related pain	4.68 ± 1.19	3.68 ± 1.14	**≤0.001**[a]
Any bleeding or spotting	4.5 ± 1.14	3.8 ± 1.2	**≤0.001**[a]
Tolerability	4.22 ± 1.11	3.33 ± 1.05	**≤0.001**[a]
Overall satisfaction	4.5 ± 1.11	3.53 ± 1.19	**≤0.001**[a]
ETSQ total score	26.87 ± 2.55	21.22 ± 2.93	**≤0.001**[b]

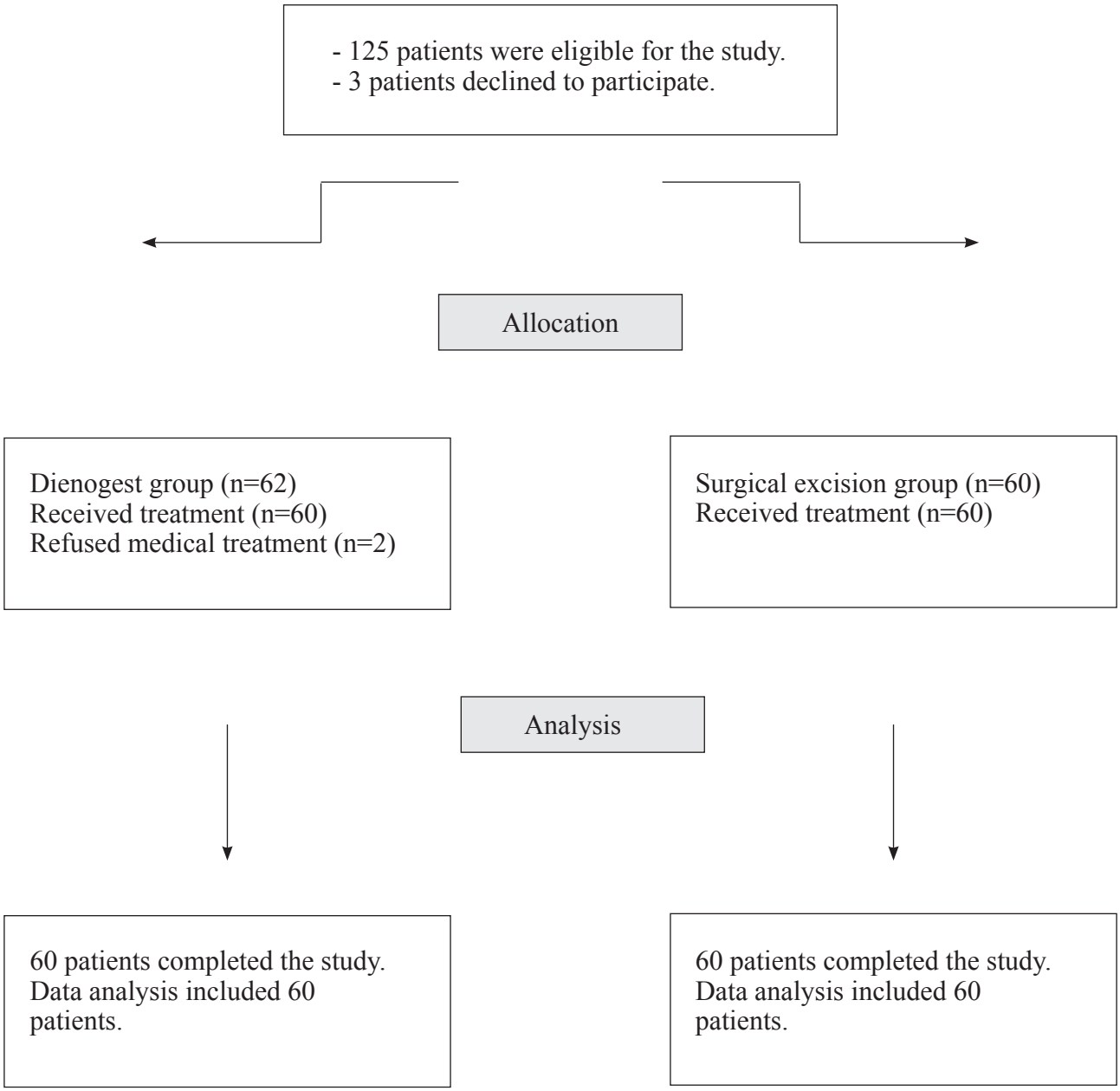
[a] Independent sample t-test, [b] Mann- Whitney U test.

