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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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(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. During laparoscopic myomectomy, methylergonovine infusion greatly decreased loss of blood and the requirement for blood transfusions. Platelet rich plasma has the ability to improve clinical and biochemical pregnancy rate. Also, it has the ability to increase endometrial thickness in women with recurrent implantation failure. Prophylactic antibiotics before the surgical intervention of first-trimester miscarriage resulted in an insignificant decrease in postoperative pelvic infection. Cesarean scare defect repair significantly improves infertility and clinical pregnancy rate through laparoscopy. Pregnancy weight gain was associated with a significant effect on birth weight regardless of BMI. Additionally, maternal weight gain could be considered as a significant predictor of fetal weight. In women with secondary infertility and a residual myometrial thickness of less than 3 mm, hysteroscopic correction of a caesarean scar defect offers a minimally invasive method with a high success rate and no risks. Tranexamic acid significantly reduced intraoperative and postoperative blood loss after cesarean section and it can be safely used for prophylaxis against postpartum hemorrhage after cesarean section in low-risk patients. Sublingual administration of misoprostol before Mirena IUCD insertion could help to increase the ease of insertion with a significant decrease in the procedure time. Furthermore, it could improve patient satisfaction and decrease the pain experience.

Best regards.

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Ejaculation frequency improves ICSI outcomes for idiopathic Oligoasthenoteratozoosepmic patients
Running title: Ejaculation frequency and ICSI in iOAT

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Abstract

Objectives: We aimed to evaluate the association between increasing the frequency of ejaculation and ICSI outcomes for idiopathic oligoasthenoteratozoospermic (iOAT) male partners of couples undergoing ICSI.

Methods: The present prospective case-control study included 81 participants of iOAT men. The participants of the intervention group (n=44) received an instruction to change the lifestyle by increasing the ejaculation frequency and prescribed antioxidant therapy for 3months before ICSI. The subjects of the control group (n=38) received only antioxidant for 3 months before ICSI.

Results: A significant increase in the rate of top-quality blastocyst in the intervention group (42.9%) than in the control (24.7%), (RR: 0.76, 95% CI: 0.65-0.89, P=0.005) was detected. No significant differences in the rates of biochemical pregnancy (59% vs. 28.6%; RR: 1.2, 95% CI: 0.80–1.83), clinical pregnancy (52.3% vs. 37.8%; RR: 1.2, 95% CI 0.76–1.92), and implantation (37.8% vs. 27.9%; RR 1.4, 95% CI 0.88- 2.06] in the intervention group as compared to control were detected. Ongoing pregnancy rate was significantly higher in the intervention group than in the control group [RR 1.96, 95% CI 1.03-3.75; P=0.04).

Conclusions: High frequency of ejaculation may significantly improve the rates of the top quality blastocyst and ongoing pregnancy on ICSI/OAT cycles when combined with antioxidant therapy. Although the study's sample size is small to detect the clinical outcomes, there is a trend toward better rates of clinical pregnancy and implantation. However, a larger sample size is warranted to detect whether these would be of true significance.

Keywords: Idiopathic oligoasthenoteratozoospermia, Male factor, Ejaculation frequency, lifestyle modification, ICSI treatment.

List of abbreviation:

ART: Assisted reproductive technologies
ET: Embryo transfer
FSH: Follicle-stimulating hormone
GnRH: Gonadotropin-releasing hormone
hCG: Human chorionic gonadotropin
HMG: Human menopausal gonadotropin
ICSI: Intracytoplasmic sperm injection
IOAT: Idiopathic oligoasthenoteratozoospermia
IVF: In vitro fertilization
LH: Luteinizing hormone
MII: Metaphase II stage oocytes
rhCG: Recombinant human chorionic gonadotropin
ROS: Reactive oxygen species
SDs: Standard deviation
SPSS: Statistical Package for the Social Sciences program
WHO: World Health Organization

Introduction

There is one worrying certainty to have emerged this century and that is the increase, year on year, in male infertility with a decline in semen quality (1-3). Environment, nutrition and lifestyle factors are arguably the most significant cause of this phenomenon, even in the absence of conclusive evidence (4).

A comprehensive semen analysis following the World Health Organization guidelines (5) is fundamental at the diagnosing of reproductive potential and the selection of appropriate clinical management. Unfortunately, about 30% of infertile men are diagnosed by idiopathic oligoasthenoteratozoospermia (iOAT) after semen analysis (6). iOAT is a complex medical disorder, in which sperm count, motility and morphology are impaired. Until recently, the cause of iOAT is unknown and cannot be diagnosed using the currently available laboratory methods (7). Treatment of iOAT is a problematic, yet no supporting evidence is present for the variety of the available drugs and antioxidants (7). Although intracytoplasmic sperm injection (ICSI) has been proposed as a solution to overcome untreatable iOAT, impaired sperm quality negatively affects embryonic development and clinical outcomes (8, 9).

Eliminating or minimizing, even one adverse factor such as smoking, alcohol and stress, are thought to have a beneficial role on assisted reproductive technologies (ARTs) outcomes (10). To date, studies of the role of ejaculation frequency on ICSI outcomes among infertile men are lacking. In the current study, we prospectively evaluated the association between increasing the frequency of ejaculation and ICSI outcomes for iOAT male partners of couples undergoing ICSI.

Materials and methods

Overall study design

This is a prospective study held at a specialized fertility and gynecology center between November 2018 and September 2019. Approval by the institute's internal review board committee was obtained and all participants signed a written informed consent form before prior to the commencement of this study.

A detailed reproductive, medical and surgical history was taken from all male participants for evaluation, including developmental history, chronic medical illness, infections, surgical procedures, drugs and environmental exposures, lifestyle habitats, sexual history, and ARTs history. Two semen samples were analyzed before the beginning of treatment strategy to evaluate semen according to the World Health Organization (WHO) recommendation (5). Couples included in the present study met the following characteristics: 18-37 years female partners, normal uterus as observed by transvaginal ultrasound, male partners suffered from severe male factor cases; defined in our study as (count>5x106/ml, motility≥30%, progressive motility ≥5 %, abnormal forms ≥96), with ejaculation frequency <6 times per month. Patients with previously achieved pregnancy after ICSI, with frozen or non-ejaculated spermatozoa, and patients

enrolled in pre-genetic diagnosis program were excluded from the analysis. Women were also excluded if they had endometriosis or poor endometrium (<8 mm diameter) on the hCG trigger day. We excluded cases of OAT that have abnormal endocrine function (serum testosterone, inhibin, estradiol, LH and FSH levels), infection (White blood cells >1x106/ml), presence of discernable cause for their subfertile status.

With respect to the two inclusion cohorts, eighty-one patients turned out that patients were randomly distributed into two groups (Intervention group, n=44; Control group, n=37). Male partners in the intervention group were instructed to change the lifestyle by increasing the ejaculation frequency for one month before ICSI (three times per week) and prescribed antioxidant therapy (L-Carnitine (2g daily; Carnivita forte, EVA Pharma, Egypt), vitamin C (1g daily; vitacid C, Cid. Giza, Egypt), and vitamin E(400mg daily; Pharco, Egypt) for 3 months before ICSI. Male patients in the control group received a 3 months treatment of antioxidants only (L-Carnitine (2g daily), vitamin C (1g daily), and vitamin E (400mg daily).

ICSI treatment

All women underwent ovarian stimulation with agonist GnRH analogs according to our standard protocols (11). When two or more follicles were ≥ 18 mm, recombinant human chorionic gonadotropin (rhCG; Ovitrelle®, Serono, Geneva, Switzerland) was administered. Oocyte retrieval was performed 36 hours after the administration of rhCG with transvaginal ultrasound guidance. Two hours later, denudation was performed and only metaphase II stage oocytes (MII) were injected using fresh sperm ejaculates according to (12).

Fertilization check was carried out 16-18 hours after injection and oocytes with two pronuclei were considered as normally fertilized. The embryos were then cultured to the blastocyst stage. Forty-eight hours after ICSI embryos were scored for quality according to a system that takes into account the number of blastomeres, the degree of fragmentation, the symmetry of the blastomeres, the presence of multinucleation, and the compaction status according to the Istanbul consensus (13). Top-quality cleaved embryos were defined as 7–8 cells on day 3, with symmetric and uninucleated blastomeres and <10% fragmentation by volume. On day 5, blastocysts were graded using Gardner and Schoolcraft grading system (14). Top-quality blastocysts were identified as expanded day 5 blastocysts (>3), with rounded and dense inner cell mass and many twin trophectoderm cells creating a connected zone. The embryos were transferred into the uterus at the day 5 blastocyst stage using an embryo transfer catheter (Labotect, Göttingen, Germany) under ultrasound guidance.

Luteal support was initiated after retrieval with vaginal progesterone suppositories twice daily (Cyclogest 400 mg, Actavis, Barnstaple,UK, Ltd.) and continued until a negative pregnancy test or until 8 weeks' gestation. A serum β-hCG test was performed approximately 2 weeks after embryo transfer to confirm a pregnancy. A clinical pregnancy was defined as the presence of a fetal heartbeat on ultrasound scan 4 weeks or more after ET. A pregnancy scan was performed between >20 weeks' gestation to identify ongoing pregnancies.

Study end points

The primary outcome was the rate of top-quality blastocysts (≥3.1.1 formed blastocysts per fertilized oocyte). Secondary outcomes were fertilization rate (the number of normally fertilized oocytes at 16–18 h after ICSI/number of injected oocytes), embryo cleavage rate (the number of cleaved zygotes/number of fertilized oocytes) and blastocyst formation rate, defined as the number of cleaved zygotes per number of fertilized oocytes. Other outcome measures included the rates of biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation (the number of gestational sacs

observed divided by the number of embryos transferred).

Sample Size and statistical analysis

Sample-size calculation was based on the observed differences in top-quality blastocysts from existing data in the center in which the study was conducted, which was shown to be increasing the rate of top-quality blastocysts from 20% to 40. For this difference of 20%, with a power of 95% and an alpha of 5%, 400 oocytes needed to be recruited into each arm. Assuming and adjusting for a worst-case scenario of 10% drop out, 440 oocytes needed to be recruited into each arm; making 880 oocytes the overall required sample size for the study.

Data were entered into the Statistical Package for the Social Sciences program (SPSS), version 20, to be statistically analyzed. Continuous variables were summarized as means with SDs. Dichotomous data were reported as percentages. The odds ratio and 95% confidence interval were calculated. A P value of <.05 was considered statistically significant.