Table 3: Comparison of the Quality of life between both groups

Group	Medication	Operation	p-value
Variable	**Mean ± SD**	**Mean ± SD**	
Physical functioning	68.58 ± 12.2	62.97 ± 7.73	**0.003**[a]
Role limitations due to physical health	70.28 ± 12.07	61.22 ± 7.9	**≤0.001**[b]
Role limitations due to emotional problems	69.42 ± 12.03	63.13 ± 6.72	**0.001**[a]
Energy/Fatigue	69.22 ± 10.75	63.17 ± 7.88	**0.001**[a]
Emotional well-being	71.47 ± 12.25	63.5 ± 7.13	**≤0.001**[a]
Social functioning	69.83 ± 11.37	63.02 ± 7.48	**≤0.001**[a]
Pain	69.87 ± 12.25	63.78 ± 8.04	**0.002**[a]
General Health	69.22 ± 11.72	62.92 ± 7.96	**0.002**[b]
Total SF-36	69.74 ± 4.42	62.96 ± 2.67	**≤0.001**[a]

[a] Independent sample t-test, [b] Mann- Whitney U test.

Figure legend:
Figure 1: Patients' flow chart
Enrollment



Inhibin A may be the Black Horse for Determination of the Optimal Triggering Time and Decision-making for Oocyte Retrieval

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Abstract

Objectives: Assessment of the applicability of estimated serum inhibin A (INHA) and/or INHB versus estradiol (E2) levels to determine the triggering time during controlled ovarian stimulation (COS) that might allow the retrieval of the optimal number of oocytes.

Patients: 196 infertile women assigned to receive COS using the flexible antagonist protocol gave blood samples for ELISA estimation of serum levels of E2 and INHs on day-2 of the cycle and on the day of retrieval depending on having serum E2 levels >2000 pg/ml and the optimal number of follicles; 11-15 follicles of ≥16 mm in diameter. The study outcome is the blinded distinguishing ability of estimated serum levels of E2 and INHs between cases that might have <11, 11-13, and 14-15 mature follicles on transvaginal ultrasonography (TUV) imaging on the day of triggering.

Results: Serum E2 levels at the time of triggering (>2000 pg/ml) showed sensitivity and specificity rates of 89.8% and 40.6% to distinguish women who had <11 mature follicles after COS. Serum levels of INHA (≥723 ng/ml) showed significantly higher diagnostic performance for differentiation between patients according to the number of mature follicles compared to serum E2 and INHB levels with significant area under the curve (AUC) for differentiating patients had <11 or >14 mature follicles, while E2 and INHB failed for this respect. Statistical analyses defined serum INHA as the significant predictor for canceling depending on the maturation of a low number of follicles after COS and for the presence of 14-15 mature follicles and deciding triggering and oocyte retrieval.

Conclusion: Estimation of serum E2 is an unreliable marker for differentiating women according to several mature follicles. Estimated serum levels of INHA are the best biomarker for the identification of women who might have <11 follicles and women who might have ≥14 mature follicles with high specificity.

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Keywords: Triggering time, the optimal number of mature follicles, Inhibins, Estradiol, Decision making.

Introduction

According to the WHO, infertility can be defined as failure to achieve a clinical pregnancy through 12 or more months of unprotected regular sexual intercourse in apparently healthy couples (1). Infertility is a worldwide problem with a high prevalence that was estimated to affect about 15% of couples [(2)].

Assisted reproductive technology (ART) as defined by the American Center for Disease Control is any fertility-related treatment in which eggs or embryos are manipulated. In-vitro fertilization (IVF), cryopreservation, and intracytoplasmic sperm injection (ICSI) are by far the most common ART procedure performed [(3)].

Inhibins (INH) belong to a large family of glycoprotein hormones and growth factors and are members of the transforming growth factor-β family [(4)]. INHB is composed of a common α-subunit that is linked to 1-2 β-subunits by disulfide linkage; βA in inhibin A (INHA) or βB in inhibin B (INHB) [(5)]. Gonadal-derived INHs act in an endocrine manner to suppress the synthesis of follicle-stimulating hormone (FSH) by pituitary gonadotrope cells [(6)] by blocking the signaling by activins, which are homodimers of β-subunits, in gonadotrope cells of the anterior pituitary [(5)].

Timing for the human chorionic gonadotrophin (hCG) triggering during ART is still unsettled because too early triggering will result in immature oocytes and endometrium with insufficient luteal phase, while with too late triggering the spontaneous LH surge will be already occurred with subsequent wrong timing of oocyte retrieval; thus the perfect timing for hCG triggering, which might be defined as the time probably allows achievement of the highest possible success rates [(7)], is crucial for ART outcome but unfortunately is still under debate.

Objectives

This study aimed to evaluate the success rate to determine the triggering timing that allows the retrieval of the optimal number of oocytes depending on the estimation of serum levels of estradiol (E2), INHA, and INHB alone or in combination in conjunction with transvaginal ultrasonography (TVU) imaging.

Design

Prospective comparative non-randomized study.

Setting

IVF centers at Benha University Hospital and multiple private hospitals.

Patients

All infertile women attending these centers were evaluated for exclusion and inclusion criteria.

Exclusion criteria

The presence of endometriosis, systemic diseases that may affect the outcomes, very poor ovarian reserve and refusal to participate in the study, manifest hypertension, diabetes mellitus, chronic kidney disease, obesity grades II or III, uterine anomalies, immunological infertility, autoimmune diseases, maintenance on immunosuppressant therapy, or refusal to participate in the study.

Inclusion criteria

Infertile women younger than 40 years, free of exclusion criteria, and who signed the written consents were included in the study.

Ethical considerations

The study protocol was approved in November 2021 and after the end of the study trial and case collection the final approval by No.: RC50.10.22 was obtained.

Blindness

Blood samples were obtained by an assistant who was blinded about the study protocol and sent as numbered innominate tubes to the lab physician who was also blinded about the indications for the requested investigations

Study procedure

All the enrolled women were clinically evaluated for the collection of demographic and clinical data. Then, patients underwent TVU to determine the number of antral follicles in each ovary and the collective number was calculated to determine baseline antral follicle count (AFC) as previously documented by the Practice Committee of the American Society for Reproductive Medicine for measuring the ovarian reserve [(8)]. During ovarian stimulation (OS), patients were frequently monitored for the follicular response by TVU for follicle number and size which was determined as the mean value of two of the orthogonal diameters of the follicle. The optimal number of follicles for deciding for oocyte retrieval was 11-15 follicles of ≥16 mm in diameter as previously documented [(9)]. Regarding serum E2 as an indicator for retrieval, as previously documented serum E2 on a day assigned for oocyte retrieval at <2000 pg/ml will yield few total numbers of oocytes and low-quality embryos [(10)].

Controlled Ovarian Stimulation (COS) protocol

The COS according to the flexible antagonist protocol was performed as a daily subcutaneous injection of 300-450 IU of Gonapure (150 IU/ml amp, Minapharm, Al-Amyrea, Cairo, Egypt) starting on the 2nd day of the cycle. When the dominant follicle reached 14 mm, cetrorelix (250 µg amp, Cetrotide®, Merck, Germany) therapy in a dose of 250 µg/day was started till the day of Human chorionic gonadotrophin (hCG) injection. The hCG injections were given in the form of Epifasi (5000 U amp, Epico, Al-Amyrea, Cairo, Egypt) injection; 10000 units as triggering agent, and oocyte retrieval was performed 36-hr later.

Blood Sampling

Two blood samples were obtained from each enrolled woman under complete aseptic conditions. Blood samples were allowed to clot and centrifuged at 3000rpm for 10 minutes and the supernatant was aspirated and collected in Eppendorf tubes that were numbered by an assistant who was blinded about the required investigations and their indications. Blood samples were collected on the 2nd day of the cycle before the start of ovarian stimulation and at the end of ovarian stimulation on the day of final oocyte maturation.

Investigations

1. Human estradiol (E2) using Abcam ELISA kit (Cat. No. ab285329).
2. Human Inhibin-A and Inhibin-B using Abcam ELISA kit (Cat. No. ab285329 and ab119449, respectively).