Results

The majority of patients were experiencing their first IVF cycle (61.7%), whereas 24.7% had previously undergone one failed, and 13.6% had undergone two failed ICSI cycles.

Demographics and cycle characteristics

No significant differences between both groups in terms of ages of the women, BMI, duration of time attempting to conceive, number of previous IVF/ICSI attempts, basal FSH (IU/L), antral follicular count, days of stimulation, total FSH/HMG, estradiol level, progesterone level, number of oocyte collected, maturity rate, or number of embryo transferred was detected (Table 1). Furthermore, there were no significant differences observed between the males' demographics and semen parameters between both groups, as detailed in Table 2.

Embryological outcomes and laboratory performance

Embryological outcomes of both groups are presented in Table 3. The rates of fertilization, cleavage and blastocyst formation were similar in the interventional and control groups. The quality of all top cleaved embryos on day 3 in the interventional group had significantly higher quality than those in the control group (74.4% vs. 59.4%; P=0.0001). Embryo compaction rate was also significantly increased in the interventional compared with the control group (36.8% vs. 18.1%; P<0.0001). Furthermore, In the interventional group there were 43% top-quality blastocyst per fertilized oocytes, whereas in the control group there was only 24.7% top-quality blastocyst per fertilized oocytes (P<0.0001; significant).

Clinical outcome measures

Clinical outcomes of both groups are presented in Table 3. The biochemical, clinical pregnancy and implantation rates were higher in the intervention group but were not statistically significant (biochemical pregnancy: intervention 59% vs. control 48.6% [RR 1.2; 95% CI 0.80- 1.83; P=0.35]; clinical pregnancy: intervention 52.3% vs. control 37.8% [RR 1.2; 95% CI 0.76- 1.92; P=0.42]; Implantation: intervention 37.8% vs. control 27.9% [RR 1.4; 95% CI 0.88-2.06; P=0.16]). Ongoing pregnancy rate was significantly higher in the intervention group (21/44), 47.7%) than in the control group (9/37, 24.3%; RR 1.96, 95% CI 1.03-3.75; P=0.04). The early pregnancy loss rate was 11.4% in the intervention group and 24.3% in control group, a difference that was not significant. Furthermore, the multiple pregnancy rate was (9/44, 20.5%) in the interventional group vs. (6/37, 16.2%) in the control group (22 of 180), resulting in no significant difference between both ET groups.

Discussion

In this prospective cohort study, we found that higher ejaculation frequency for one month before ICSI combined with antioxidant treatment for 3 months prior ICSI cycles were associated with statistically significantly higher top-quality cleaved embryos on day 3, compaction and top-quality blastocysts rates compared with antioxidant treatment only for 3 months in iOAT. We did observe differences in the rates of biochemical pregnancy (~10%), clinical pregnancy (~12%) as well as implantation (~10%) in favor to intervention group. However, these remarkable differences failed to detect statistical significance because of our limited small sample size. Moreover, our results showed a significant increase in ongoing pregnancy rate in intervention group.

iOAT has been attributed to increase of reactive oxygen species (ROS) in the tubules and seminal plasma with a reduce in total antioxidant capacity. This may cause apoptosis and consequently affecting semen parameters (15). Undeniably, excess ROS generation negatively affects the outcome of assisted reproduction, leading to lower fertilization, implantation as well as pregnancy rates (16). Methods to treat iOAT are scarce and controversial and mainly based on elevating excessive ROS. Pharmacotherapy of oral supplementation with antioxidants is promising in decreasing ROS, improving semen parameters and ART outcomes of subfertile men suffering from iOAT. Patients included in this study were supplemented with L-carnitine, Vitamin C and vitamin E as a combinational antioxidant for 3 months. A 3-month period of treatment was chosen in our study to allow for a full cycle of spermatogenesis

Multiple confounding factors such as frequency of ejaculation, abstinence time, excessive heat exposure and obesity act as potential sources of ROS and should be considered and modified as possible. Although there is a paucity of information about the effect of lifestyle modification on semen parameters and ART outcomes, it thought to be beneficial without risk in men with iOAT. Little attention has been paid to the effects of ejaculation frequency on fertility. A low frequency of ejaculation may be an important cause of impaired male reproductive function (17). Increased frequency of ejaculation was observed to be associated lower oxidative stress exposure on sperm and could overcome the adverse effect of other lifestyle (18) as well as iOAT (19) was observed to be related to daily ejaculation. On the basis of the results of our study, increasing ejaculation frequency was significantly associated with better embryo quality and ongoing pregnancies in ICSI cycles. This is in agreement with a previous preliminary report, which showed a significant increase in sperm vitality, embryonic development and the probability of subsequent pregnancy after ICSI among 3 infertile couples with high repeated ejaculation frequency in necrozoospermic males (20).

The apparent limitations of our study are mainly attributed to its nature, being prospective non-randomized study with small sample size to detect difference in clinical outcomes and the lack of blinding. Furthermore, the data of live-birth and perinatal outcomes were not available for the entire cohort. The study also included only iOAT patients, which limits the generalizability of the study findings. Therefore, large scale multicenter randomized controlled studies are required to confirm and validate our findings.

In conclusion, our results suggest that increasing the frequency of ejaculation may be an effective option when combined with antioxidant therapy for iOAT treatment. Although the conclusions reached in terms of top-quality cleaved, compaction, top-quality blastocysts and ongoing pregnancy are validated by an adequate statistical power; further additional studies with larger sample size are encouraged to validate our results.

Conflicts of interest

None declared.

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Table I: Baseline and clinical outcomes of both groups

Variable	Intervention group (n=44)	Control group (n=37)	95% CI
Mean female age (Years)	30.6±4.12	30.1±4.18	-0.5(-2.34-1.34)
Mean female BMI (Kg/m^2)	27.02±2.5	26.97±3.0	0.05(-1.26-1.16)
Mean duration of infertility (Years)	6.0±3.1	5.7±2.5	-0.3(-1.56-0.96)
Previous ICSI /IVF attempts	1.8±1.2	1.7±0.8	-0.1(-0.56-0.36)
Etiology Male Combined	 (28/44) 63.6% (16/44) 36.4%	 (23/37) 62.2% (14/37) 37.8%	1.4 %(-20.7-23.7)
Basal FSH (mIU/mL)	6.9±1.1	6.5±0.9	-0.4(-0.85-0.05)
AFC	15.8±5.7	14.4±5.8	-1.4(-3.95-1.15)
Days of stimulation	10.7±0.9	11.0±0.9	0.3(-0.1-0.7)
Total dose of gonadotropin (IU)	2629.4±666.7	2749.3±634.4	119.9(-169.66-409.46)
E2 trigger (pg/ml)	2667.7±799.4	2413.3±902.7	-254.4(-630.91-122.11)
P4 trigger (ng/mL)	1.0±0.4	1.1±0.3	0.1(-0.06-0.26)
COC retrieved	13.8±5.3	14.2±3.2	0.4(-1.58-2.38)
MII injected	12.1±4.8	11.9±3.3	-0.2(-2.06-1.66)
Mean No. of embryos transferred	2.2±0.5	2.3±0.5	0.1(-0.12-0.32)
Mean endometrial thickness (mm) on ET day	11.8±2.0	12.1±1.5	0.3(-0.49-1.09)

Note: Values are mean ± SD or percentages.
P < 0.05 was considered to be significant when compared with the antioxidant only control group.
ET= **embryo transfer**; BMI= **body mass index**; ICSI= **intracytoplasmic sperm injection**; E2= **estradiol**; COC= **cumulus corona cell oocyte complexes**; FSH= **follicle-stimulating hormone**; AFC =**Antral follicle count**; P4= **progesterone**.

Effect of Methylergonovine Infusion on Blood Loss during Laparoscopic Myomectomy
Running title: Methylergonovine infusion and blood loss in LM

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Abstract

Background: These benign tumors are the most frequent in women, with an estimated lifetime risk of 70–80% before menopause. Laparoscopic myomectomy (LM) had less postoperative discomfort, lesser postoperative fever, and a decreased hospital stay than open myomectomy. However, control of blood loss is meanwhile a persistent challenge. Many drugs were investigated to minimize blood loss during myomectomy. Methylergonovine is used to treat postpartum uterine hemorrhage.

Objective: to see whether a methylergonovine peri-operative infusion may help reduce loss of blood during a laparoscopic myomectomy.

Patients and methods: The Obstetrics and Gynecology Department of Benha University performed this randomized controlled research. It was involved 80 patients allocated either into group A treated with methylergonovine infusion or group B receiving placebo in the form of normal saline.

Results: In baseline parameters, there was no substantial variation among the two groups. The length of the surgery projected intra-operative bleeding, post-operative hemoglobin, post-operative hematocrit, number of packed RBC units transfused, and postoperative hospital stay were all substantially different between the two groups. In the number of patients who need blood transfusions, there was a substantial variation. When it came to the negative effects of methylergonovine, there was no substantial difference.

Conclusion: During laparoscopic myomectomy, methylergonovine infusion greatly decreased loss of blood and the requirement for blood transfusions.

Keywords: Leiomyoma, myomectomy, laparoscopy, Methylergonovine, laparoscopic myomectomy, Blood loss.

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Introduction

Uterine myomas have been the most common benign lesions of the female genital tract before menopause, with a lifetime prevalence of 70-80%. (1).

They may cause severe morbidity, such as prolonged or heavy menstrual flow, pelvic pressure, discomfort, or infertility, and are clinically visible in up to 25% of women. (2).

The laparoscopic method is linked with reduced postoperative discomfort, a reduced risk of postoperative fever, and a reduced hospital stay as compared to standard open myomectomy. (3). Other possible benefits of the laparoscopic method have a faster recovery period and a speedier come back to work and everyday activities. (4). Controlling blood loss during LM, on the other hand, remains a difficulty.

The incidence of hemorrhage or blood transfusion in a series of 500 or more LM ranged from 0.1 percent to 6%, with a mean intraoperative bleeding of 80–248 mL (range 20–1000 mL). (5).

Several medicinal interventions, including uterotonics such prostaglandins, misoprostol (6) and dinoprostone (7), oxytocin (8; 9) and carboprost (10), and more recently, vitamin c, have been employed to minimize loss of blood after myomectomy with varying degrees of success. (11).

Methylergonovine is used to prevent and manage uterine bleeding that might occur after delivery. It belongs to a family of drugs known as ergot alkaloids. This medication works by directly acting on the smooth muscles of the uterus, producing contractions and preventing postpartum hemorrhage (12).

The purpose of this observational research was to see whether administering methylergonovine infusion during laparoscopic myomectomy can decrease blood loss or not.

Material and methods

Study design and settings: Between the start of December 2018 and the end of December 2021, this randomized controlled trial was undertaken at Benha University's Department of Obstetrics and Gynecology in Bemha, Egypt.

Sample size calculation: The sample size was calculated based on the findings of a previous study by Congzhe et al. (13), who found that with a power of 0.9 and a significant level of 0.05, 40 patients in each group were needed to achieve an inter-group mean (SD) variance of 200 mL in bleeding during laparoscopic myomectomy.

Patients: After a complete history gathering and ultrasound scanning, eighty-two participants with symptoms recurrent intramural uterine myomas (≥4) of various sizes were included. Patients with high blood pressure, cardiovascular disease, bronchial asthma, diabetes mellitus, hemorrhagic tendency, preoperative hemoglobin levels less than 10 gm/dL, body mass index greater than 35, submucosal myomas, known sensitivity to ergot alkaloids, or any contraindication to procedure or methylergonovine administration were all excluded from the study.

None of the patients received preoperative GnRH analogues or any other hormonal or nonhormonal medication to reduce myoma size or bleeding during laparoscopic myomectomy.

Randomization and allocation: Randomization was done using simple randomization based on online web-based network. Patients were allocated with 1:1 ratio in two groups 1&2. Enrolled patients were given sealed envelopes containing either letter M or S denoting the allocated group. The letter M denotes methylergonovine while S denotes saline. Study group comprised 40 patients who were treated with methylergonovine (Methergine 1m 0.2mg, ***) diluted in 1000ml of normal saline infused at a rate of ….ml/hour during operation while The control group consisted of 40 participants who received just regular saline infusions.

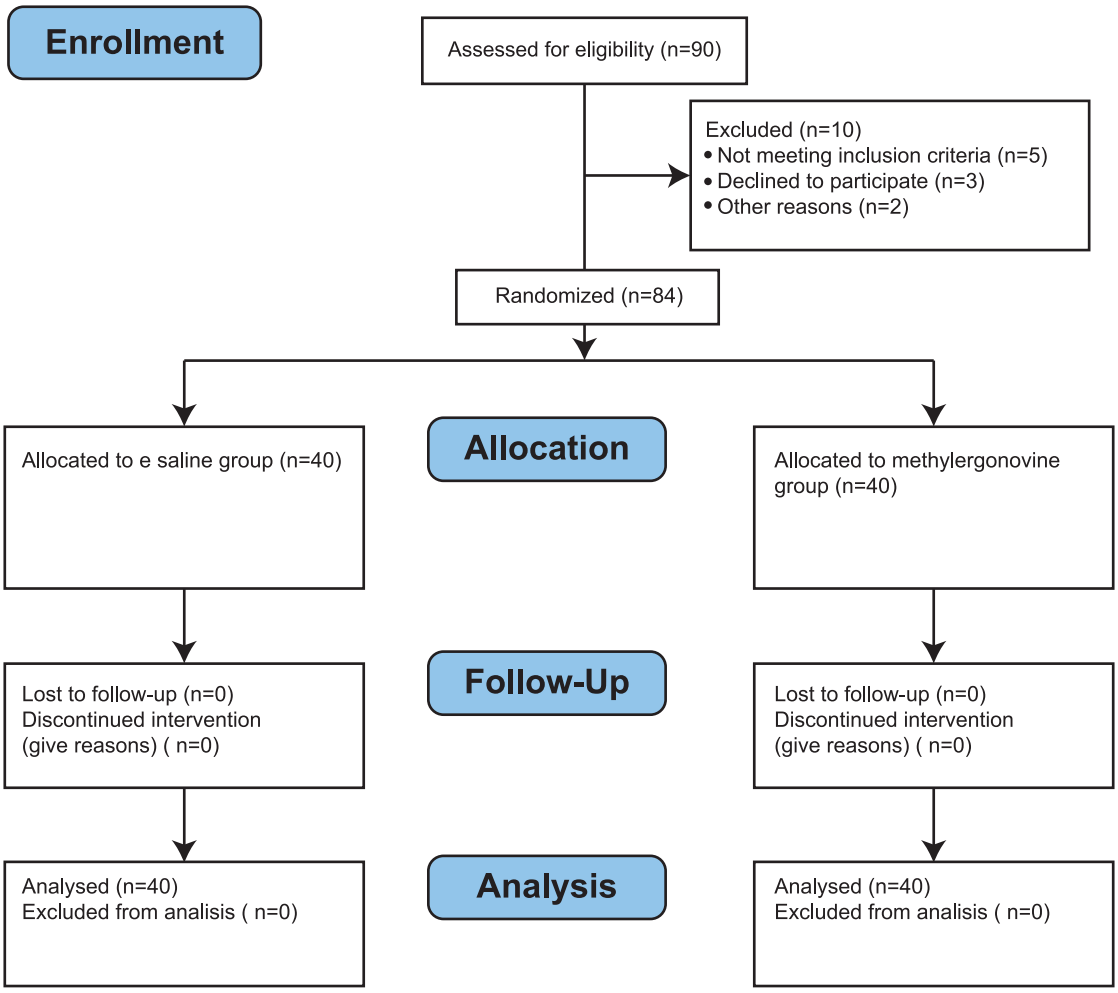

Figure (1): The study's consort flow diagram.

Intervention: Laparoscopic myomectomy

Anesthesia and Preoperative Settings: The patient was put under general anesthesia for all of the surgeries. The patients were prepped for lithotomy, and the uterine Manipulator was inserted into the uterine cavity for uterine mobilization.

Positioning of the Trocar: The closed technique was used for laparoscopic surgeries. A 10-mm scope was inserted periumbilically after pneumoperitoneum was achieved. The following three puncture sites were created: On both sides, two 5-mm sites are located 2 cm above the anterior superior iliac supine, and a 5-mm midline port is located 3 cm above the symphysis pubis, offering an optimal laparoscopic position with a broad operational field. The surgeon stood on the patient's left side, manipulating the left lower 5-mm trocar with his right hand and the midline trocar with his left. The assistant stood on the right side, his left hand directing the camera and his right hand the right 5mm trocar.

Laparoscopic myomectomy technique:

The same surgeon (HT) conducted all of the surgeries, and they were all done in the same way. Vasopressin was injected between the myometrium and the myoma capsule before excision at a dose of 20 IU/100 mL diluted saline solution to reduce the size of the blood vessels and hemorrhage.

The uterine manipulator was operated by the second assistant, who used an anteverted position for a posterior myoma and a

retroverted position for an anterior myoma. The myoma was kept in a prominent location on the operating field. A monopolar needle was used to make a horizontal incision (Fidure 2). The myoma was removed from its capsule using a gripping forceps, monopolar needle, and myoma screw introduced into the left upper trocar port. Dissection was aided by traction on the myoma, as well as the use of the uterine manipulator and myoma screw (Figure 3). A monopolar needle was used to complete hemostasis of the uterine bed after the myoma had been enucleated.

Depending on the depth of the hysterotomy, the uterine wall was sutured in 1 to 3 layers. A separate stitch was utilized to repair the perimetrium using a 5-mm needle holder and 2/0 Vicryl. Normally, sutures are put every 5 mm along the hysterotomy. A baseball suture was used to reconnect the serosa's margins. The endoknife was used to remove almost all myomas from the abdominal cavity. After a full myomectomy, fibrin glue spray was employed to avoid postoperative adhesion development (Figure 4).

Follow up: We followed patients after the operation to detect any bleeding or other complications. ICU admission and postoperative hospital stay were recorded if any.

Outcome of the study: The projected intraoperative bleeding was the primary outcome (ml). **Secondary outcomes**: Operative time, need for blood transfusion, hospital stay, ICU admission, operative and postoperative complications and adverse effects of methylergonovine.

Blood loss was estimated using preoperative and postoperative hemoglobin and hematocrit levels **(taken 8 hours before and one hour after surgery)**. We estimated Hb and Hct before operation (Hb1, Hct1) and one hour after the operation (Hb2, Hct2). We also, estimated blood loss at the operation with application of Bourke and Smith equation **(14)** which is one of the acceptable formulae to calculate the intra-operative loss of blood utilizing preoperative and post-operative hematocrit values. Blood loss = Blood Volume [(Hct1-Hct2)/ Hct1]

Blood Volume = Weight (Kg) * 70ml

Ethical issues and study registration: The ethics committee at Benha University Faculty of Medicine examined and approved the research protocol, and all patients completed an informed consent form prior to the start of the trial.

Statistical analysis:IBM SPSS version 22.0 was used to analyze computer-generated data. To express quantitative data, percentages and numbers were employed. Before utilizing the median in nonparametric analysis or the interquartile range in parametric analysis, it was required to perform Kolmogorov-Smirnov tests to ensure that the data were normal. We used the **(0.05)** significance threshold to establish the significance of the findings. The Chi-Square test is used to compare two or more groups. The Monte Carlo test may be used to adjust for any number of cells with a count less than 5. Fischer Chi-Square adjustment was applied to 2*2 tables when at least a quarter of cells had a count of less than 5.

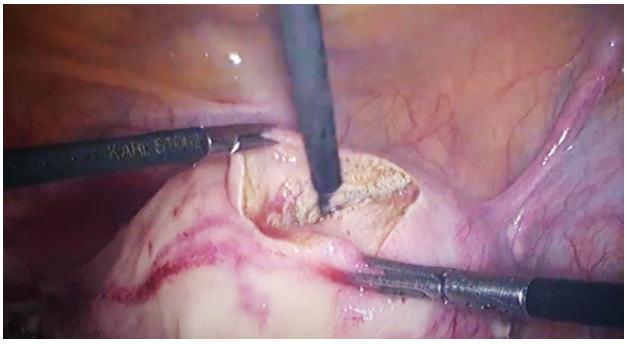

Figure (2): Incision of uterine surface.