Study outcome

The study outcome is the ability of estimated serum levels of E2, INHA, and INHB to distinguish between cases that showed <11, 11-13, and 14-15 oocytes on TUV imaging on the day of hCG triggering in comparison to the retrieved number of the oocyte as the gold standard for comparison.

Statistical analysis

Results were analyzed using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) by applying the paired t-test for analysis of intra-group variance and Chi-square test (X2 test) for analysis of non-numeric data. Kaplan-Meier Regression analysis was used to suggest the most probable cutoff point of serum levels of studied variables for prediction of the number of mature follicles on time of TVU. The receiver characteristic curve (ROC) analysis was used to determine the best predictor for the decision-making regarding to cancel or continue as judged by the significane of the area under curve (AUC) in relation to the area under the reference line (AUC=0.5) for Windows statistical package. Significance was considered if P value was <0.05.

Results

The study included 196 women fulfilling the inclusion criteria after the exclusion of 4 women of obese grade II or III, 3 women who had immunological infertility, 3 women who had uterine anomalies, 5 women who had endometriosis, and 3 women who were older than 40 years. Also, during the follow-up for the response to COS, 12 women were missed and were excluded from the study as shown in figure 1; patients' enrolment data are shown in table 1.

Table (1): Enrolment data of studied infertile women

Variables		Findings
Age (years)	**<25**	40 (20.4%)
	25-29	85 (49.4%)
	30-35	58 (29.6%)
	>35	13 (6.6%)
	Mean (±SD)	28.5±4.2
Body mass index (kg/m^2)	**Average weight (<25)**	6 (3.1%)
	Overweight (25-30)	69 (35.2%)
	Obese I (>30-34.99)	121 (61.7%)
	Mean (±SD)	30.3±2.5
Duration of infertility (years)	**1-2**	116 (59.2%)
	3-5	74 (37.7%)
	>5	6 (3.1%)
	Mean (±SD)	2.4±1.3

At the triggering time as decided according to TVU-determined AFC, the detected AFC, and serum levels of E2, INHA, and INHB were significantly higher in comparison to the corresponding data determined on day 2 of the cycle. TVU detected 69 women (35.2%) had <11 oocytes, 83 women (42.4%) had 11-13 oocytes and 44 women (22.4%) had 14-15 oocytes (Table 2).

Table (2): Mean AFC and serum levels of E2, INHA, and INHB of the studied women

Variables			Findings
Bilateral antral follicular count	**Day 2 of the cycle**		4.5±0.9
	At Triggering time	**<11**	69 (35.2%)
		11-13	83 (42.4%)
		14-15	44 (22.4%)
		Mean (±SD)	11.7±2.2
Serum E2 (pg/ml)	**Day 2 of the cycle**		66.2±45.8
	At Triggering time		2856.7±967.8
Serum Inhibin-A (ng/ml)	**Day 2 of the cycle**		8.9±3.5
	At Triggering time		639.6±178.5
Serum Inhibin-B (ng/ml)	**Day 2 of the cycle**		146.1±123.3
	At Triggering time		4405±3117.9

Using Kaplan-Meier regression analysis to define the cutoff points for serum levels of E2, INHA, and INHB at which the possibility of having oocyte number of 11-15 was increased, showed that serum levels of E2, INHA, and INHB at cutoff points of 3300pg/ml, 723 ng/ml and 5835 ng/ml, respectively might predict the increased possibility of getting 11-15 oocyte on retrieval by about 65%, 50% and 70%, respectively (Fig. 2a-c).