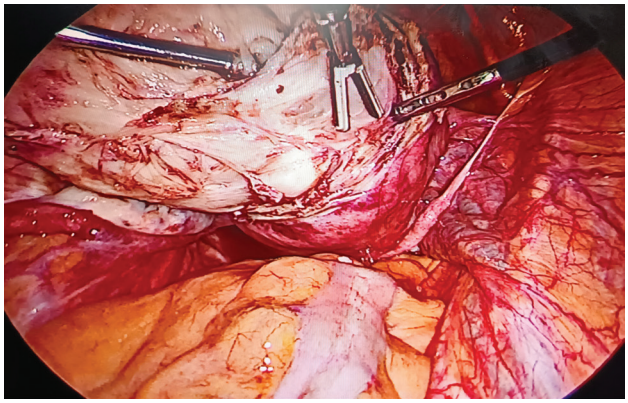

Figure (3): Dissecting the myoma from myometrium after methergine

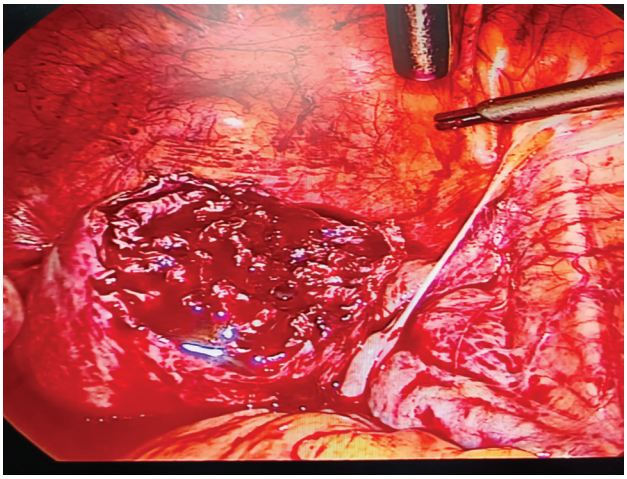

Figure (4): After complete myomectomy

Results

Table (1): Patients basal features.

	Study group (n=40)	Control group (n=40)	p
Age (Years)	32.5 **(2.5)**	31.4 **(2.3)**	>0.05[2]
BMI	26.9 **(5.9)**	27.3 **(7.2)**	>0.05[2]
Uterine Size (Week)	15.6 **(0.8)**	15.3 **(0.5)**	>0.05[2]
Measurement of the largest Fibroid			>0.5[2]
Length (cm)	7.5 **(2.4)**	7.6 **(2.3)**	
Width (cm)	5.6 **(1.3)**	5.6 **(1.6)**	

2: t-test

P >0.05: No substantial difference

As demonstrated in table (1), there was no substantial variance in basal features among the two groups.

Table (2): Preoperative details

	Cases (N=40)	Controls (N=40)	
Operation Duration (min)	100.3 **(20.5)**	145.5 **(13.6)**	<0.001[1]
Estimated intra-operative blood loss (ml)	220.8 **(45.6)**	440.3 **(58.9)**	<0.001[1]
Number of removed myomas	6.7 **(2.6)**	6.2 **(2.1)**	>0.05[1]
Pre-operative Hemoglobin (gm%)	13.2 **(0.8)**	13.5 **(1.1)**	>0.05[1]
Post-operative Hemoglobin (gm%)	12.6 **(0.5)**	10.6 **(0.6)**	<0.001[1]
Pre-operative Hematocrit (%)	39.5 **(0.4)**	38.8 **(0.8)**	>0.05[1]
Post-operative Hematocrit (%)	35.9 **(0.6)**	31.2 **(0.3)**	<0.001[1]
Number of patients needed blood transfusion	4 **(10%)**	16 **(40%)**	<0.5[3]
Number of packed RBCs units transfused	2.1 **(0.2)**	3.5 **(0.6)**	<0.001[1]
Postoperative hospital stay (days)	1.9 **(0.1)**	3.6 **(0.2)**	<0.001[1]
Venous Thromboembolism	0	0	-
Admission to Intensive care unit	0	0	-

1: Fisher's exact test | 3: chi square test
P> 0.05: No substantial difference.
P< 0.05: substantial difference.
P< 0.001: High substantial difference.

The length of surgery evaluated intra-operative bleeding, post-operative hemoglobin, post-operative hematocrit, number of packaged RBC units transfused, and post-operative hospital stay were all substantially differ comparing the two groups. In the number of patients who need blood transfusions, there was a substantial variation. The number of myomas excised, pre-operative hemoglobin level, and pre-operative hematocrit value, however, did not vary significantly as shown in table (2).

Table (3): Adverse effects of methylergonovine administration

	Cases (N=40)	Controls (N=40)	
Changes in blood pressure	5 **(12.5%)**	3 **(7.5%)**	>0.05[3]
Nausea and vomiting	7 **(17.5%)**	5**(12.5%)**	>0.05[3]
Chest pain	0	0	
Difficult breathing.	0	0	

3: chi square test.

P> 0.05: No substantial difference.

There was no substantial difference regarding Adverse effects of methylergonovine administration **(Changes in blood pressure, nausea and vomiting)** as shown in table (3).

Discussion

This research found that intravenous Methylergonovine infusion dramatically decreased blood loss during laparoscopic myomectomy, resulting in fewer patients needing blood transfusions and a shorter hospital stay after surgery. Throughout myomectomy, methylergonovine infusion had no significant side effects that required attention, such as blood pressure fluctuations, nausea and vomiting, chest discomfort, or difficulty breathing.

There was a substantial difference regarding the number of patients who needed blood transfusions. Only 4% of the case group needed blood transfusions, while 40% of the control group needed blood transfusions. According to previous findings, roughly 20–30% of patients having myomectomy needed blood transfusions. (15; 16).

The effect of methylergonovine on uterine contractility in a non-pregnant uterus was previously studied in an observational study comparing the pharmacokinetics and pharmacodynamics features of oral versus intravenous methylergometrine on uterine motility throughout menstruation, which discovered that after intravenous infusion, a rapid increase in the frequency and basal tone of uterine contractions took place with a decrease in their amplitude, which lasted (17).

There was no substantial variance regarding the number of removed myomas. However, Asgari et al., 2021(16) reported a highly substantial variance between the two included groups. According to randomization, there must be no difference in the myomas that need to be removed.

Operative duration mean reached up to 145.5 minutes in control groups. Similar data were found in Asgari et al., 2021 (16), where it reached up to 140 minutes. In our clinical trial, there was no substantial variance in complication occurrence. The same was

reported by Dawood et al. (2018). (18)

There was no substantial variance regarding hemoglobin level preoperatively; however, postoperative hemoglobin level showed a substantial variance between the two groups. The same was reported by (Podzolkova et al., 2020) (19).

Most similar study was conducted by Frass et al., 2019 (20) utilizing ergometrine and concluded that, the median loss of blood during surgery was 110.8±68.9 ml for the Ergometrine treated group and 490.6 ± 86.4 ml for the control group (P<0.001). Similar to our study as we reported Estimated intra-operative blood loss men to be 220 in Methylergonovine group with SD of 45.6 ml and it reached up to 440.3 ml with SD of 58.9 in controls (P<0.001).

Seven patients (17.9%) in the control group required intraoperative blood transfusions. In the control group, 7 patients (17.9%) required intraoperative blood transfusion.our study differ with their results as 10% of cases group needed blood transfusion and 40% of controls needed blood transfusion.

The median decline of hemoglobin level was 1 ± 0.237 for the treated group vs 1.9 ± 0.397 for the control group. The median decline of hemoglobin level was similar in treated group in our study however it was much more in controls as it reached mean of 3 with SD of 0.5 gm%.

The Ergometrine group's postoperative hospital stay was 2.7 ±1.1 days, whereas the control group was 4.1 ± 1.3 days (P <0.001). The duration of post-operative hospital stay in our research was shorter in the treated group, with a median of just 1.9 days and an SD of 0.1. In addition, there was a substantial variance in postoperative hospital stay between the two groups (P <0.001).

Only 3/40 (7.5%) of patients in the experimental group needed blood transfusion, compared to 12/42 (28.6%) in the control group, similar to our results in Dawood et al., (21) research on abdominal myomectomy. They found that infusing Methylergonovine during abdominal myomectomy decreased bleeding and the requirement for blood transfusions considerably. According to previous research, roughly 20-30% of patients having myomectomy needed blood transfusions. (22; 23).

Misoprostol, bupivacaine plus epinephrine, tranexamic acid, gelatin-thrombin matrix, a peri-cervical tourniquet, vitamin c, dinoprostone, loop ligation, and a fibrin sealant patch were found to decrease loss of blood during myomectomy in a previous Cochrane review, while oxytocin, morcellation, and temporary clipping of the uterine (24). Although previously debunked by a Cochrane review, the use of intravenous oxytocin infusions to reduce bleeding in laparoscopic myomectomy has been thoroughly investigated in recent years with proven effectiveness. (25; 26).

Conclusion

During laparoscopic myomectomy, methylergonovine infusion greatly decreased loss of blood and the requirement for blood transfusion.

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Efficacy of intra-uterine infusion of PRP for pregnancy related outcomes in women with recurrent implantation failure; systematic review and meta-analysis of published trials

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Abstract

Background: We aim in our systematic review and meta-analysis to summarize and evaluate the efficacy of intra uterine infusion of PRP for improving pregnancy related outcomes compared to a control group during infertile treatment in women suffering from recurrent implantation failure (RIF).

Methods: Our systematic review (SR) and meta-analysis (MA) was carried out according to the PRISMA guidelines for randomized studies. we searched PubMed, Web of Science, Scopus, and Cochrane library for included studies. We chose randomized controlled trials (RCTs) assessing the efficacy of PRP in women with RIF, then we used Review Manager Software to pool the outcomes of our MA.

Results: We included seven studies in our analysis. The results were significant and favor PRP group regarding clinical, biochemical pregnancy rate and endometrial thickness as following [RR=1.79 CI 95% (1.37-2.32)], [RR=1.97 CI 95% (1.40-2.79)], and [RR=1.79 CI 95% (1.13-2.44)] respectively.

Conclusion: PRP has the ability to improve clinical and biochemical pregnancy rate. Also, it has the ability to increase endometrial thickness in women with RIF.

Keywords: platelet-rich plasma (PRP); Implantation rate (IR); multiple pregnancy rate; miscarriage rate; assisted reproductive technique; IVF/ICSI; controlled ovarian hyperstimulation; repeated implantation failure.