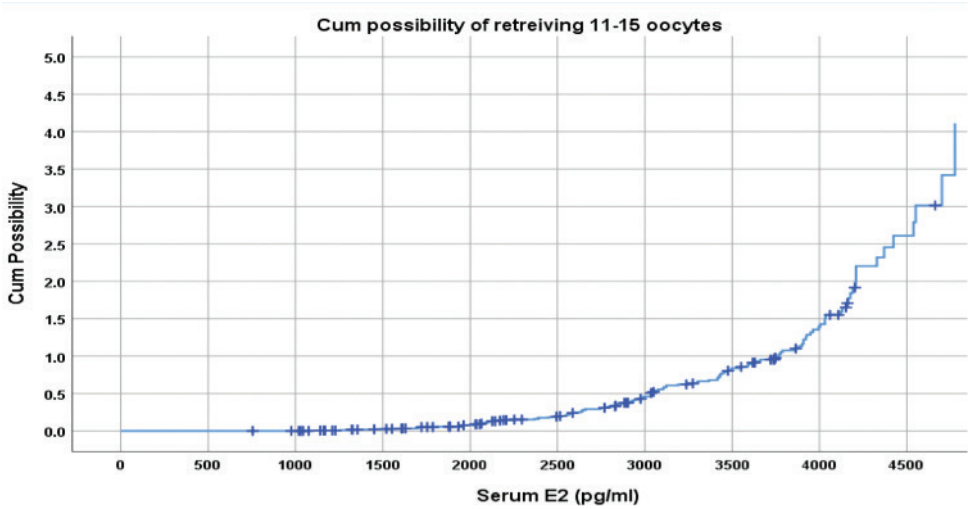

Fig. (2a): Kaplan-Meier regression of serum E2 levels for defining a cutoff point for prediction of 11-15 oocyte retrieval

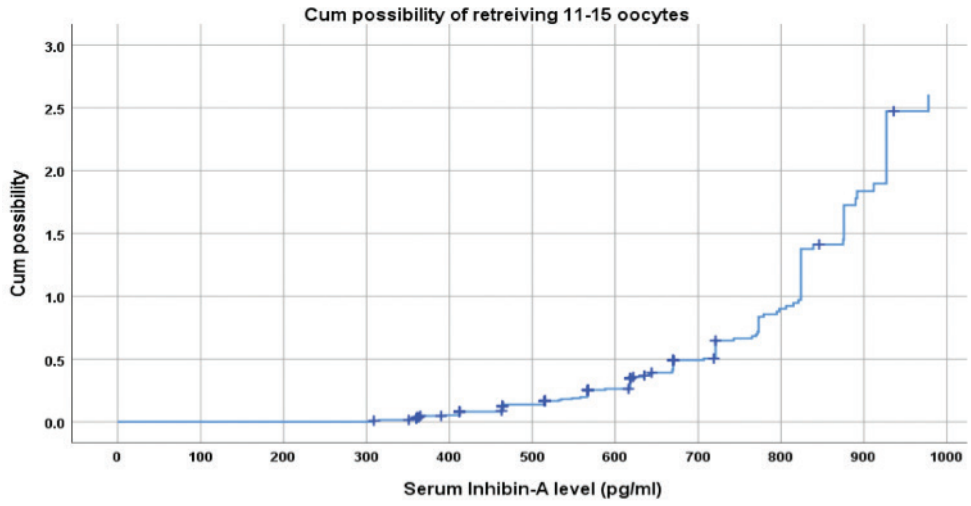

Fig. (2b): Kaplan-Meier regression of serum INHA levels for defining a cutoff point for prediction of 11-15 oocyte retrieval

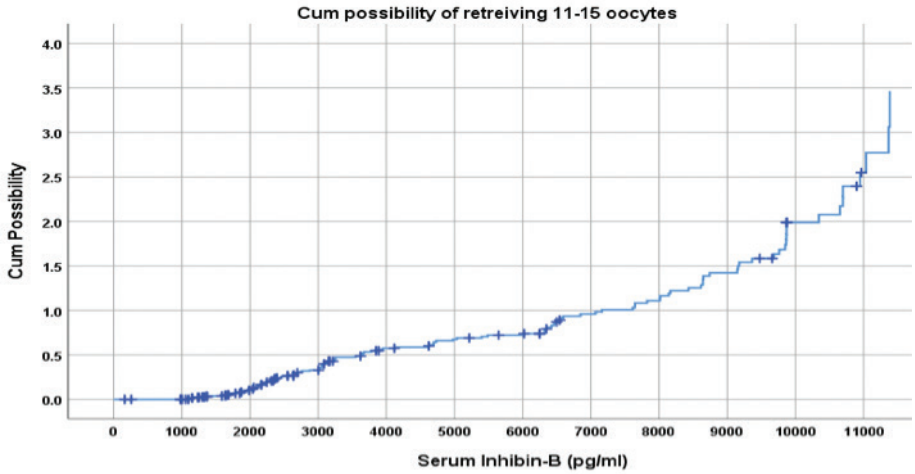

Fig. (2c): Kaplan-Meier regression of serum INHB levels for defining a cutoff point for prediction of 11-15 oocyte retrieval