Introduction

Implantation failure (IF) may happen in any stage of the implantation process which are apposition, adhesion, and invasion. There are many causes of IF which are categorized into main 4 classes; change in the endometrial receptive state, embryonic causes, abnormalities in endometrial to embryo crosstalk and immunological causes(1). It is well

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known that the state of the uterine cavity and endometrium thickness have a golden role to ensure pregnancy process (2). Nearly, 13% of the global population have difficulties to conceive for many different reasons (3). If we are talking about the normal natural menstrual cycle, the receptivity of the endometrium is best five to seven days after ovulation which is the same time needed to reach blastocyst stage(4). Endometrial thickness fewer than 7 mm is probably related to disappointing conception outcomes such as, (RIF) and subsequently decreasing pregnancy rates(5).

To increase both quality and endometrial thickness many drugs and interventions have been tried like, different forms of estradiol hormonal(6); vasoactive components like sildenafil(7), intrauterine granulocyte colony-stimulating factor (G-CSF)(8), vitamin E (9)and even pentoxifylline(9); scratching the endometrium(10), immune-modulators usage(11), and correcting the endometrial cavities using hysteroscopy(12). All of which were used as and adjuvant management modality to improve the receptive state and thickness of the endometrium.

In the last decades, there has been a great progress in the treatment of RIF and increasing endometrial thickness such as the usage of platelet rich plasma (PRP). PRP are widely used in many medical fields such as plastic surgery(13), derma(14), ortho(15), and cardio-thoracic surgery(16). It is an autologous conditioned platelets concentrated in plasma and are derived from fresh whole blood, centrifuging it in order to remove red blood cells(17).

PRP has grown in prominence in the field of reproduction in recent years, and several studies have previously looked into its influence on ovarian "rejuvenation" by rousing dormant oocytes in humans, such as those with low ovarian reserve.(18), cases with premature ovarian failure (POF)(19), patients in the post-menopausal period(19, 20).

The main idea of PRP mechanism of action in patients with previous RIF is thought to be mediated through the endometrium itself where the expression of growth factors and cytokines is increased significantly (21).

in our systematic review (SR) and meta-analysis (MA), we are aiming to investigate the previous studies that estimated the efficacy of PRP infusion intra-uterine for infertile females with RIF.

Methodology

Our systematic review (SR) and meta-analysis (MA) was reported according to the guideline reported in the PRISMA statement and that mentioned in "Cochrane handbook for systematic reviews of interventions(22).

Search strategy

We conducted online search of the database till December 2021. The following keywords were used to our database: Intrauterine OR autologous OR platelet-rich plasma (PRP) OR Implantation rate (IR) OR multiple pregnancy rate OR miscarriage rate OR assisted reproductive technique OR IVF/ ICSI controlled ovarian hyperstimulation OR repeated implantation failure to identify the studies that meet our PICO criteria. We also searched the references to identify any other eligible study. We managed our references by Endnote X8.0.

Study selection process and outcome measurement

As mentioned above, we conducted Our SR&MA according to the PRISMA checklist for Randomized controlled trials (RCT).

Inclusion criteria:

RCTs in English with available full text met the following criteria: 1) age between 18 to 45Y 2) infertile women with primary or secondary infertility; 3) with regular menstrual cycles;

4) normal semen parameters of the husband; 5) BMI less than 35k/m2; 6) history of thin endometrium or poor endometrial response, 7) history of RIF

The exclusion criteria:

1)Patientsagedmorethan40years;2)endocrine and thyroid disorders; 3) tubal infertility as detected by Hysterosalpingogram (HSG); 4) cardiovascular, renal, or hepatic disorders; 5) congenital uterine deformities (Asherman Syndrome, fibroid), 6) endometritis; 7) tubal factors such as hydrosalpinx).

The outcome measured were as following clinical pregnancy rate; biochemical pregnancy rate; and ongoing pregnancies.

Data extraction

Data extraction including baseline characteristics (such as, patients age, (BMI) etc.) and outcomes (clinical, biochemical pregnancy rate, and ongoing pregnancies). RCTs were assessed by using the Cochrane Handbook for SR, the 2nd edition(23).

Statistical analysis

This MA was done using Rev-Manager 5.4.0 (Cochrane Collaboration, Oxford, UK). When describing the results of this study, researchers used RR and 95% CI (DerSimonian and Laird 1986). The degree of heterogeneity was established using Cochrane's Q tests and I2 stats. There is considerable heterogeneity if the I2 is more than 50% and the P-value is less than 0.1. To decrease the heterogeneity, the study used a random-effect model. When the p-value was more than 0.1, it was deemed significant statistically. There wasn't subgroup analysis due to lack of data in the included papers.

Results

characteristics of included studies

72 articles were concluded in the searched databases. 15 articles were excluded after title and abstract screening. Of the remaining 25 articles, we ruled out 18 articles. Finally, seven studies were involved. (24-30) All of them were included (fig 1). Summary and baseline characteristics of included studies mentioned in **Tables 1 and 2**.

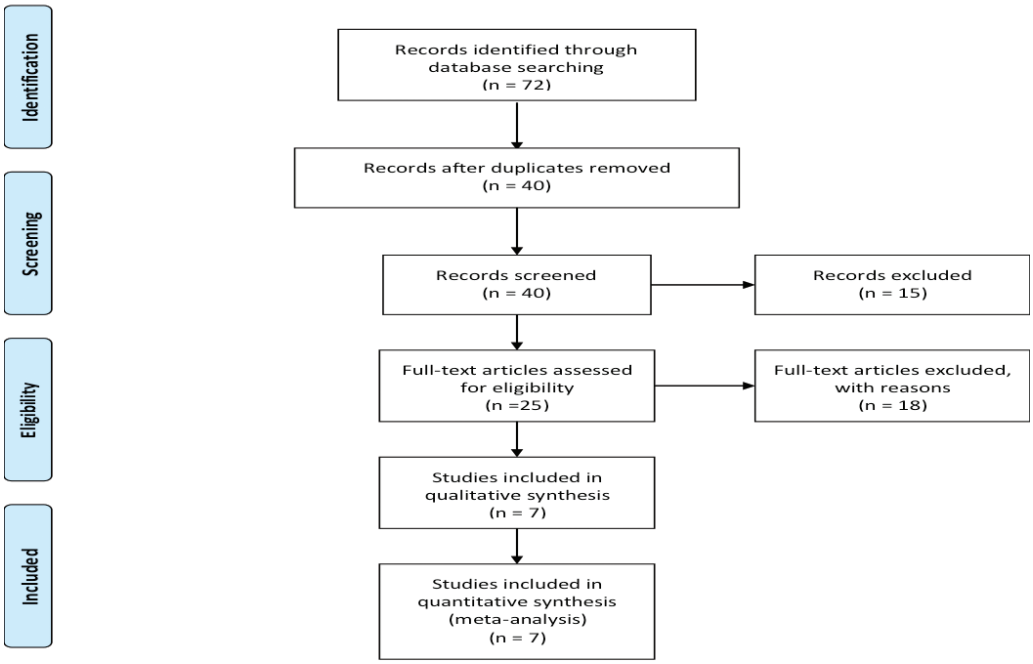

Fig1; Prisma flow diagram

study ID	Study arms	Age of cases	BMI	Basal FSH	AMH level	Endometrial thickness	Previous pregnancy	Duration of infertility (years)	Transferred blastocysts	Previous ET cycles	History of abortion
Tehranine-jad 2020	PRP group: 42	33.5 ± 2.5	26.2 ± 2.8	6.4 ± 2.2	2.4 ± 3.7	7.7 (7.0–8.9)	20 (47.6%)	8.9 ± 6.2	2 (2–2)	4 (3–5)	18 (42.9%)
	control group:43	32.9 ± 3.0	26.3 ± 3.3	6.3 ± 2.4	2.0 ± 2.7	7.7 (7.0–8.8)	21 (48.8%)	11.0 ± 7.0	2 (2–3)	4 (3–5)	19 (44.2%)
Bakhsh 2022	PRP group	35	25.3	7		.	.	4.5	2.8	.	.
	control group	32.7	25.9	5.4		.	.	6.5	3.3	.	.
Nazari 2022	PRP group: 49	35.73 ± 3.49	25.61 ± 3.13	.	.	.	.	.	1.9 ± 0.8	5.38 ± 2.3	.
	control group:48	34.95 ± 4.23	25.46 ± 2.68	.	.	.	.	.	1.7 ± 0.6	4.97 ± 2.8	.
Coksuer 2019	PRP group: 34	29.41 ± 4.54	26.35 ± 4.41	7.3 (4.6–9.5)	.	10 (8–14)	.	7 (4–16)	9.32 ± 0.47	.	.
	control group:36	28.89 ± 3.91	26.78 ± 3.79	6.9 (3.5–9.7)	.	10 (8–13.5)	.	8 (5–15)	9.39 ± 2.46	.	.
Chang 2019	PRP group: 34	34.77± 0.75	22.42± 0.42	5.91± 1.77	.	6.32±0.54	.	3.57±1.82	.	.	.
	control group:30	32.64± 1.70	22.39± 0.80	6.36± 1.84	.	6.39±0.72	.	3.71±1.66	.	.	.
Mehrafza 2019	PRP group: 34	31.85± 5.22	25.52± 3.47	4.59± 1.71	3.02±1.85	.	.	.	3(2-9)	.	.
	control group:30	33.46± 5.17	26.44± 3.61	5.29± 2.18	2.08±2.59	.	.	.	2(2-5)	.	.
Russell 2022	100 patients	37.07 ± 3.77	22.44 ± 2.99	.	.	.	.	1.64 ± 2.32	.	2.19 ± 0.95	22% (19)

Table 2 baseline of included studies

Study ID	setting	Study design	study period	Study arms and sample	Inclusion criteria	Exclusion criteria	intervention group	control group	results
Tehranine-jad 2020	Iran	nonrandomized CT	between 2016 and 2018	PRP: 42 patients control: 43 patients	patients with RIF	age ≥35 y, ET <7 mm, FSH >10 mIU/Ml, males with azoospermia, intrauterine disorders, thrombophilia thyroid dysfunction, positive antiphospholipid antibodies or chromosomal abnormality in a couple.	PRP	non	no role for PRP in improving pregnancy outcomes
Bakhsh 2022	Iran	RCT	.	.	age less than 40 years BMI less than 30kg/m2.	hematological, hormonal, immunological, chromosomal, and genetic disorders, and cancers	PRP	non	PRP improve all pregnancy outcomes
Nazari 2022	Iran	RCT	2016 and 2017	PRP: 49 patients control: 48 patients	age less than 40 years (BMI) less than 30 kg/m2	uterine abnormalities (congenital or acquired), hormonal disorders, immunological and hematological disorders, azoospermia, testicular sperm extraction or aspiration, anatomical disorders of the male genital tract, varicocele and chromosomal abnormalities	PRP	non	PRP improve all pregnancy outcomes

Coksuer 2019	.	retro-spective analysis	Jan 2014 and Jan 2017	PRP: 34 patients control: 36 patients	normal hys-teroscopy and karyotype, regular menstrual cycle of 21–35 days, FSH <10 IU/L, normal semen analysis, mean BMI 18 to 28, mean age 21 to 39, without systemic or immunologic disorders.	cases who obtained donor eggs, previously taken PRP, poor embryo quality	PRP	non	PRP im-prove all pregnancy outcomes
Chang 2019	Chi-na	prosp ective cohort	July 2015 to July 2016	PRP: 34 patients control: 36 patients	(1) age less than 40, FSH<10IU/L (2) endometrium thickness(<7mm) (3) no structural uterine anomalies	pelvic cancer, endometriosis, and adenomyosis	PRP	non	PRP im-prove all pregnancy outcomes
Mehrafza 2019	Iran	retro-spective cohort	during the peri-od from 2016-2017	PRP: 67 patients control: 56 patients	.	.	PRP	non	PRP im-prove all pregnancy outcomes
Russell 2022	Can-ada	retro-spective cohort	October 2018 to July 2021	100 patients	24–52y who diag-nosed with RIF or thin endometrium had PGT-A-tested euploid embryos received one or more intrauterine PRP infusions	inactive endometrium multiple embryos transferred genetic, hematologic, or auto-immune disease Diploid-aneuploid mosaic embryo transfers	PRP	non	PRP can improve both en-dometrial thickness and im-plantation rate

Summary of included studies: PRP: Platelet rich plasma; RIF: recurrent implantation failure; RIF: by mean is the failure to get pregnant following multiple embryo transfers (ET) cycles (three embryos of a high quality, or ≥ ten embryos on a different transfer cycles) or nonex-istence of sac on ultrasound at or after 5 weeks of ET.

Bias and quality assessment

Regarding the quality assessment of included RCTs, the included studies were of low risk of randomization, allocation, attrition bias, reporting bias, and any other biases. Regarding blinding, all studies reported that participants were not blind, and the nature of the interven-tion can explain this. Fig2

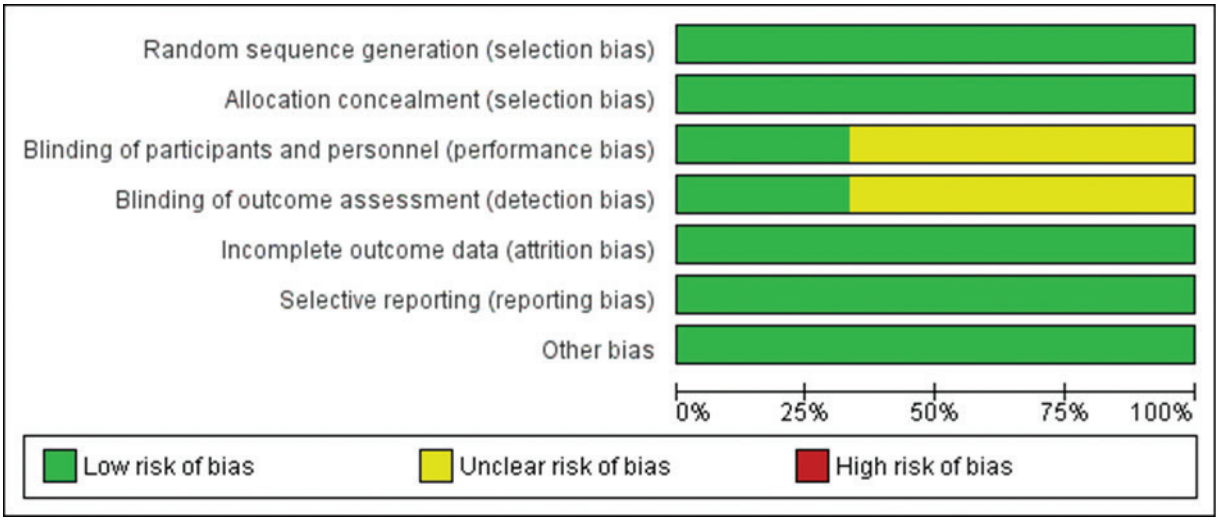

Fig2; risk of bias assessment

Clinical pregnancy rate:

Seven studies discussed the efficacy of PRP on the clinical pregnancy, of which 3 RCTs studies (total number of 59 in the intervention group and 25 in the control group) and 4 cohort studies (total number of 74 in the intervention group and 50 in the control group). (24-30) the results were significant and favor PRP (intervention) group and proved its ability to increase clinical pregnancies as following [RR=1.79 CI 95% (1.37-2.32)] (fig3. All our results were homogenous.

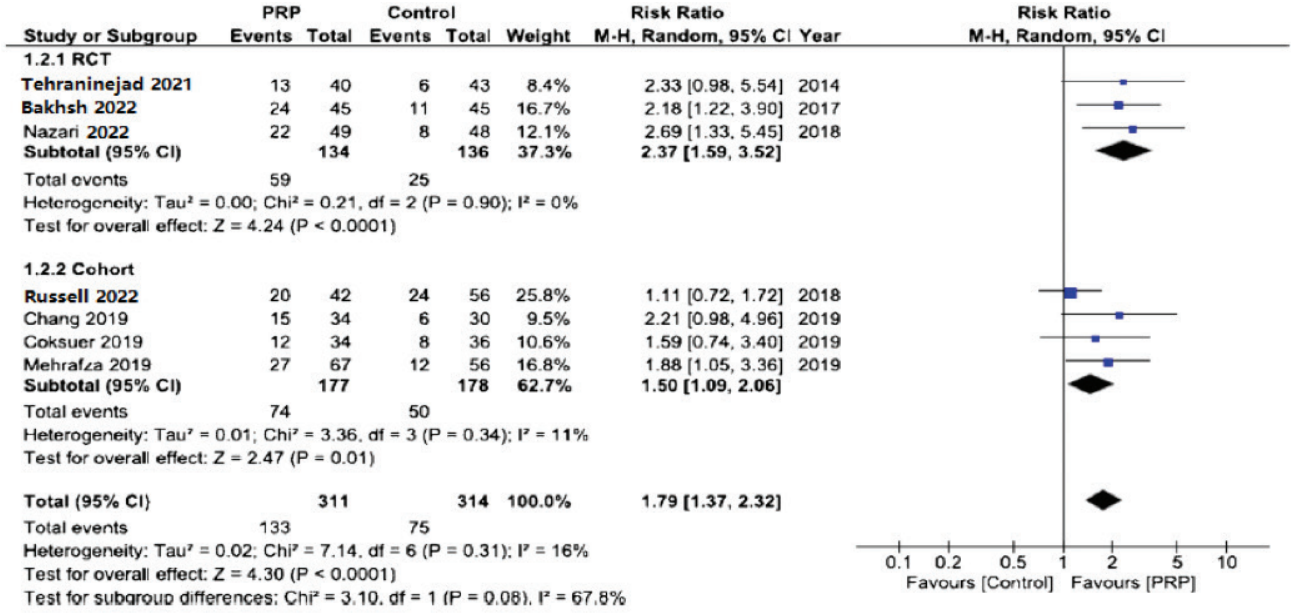

Fig3 Forest plot detailed for clinical pregnancy rate

Biochemical pregnancy rate:

four studies discussed the efficacy of PRP on bio-chemical pregnancies (24, 25, 27) with total number of 71 in the PRP group and 32 in the control group. Our results were significant and favor PRP group [RR=1.97 CI 95% (1.40-2.79)]. Our data was homogenous as following [(P = 0.83); I^2 = 0%] (fig. 4).

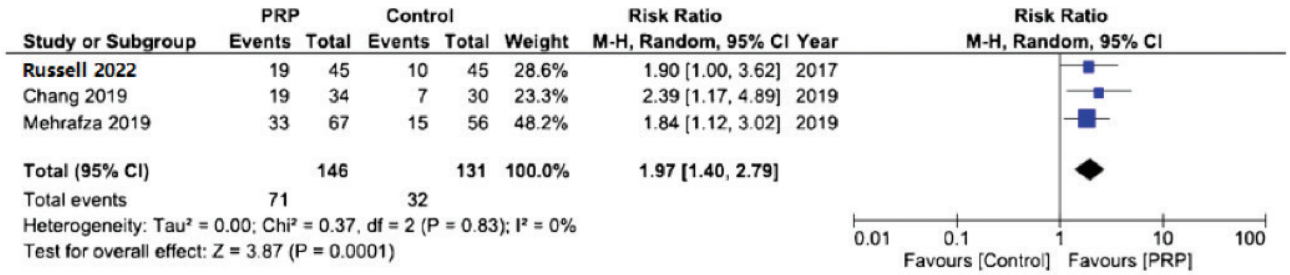

Fig4 Forest plot detailed for biochemical pregnancy rate

Endometrial thickness:

two studies discussed the role of PRP on patients with thin endometrium (24, 28). The results were significant and favor patients in the PRP group as following [RR=1.79 CI 95% (1.13-2.44)]. Our data was homogenous as following [(P = 0.10); I^2 = 64%] (fig. 5).

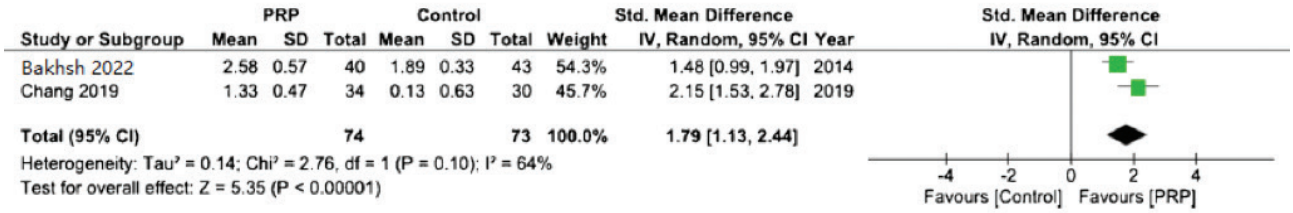

Fig5 Forest plot detailed for endometrial thickness

Discussion

seven studies were included in our meta-analysis that evaluating the efficacy of PRP as an add on therapy in fertile women with RIF. In the PRP group we noticed better improvement regarding the clinical and bio-chemical pregnancy rate. Also, the endometrium showed a significant increase in thickness. All of our results were homogenous.