Evaluation of the diagnostic performance of the suggested cutoff points for the lab variables to discriminate women had 11-15 mature follicles as shown in table 3, defined significantly higher diagnostic performance of serum INHA in comparison to that of E2 (P=0.0005) and INHB (P=0.0028) with the non-significant difference between the diagnostic performance of E2 and INHB (P=0.711).

Table (3): The diagnostic performance of the suggested cutoff point for serum levels of E2, INHA, and INHB to discriminate women had 11-15 mature follicles compared versus the TVU findings

Variables / Markers		Serum Estradiol (pg/ml)	Serum Inhibin-A (ng/ml)	Serum Inhibin-B (ng/ml)
Cutoff point	Value (±SE)	3300±69.3	723±13.9	5835±283
	% of the increased possibility	65%	50%	70%
	95% CI of the value	3170-3440	696-750	5280-6390
Sensitivity rate (%)		54.33 (45.3-63.2)	64.1 (55.28-72.3)	56.3 (46.9-65.4)
Specificity rate (%)		72.5 (60.4-82.5)	96.9 (89.3-99.6)	77.9 (67-86.6)
Positive predictive value (%)		78.4 (70.6-84.6)	97.7 (91.4-99.4)	79.8 (71.6-86.1)
Negative predictive value (%)		46.3 (40.4-52.3)	57.3 (51.5-62.9)	53.6 (47.7-59.4)
Accuracy (%)		60.7 (53.5-67.6)	75 (68.3-80.9)	64.8 (57.7-71.5)

Evaluation of the discriminative ability of the estimated lab variables between the studied women according to the number of mature follicles that might be detected on TVU defined serum INHA as the significant predictor for canceling depending on the maturation of a low number of follicles (n<11 follicles) after COS (Fig. 3a), while serum E2 and Inhibin-B showed non-significant AUC for prediction of such low number of mature follicles, so cancellation decision could not depend on both markers. However, serum E2 and INHB could define women who may have 11-13 mature follicles with significant AUC, while INHA showed non-significant AUC for this targeted number of follicles as shown in figure 3b. For prediction of the possibility of the presence of 14-15 mature follicles, serum INHA may be a significant indicator for triggering and oocyte retrieval for this high number of follicles, while serum E2 and INHB could not discriminate these women (Table 2, Fig. 3c).

Table (3): Receiver characteristic curve analysis of serum biomarkers for discrimination between the studied women according to the number of mature follicles that might be detected on TVU

No. of oocytes	<11			11-13				14-15	
Variables	**AUC (SE)**	**P-value**	**95% CI**	**AUC (SE)**	**P-value**	**95% CI**	**AUC (SE)**	**P-value**	**95% CI**
Serum estradiol	0.498 (0.064)	0.971	0.372-0.623	0.712 (0.069)	0.014	0.576-0.847	0.598 (0.051)	0.079	0.496-0.701
Serum Inhibin-A	0.366 (0.051)	0.045	0.266-0.466	0.545 (0.120)	0.605	0.309-0.780	0.663 (0.056)	0.004	0.554-0.772
Serum Inhibin-B	0.402 (0.064)	0.141	0.277-0.623	0.690 (0.084)	0.028	0.526-0.854	0.592 (0.051)	0.098	0.492-0.693

AUC: Area under the curve; SE: Standard error; CI: Confidence interval

Regression analysis of the three lab variables assured the finding of ROC curve analysis as regards the prediction of the presence of 14-15 mature follicles and defined serum INHA as the significant predictor for the timing of oocyte triggering and retrieval (β=0.378, P<0.001), while excluded E2 and INHB.