PRP is an autologous condition where the platelets are found in an absolute concentration. Its injected through many different routes according to the used protocol(31). Our results go in the same direction with Bakhsh et al 2022(28). The study was done on 100 patients and could prove the magic role of PRP in increasing the pregnancy related outcomes in patients with RIF. On the other hand Tehraninejad et al 2021(29) said that PRP has no role in patients with RIF undergoing embryo transfer. Unfortunately, there aren't enough well-designed trials summarizing the efficacy and role of PRP in patients with thin endometrium, so we can't credit PRP's ability to improve the pregnancy outcomes in women with thin endometrium solely. As a result, future research should look into other endometrial receptivity markers.

Limitations and Strength points

Our study has several strength points (1) we conducted all steps in strict accordance with the Cochrane Handbook of Systematic Reviews for interventions, (2) we followed the standard reporting guidelines of PRISMA statement to report this work, (3) we ran a comprehensive search of multiple electronic databases to identify all relevant studies, and finally (4) Our study reported class 1 evidence about the efficacy of GDFT during pregnancy. Nonetheless, our study has a few limitations.

Conclusion

In conclusion, our MA showed significant difference between PRP group and the control groups regarding clinical, biochemical pregnancy and endometrial thickness. So, PRP shows promising results in all pregnancy related outcomes. Also, PRP may provide benefit to healthy parturient women and their newborns

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Role of prophylactic antibiotics in preventing pelvic infection after surgical management of first-trimester miscarriage

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Abstract

Background: Prophylactic antibiotics have been traditionally used to prevent postoperative infection after surgical intervention for the first-trimester miscarriage. This work aims to study the role of prophylactic antibiotics in preventing pelvic infection after surgical management of first-trimester miscarriage.

Methods: This study was conducted on 138 women who underwent surgical management of first-trimester miscarriage. They were equally divided into two groups; the women in the study group were given a single dose of oral doxycycline (200 mg) and metronidazole (500 mg) 2 hours before the surgical procedure. The other group was given a placebo. Both groups were followed up for assessment of postoperative infection within two weeks.

Results: According to the original strict criteria, the prevalence of pelvic infection was found in 8.7% in the antibiotic group (6 out of 69) and 13% in the placebo group (9 out of 69), P=0.412. On follow-up, there was no significant difference between the studied groups concerning postoperative complications.

Conclusion: Prophylactic antibiotics before the surgical intervention of first-trimester miscarriage resulted in an insignificant decrease in postoperative pelvic infection.

Keywords: prophylactic antibiotics; pelvic infection; first-trimester miscarriage.

Introduction

Miscarriage is the termination of pregnancy before fetal viability (less than 20 weeks of pregnancy) or with a fetal weight of below 500 g, i.e., termination of pregnancy before the fetus is capable of extrauterine living (1). It is one of the commonest outcomes in pregnancy, accounting for about 25% of all pregnancies worldwide (2). If occurred within the first 13 weeks of gestation, it is called early or first-trimester miscarriage.

According to the American College of Obstetrics and Gynecology (ACOG), treatment options for miscarriage

include expectant, medical, or surgical management. Surgical options include aspiration and the traditional dilatation and curettage (D&C) (3). Currently, hysteroscopic management and ultrasound-guided surgical evacuation are superior to the blind evacuation technique (4).

The overall complication rate for surgical evacuation of the uterus is approximately 6%. Complications include bleeding, infection, retained placental or fetal tissue, intrauterine adhesions, perforation, and cervical trauma. Up to 30% of women in low-income countries get a pelvic infection after miscarriage surgery, which can have substantial consequences for morbidity and death. National and international guidelines on the surgical management of miscarriage advocate using prophylactic antibiotics to reduce the risk of infection (5).

The localized pelvic infection has been reported in up to 40 in 1000 women after surgical evacuation. According to the Royal College of Obstetrics and Gynecology (RCOG), routine use of prophylactic antibiotics at the time of surgical management of miscarriage is the best practice as it reduces the risk of infection after the procedure (6).

However, current recommendations do not suggest the use of antibiotics prior to miscarriage surgery unless there is evidence of infection since there is insufficient data to support the regular use of antibiotic prophylaxis in the surgical management of miscarriage (5). There are conflicting international recommendations for antibiotic prophylaxis before surgery for incomplete spontaneous abortion. Due to a lack of proof of their effectiveness, some people do not advise using antibiotics (5). So, we aimed to determine the role of prophylactic antibiotics in preventing pelvic infection after the surgical management of miscarriage.

Methods

This clinical trial was conducted at Kasr El-Ainy university hospital and Bolak hospital from January 2021 to May 2022, during which about 138 women were included for management of early miscarriage. The study was approved by the ethical committee of the Gynecology and Obstetrics and was registered at the Clinical trial.gov (registration no. NCT05167838).

The included women had signed written informed consent before participating in this study after being informed of the purpose, interventions, outcome, and possible complications.

Inclusion criteria were female patients between 18 and 35 years old with singleton miscarriage (incomplete or missed), gestational age less than 13 weeks (confirmed by a reliable date for the last menstrual period or/and first-trimester ultrasound scan), and being subjected to the surgical management within two weeks of diagnosis of miscarriage. Women were excluded if they had induced or septic miscarriage, any evidence of infection, morbid obesity (BMI $\geq$40 kg/m^2), or allergy to prophylactic antibiotics (i.e., doxycycline or metronidazole). Women were also excluded if antibiotics were given within 7 days before randomization.

Women were randomly distributed into two equal groups; the study group (Group A), in which women received prophylactic antibiotics (single dose of oral doxycycline 200 mg and metronidazole 500 mg) 2 hours before the surgical management, and the control group (Group B), in which women received placebo 2 hours before the surgical management. Randomization was done via random numbers generated using Microsoft Excel software, while masking was done using 138 identical envelopes, half of them filled with the label "Group A", while the other half filled with the label "Group B". All envelopes were prepared by the investigator and sealed before starting enrollment. After enrollment, each participant was allowed to choose one envelope to determine which group was assigned.

All women in both groups were subjected to detailed history and clinical examination to ensure adherence to inclusion criteria. Vaginal ultrasound was done to confirm the diagnosis of miscarriage and its type. Routine laboratory tests were done, including complete blood count (CBC), coagulation profile (PT, PC, INR), c-reactive protein (CRP), liver functions (ALT, AST), and kidney functions (Creatinine). All patients underwent surgical management in the form of surgical evacuation or dilatation and curettage (D&C). Patients were followed at regular visits on the 5th, 10th, and 15th day of the postoperative period regarding the change in the vital signs and the laboratory tests.

Pelvic infection was diagnosed upon the presence of two of the following clinical parameters: purulent vaginal discharge, pyrexia (>38°C), uterine tenderness, white cell count > 12000 cells /mL^3, and the need for administration of antibiotics for the management of presumed pelvic infection.

Sample size calculation: Sample size was calculated by comparing the incidence of post-abortive pelvic infection between women undergoing surgical evacuation and given prophylactic antibiotics and those not given antibiotic prophylaxis. The calculation was based on comparing two proportions

from independent samples using the Chi-square test, the α-error was set at 0.05, and the study power was set at 80%. According to Goranitis et al. (2019), the incidence of pelvic infection after surgical evacuation in the non-treated high-risk group was approximately 43% (5), and we assumed that using prophylactic antibodies is expected to achieve a 50% reduction in this incidence, the optimum sample size should be 69 participants in each group.

Statistical methods: Statistical analysis was done using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data were summarized using mean ±standard deviation or number of cases with percentages. The independent samples t-test was used to compare groups regarding the quantitative variables, while the Chi-square test was for to compare the categorical variables. P-values <

0.05 were considered statistically significant.

Results

Patients were distributed into two groups; the study group (n=69), in which women received prophylactic antibiotics (single dose of oral doxycycline 200 mg and metronidazole 500 mg) 2 hours before the surgical management, and the control group (n=69), in which women received placebo 2 hours before the surgical management. There was no statistically significant difference between the two groups regarding the demographic and clinical characteristics, as shown in Table 1.

Table 1: Demographic and clinical characteristics of all patients

	Antibiotics group (n=69)	Placebo group (n=69)	p-value
Age	28.32 ± 5.24	28.75 ± 5.42	0.633
BMI	29.13 ± 4.32	28.13 ± 3.69	0.146
Parity	1.90 ± 1.15	1.88 ± 1.26	0.944
Previous mode of delivery **-** Nullipara - Previous NVD - Previous CS	 11 (15.9 %) 20 (29 %) 38 (55.1 %)	 10 (14.5 %) 31 (44.9 %) 28 (40.6 %)	0.140
Previous abortions	0.68 ± 0.89	0.71 ± 0.94	0.854

Medical History - Free - Hypertension - DM - Hyperthyroidism - Hypothyroidism - Antiphospholipid	 55 (79.7 %) 9 (13 %) 3 (4.3 %) 1 (1.4 %) 1 (1.4 %) 0	 55 (79.7 %) 7 (10.1 %) 3 (4.3 %) 0 3 (4.3 %) 1 (1.4 %)	0.662
Current G.A.	8.99 ± 1.68	8.94 ± 1.58	0.876
Type of abortion - Missed - Incomplete	 42 (60.9 %) 27 (39.1 %)	 37 (53.6 %) 32 (46.4 %)	0.390

Table 2 compares the antibiotics and placebo groups regarding the management procedure, the occurrence of postoperative bleeding, and the prevalence of pelvic infection. The surgical management was in the form of either surgical evacuation or dilatation and curettage (D&C) and showed no significant difference between the two groups (P=0.306). There was no significant difference between both groups regarding the bleeding that occurred postoperatively on days 0, 5, 10, and 15 (P=0.430, 0.196, 0.079, 0.116, respectively). According to the original strict criteria, pelvic infection was diagnosed in 8.7% in the antibiotic group (6 out of 69) and 13% in the placebo group (9 out of 69); P= 0.412. There is no privilege to use prophylactic antibiotics before the surgical intervention.