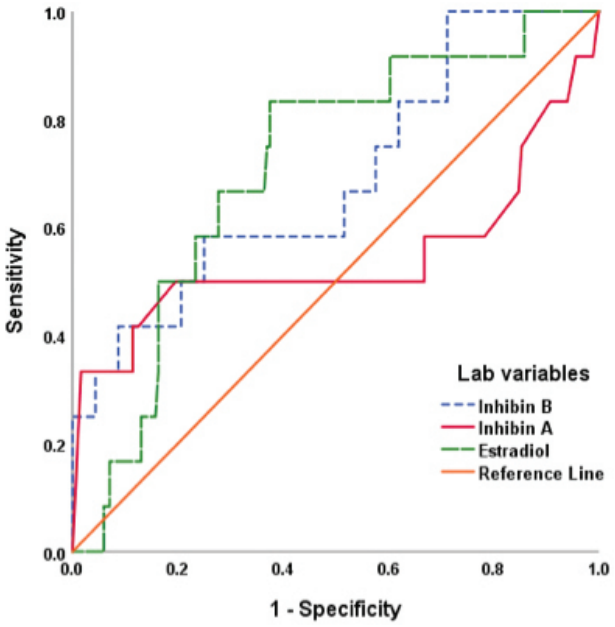

Fig. (3a): ROC curve analysis for identification of women who had <11 mature ovarian follicles on COS and cancellation of triggering

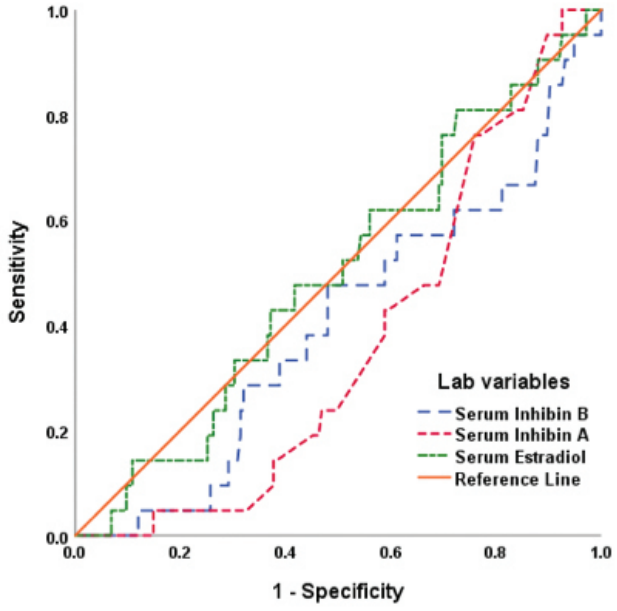

Fig. (3b): ROC curve analysis for identification of women who had 11-13 mature ovarian follicles on COS

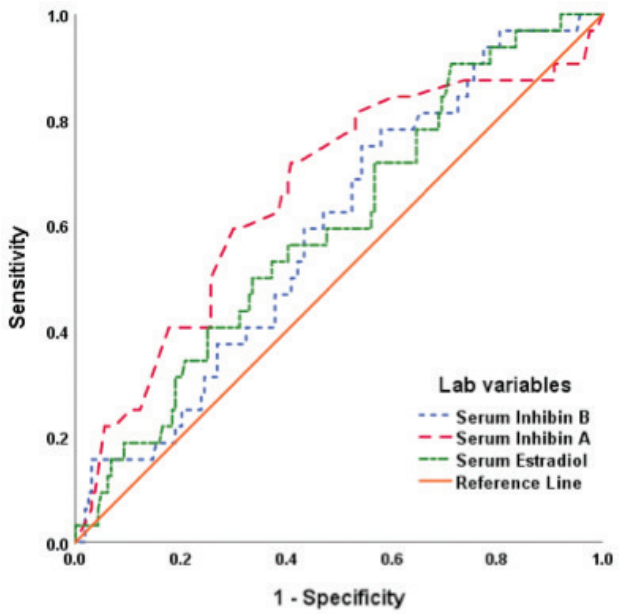

Fig. (3c): ROC curve analysis for identification of women who had 14-15 mature ovarian follicles on COS and triggering indication

Discussion

This study tried to resolve the dilemma of the relationship between the timing of triggering after COS and the number of retrieved oocytes, evaluation of the diagnostic performance of the previously documented cutoff point of serum E2 at the time of triggering (>2000 pg/ml) to distinguish women had >11 mature follicles after COS [9] showed sensitivity rate of 89.8%, while the specificity rate was 40.6% due to the detected high number of false positive cases (59.4%) among women had <11 mature follicles. This finding allows for suggesting the unreliability of the dependence on the estimation of serum E2 as a marker for initiation of triggering and oocyte retrieval and points to the need for another differentiating marker. In line with this data, a previous study documented that the maturity rate of ovarian follicles did not significantly differ among E2 levels [11]. Also, a recent study documented that oocyte maturity was associated with E2 concentration and follicle size as well as the interaction of both parameters; however, the live birth rate per follicle showed a non-significant difference according to follicles sizes at the time of oocyte retrieval [12]. Moreover, the observed data and the provided suggestion goes in hand with the recently documented that E2 measurement is unreliable as a determinant of oocyte maturity and to determine the optimal time point for triggering and attributed this to the multi-follicular growth of follicles of varying size on OS that yields supra-physiological serum E2 levels [13].

On contrary, the estimation of serum levels of INHs could differentiate patients according to the number of mature follicles that might be detected on TVU and help the decision-making for canceling or proceeding, wherein serum levels of INHA at the cutoff point of 723 ng/ml showed significantly higher diagnostic performance for differentiation between patients according to the number of mature follicles in comparison to serum E2 and INHB levels and showed significant AUC for differentiating patients had <11 or >14 mature follicles, while E2 and INHB failed for this respect, but their high levels showed high AUC for defining women had 11-13 mature follicles, while AUC for INHA was non-significant.

These findings supported the previously reported that on the day of final oocyte maturation serum INHA is strong, while serum E2 is moderately correlated to the number of follicles ≥15 mm and to the number of retrieved and mature oocytes with AUC of 0.91 and 0.84, respectively and concluded that serum INHA may be a more powerful tool in conjunction with TVU in defining the triggering time and in the decision making for oocyte retrieval than E2 [14].

The reported relation between high serum levels of INHA and a high number of mature follicles which was not evident for INHB could be attributed to the previously detected in an animal study that found INHA, not INHB can affect follicular maturity through impairing the synthesis of FSH via the competitive binding to activin type II receptors, which stimulates FSH production,

especially in the presence of the TGFβ type III receptor (15). Another in-Vitro study attributed the prolonged effect of INHA on ovarian follicles during OS to the finding that cumulin, which is a heterodimer of the oocyte-secreted factors bone morphogenetic protein 15 and growth differentiation factor 9 that regulate folliculogenesis and ovulation rate, did not significantly alter the ovarian INHA secretion or action, irrespective of the presence of FSH, while cumulin exerts paracrine control of FSH-induced regulation of INHB [(16)].

Also, experimental treatment of the primary granulosa cells that were isolated from ovarian follicles with different concentrations of INHA for 24 h resulted in increased cell viability in a dose-dependent manner of INHA with significant enhancement of the mitochondrial membrane potential, improvement of the progression of the G1 phase of the cell cycle and increased cell number in the S phase and decrease of the apoptotic rate in granulosa cells with higher INHA concentrations [(17)]. Another study attributed the relationship between INHs and the number of mature follicles to the discordant pattern of secretion of ovarian INHs where smaller follicles produce INHB, while the dominant follicle produces INHA [(5)]. Recently, an In-Vivo animal study, reported that the functional molecule of the INHA gene can induce follicular development via regulation of proliferation and apoptosis of granulosa cells with increased secretion of folliculogenesis-related hormones [(18)].

Conclusion

Estimation of serum biomarkers in samples that were obtained on the date assumed for initiation of oocyte triggering might predict the number of mature follicles before TVU examination. Estimation of serum E2 is an unreliable marker for differentiating women according to several mature follicles. Estimated serum levels of INHA are the best biomarker for the identification of women who might have <11 follicles and women who might have ≥14 mature follicles with high specificity. The diagnostic performance of INHB is in the gray zone and its reliability is uncertain.

Limitation

Estimation of the studied cytokines in follicular fluid was missed and so its relation to serum levels was not performed. Also, the relation between these markers and serum FSH was not considered.

Recommendations

Further studies to evaluate the relation between serum INHs and successful pregnancy outcomes of ICSI were mandatory.

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