Table 2: Management of both groups and postoperative sequelae

	Antibiotics group (n=69)	**Placebo group (n=69)**	**p-value**
Procedure of management - D&C - Surgical evacuation	 40 (58 %) 29 (42 %)	 34 (49.3 %) 35 (50.7 %)	0.306
Bleeding on procedure day - No bleeding - Mild bleeding - Moderate bleeding - Severe bleeding	 8 (11.6 %) 34 (49.3 %) 16 (23.2 %) 11 (15.9 %)	 11 (15.9 %) 31 (44.9 %) 21 (30.5 %) 6 (8.7 %)	0.430
Bleeding on after 5 days - No bleeding - Mild bleeding - Moderate bleeding - Severe bleeding	 13 (18.8 %) 42 (60.9 %) 14 (20.3 %) 0	 16 (23.2 %) 46 (66.7 %) 6 (8.7 %) 1 (1.4 %)	0.196
Bleeding on after 10 days - No bleeding - Mild bleeding - Moderate bleeding	 39 (56.5 %) 28 (40.6 %) 2 (2.9 %)	 50 (72.5 %) 19 (27.5 %) 0	0.079
Bleeding on after 15 days - No bleeding - Mild bleeding	 61 (88.4 %) 8 (11.6 %)	 66 (95.7 %) 3 (4.3 %)	0.116
Pelvic infection (Two signs) - Pelvic infection - No pelvic infection	 6 (8.7 %) 63 (91.3 %)	 9 (13 %) 60 (87 %)	0.412

The vital signs and laboratory results in both groups were recorded on the day of surgical management and on the 5th, 10th, and 15th days postoperative. Table 3 demonstrates these changes that occurred in each group. Overall, there is no significant difference between both groups regarding the change in blood pressure, pulse, temperature, Hb level, total leukocytic count, platelets count, coagulation profile (PT, PC, INR), c-reactive protein (CRP), liver functions (ALT, AST), and kidney functions (Creatinine).

Table 3: Changes in the vital signs and laboratory findings

	Antibiotics group (n=69)	Placebo group (n=69)	p-value
Change in Blood pressure			0.513
- Decreased	22 (31.88 %)	16 (23.19 %)	
- No Change	14 (20.29 %)	15 (21.74 %)	
- Increased	33 (47.83 %)	38 (55.07 %)	
Change in pulse			0.314
- Decreased	45 (65.22 %)	53 (76.81 %)	
- No Change	10 (14.49 %)	6 (8.70 %)	
- Increased	14 (20.29 %)	10 (14.49 %)	
Change in temperature			0.119
- Decreased	32 (46.38 %)	23 (33.33 %)	
- No Change	24 (34.78 %)	36 (52.17 %)	
- Increased	13 (18.84 %)	10 (14.49 %)	
Change in Hb			0.871
- Decreased	55 (79.71 %)	53 (76.81 %)	
- No Change	2 (2.90 %)	3 (4.35 %)	
- Increased	12 (17.39 %)	13 (18.84 %)	
Change in WBCs			0.729
- Decreased	60 (86.96 %)	57 (82.61 %)	
- No Change	1 (1.45 %)	2 (2.90 %)	
- Increased	8 (11.59 %)	10 (14.49 %)	
Change in platelets			0.086
- Decreased	40 (57.97 %)	27 (39.13 %)	
- No Change	2 (2.9 %)	3 (4.35 %)	
- Increased	27 (39.13 %)	39 (56.52 %)	
Change in CRP			0.930
- Decreased	50 (72.46 %)	50 (72.46 %)	
- No Change	15 (21.74 %)	14 (20.29 %)	
- Increased	4 (5.80 %)	5 (7.25 %)	
Change in PT			0.950
- Decreased	49 (71.01 %)	49 (71.01 %)	
- No Change	9 (13.04 %)	8 (11.59 %)	
- Increased	11 (15.94 %)	12 (17.39 %)	
Change in PC			0.782
- Decreased	38 (55.07 %)	34 (49.28 %)	
- No Change	4 (5.80 %)	5 (7.25 %)	
- Increased	27 (39.13 %)	30 (43.48 %)	

Change in INR - Decreased - No Change - Increased	 45 (65.22 %) 18 (26.09 %) 6 (8.70 %)	 44 (63.77 %) 21 (30.43 %) 4 (5.80 %)	0.725
Change in ALT - Decreased - No Change - Increased	 33 (47.83 %) 2 (2.90 %) 34 (49.28 %)	 40 (57.97 %) 4 (5.80 %) 25 (36.23 %)	0.258
Change in AST - Decreased - No Change - Increased	 29 (42.03 %) 11 (15.94 %) 29 (42.03 %)	 40 (57.97 %) 5 (7.25 %) 24 (34.78 %)	0.107
Change in creatinine - Decreased - No Change - Increased	 34 (49.28 %) 16 (23.19 %) 19 (27.54 %)	 38 (55.07 %) 8 (11.59 %) 23 (33.33 %)	0.195

Discussion

Globally, an estimated 23 million miscarriages occur every year (7). Moradinazar et al. estimated the lifetime prevalence of abortion in 4831 women aged 35 to 65 years who participated in Ravansar Non- Communicable Disease (RaNCD) cohort study and gave birth. They found that 25.7% of patients experienced spontaneous abortion

(8). Unfortunately, many of these abortions become incomplete and require surgical intervention to complete the evacuation of the uterine components (9). This type of surgery is considered one of the most common operations in the field of obstetrics and gynecology.

Infection is one of the most common complications that occur postoperatively in cases with surgical miscarriage. It may lead to increased morbidities and mortalities; that may even end with death (10). That is why there was a debate concerning the use of preoperative antibiotic prophylaxis to decrease the incidence of postoperative infection. Some authors were with, and others were against and preferred not to use antibiotics preoperatively due to lack of evidence (3).

So, we tried to investigate the role of preoperative antibiotic prophylaxis in the prevention of postoperative complications of abortion. One hundred thirty-eight patients were included in the study. They were randomized into two groups, group A, including 69 participants who were given a single dose of oral doxycycline 200 mg and metronidazole 500 mg 2 hours before the surgical management, and group B, including 69 participants who were given placebo tablets before their operation.

We found that pelvic infection occurred in 10.9% of all patients. Although its prevalence was 6 out of 69 patients in the antibiotic group (8.7%) versus 9 out of 69 patients in the placebo group (13%), this ratio was statistically insignificant. This nearly matches what was found by Lissauer et al., who conducted a double-blinded placebo-controlled trial including 3412 patients who were admitted for first-trimester abortion. They were given a combination of oral metronidazole and oral doxycycline and followed up for 14 days to develop postoperative signs of infection. They found that 4.1% of patients in the antibiotic group compared to 5.3% of the other group developed infection postoperatively with no significant difference between both groups at the end of follow-up (11).

Titapant did another trial in 2012; they included 84 patients who were randomly assigned into one of two groups; the intervention one was given 1 g of cefoxitin as the source of preoperative antibiotic. They were followed up for one week postoperatively. They found that postoperative infection accounted for only 2 cases in the control group compared to no cases in the antibiotic group. However, this was also statistically insignificant (12).

On the other hand, Islam et al. performed a systematic review on 16178 participants from 24 RCTs. They found that antibiotic prophylaxis was effective in reducing the rate of postoperative genital tract infections (RR 0.72, CI 0.58: 0.90). However, these results were only marked in high-income countries but not significant in low and middle-income countries due to lack of evidence in these countries (13).

It is known that bleeding is one of the most common postoperative complications, whether primary or secondary. Our study found that postoperative bleeding was not significantly obvious among patients in both groups. This may be explained by the fact that the surgical induction of abortion results in minimal blood loss. On the other hand, medical induction of abortion was associated with heavier and prolonged bleeding, which significantly decreased the hemoglobin level (14).

Concerning obesity, we found in our study that the mean BMI for all patients was

28.63 ± 4.04 kg/m^2 lying in the category of overweight and obesity. This matches what we found in the literature. Benson et al. studied 4968 women undergoing surgical induction of abortion between September 2012 to July 2014 and found that 25% of patients were obese, in addition to 4% who suffered from morbid obesity. However, they could not establish a causality relationship between obesity and abortion due to the insufficiency of presented data (15).

No doubt that maternal age affects the outcome of pregnancy. Many researchers stated that increasing maternal age could lead to many adverse effects, e.g., gestational diabetes, congenital abnormalities, stillbirth, and even miscarriage (16). Khalil et al. reviewed 76158 cases presented for routine antenatal care to 3 UK hospitals and found that the risk of abortion increased with increasing maternal age at pregnancy, with the highest percentage occurring in more than 35 years old pregnant females (17).

In our study, we found that the mean age of patients who underwent surgical abortion was

28.54 ± 5.32 years old, with no significant difference between both studied groups. This was similar to what was found by Meaidi et al., who followed up patients who underwent surgical induced abortion between 2005 and 2015 and found that gestational age between

25 and 29 years old was significantly associated with a higher incidence of early abortions (18).

Conclusion

Prophylactic antibiotics before surgical management of first-trimester miscarriage resulted in an insignificant decrease in postoperative pelvic infection after 15 days of follow-up. We recommend performing this study on a larger number of patients for longer follow-up periods.

Declarations

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

Funding: This research received no specific grant from any funding agency.

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

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Laparoscopic isthmocele repair: impact on secondary infertility after cesarean sections

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Abstract

Objective: study the effect of uterine isthmocele repair on cases with secondary infertility, abdominal pain and abnormal uterine bleeding.

Setting: Zinat Alhayat hospital in Benha from June 2019 to January 2021.

Methods: Cases recruited from those who complained from secondary infertility and delivered by cesarean section and presented with infertility and abnormal uterine bleeding in examination a lower segment cs defect was evident by vaginal ultrasound

Total number of 50 cases divided into two groups

Group one laparoscopic isthmocele repair group 25 cases (laparoscopic repair of scar defect done)

Group two controls conservative management group

Cases given chance for spontaneous pregnancy at month one

Second and third month cases given induction of ovulation with a fixed protocol of letrozole 2.5 mg twice daily from day 2 for 5 days and HMG Meriofert injection 75 u at day 3, 5, 7 of menstrual cycle.

Then follicular maturation follicular maturation was monitored with vaginal ultrasound

Primary outcome measures: pregnancy rate by the end of 3 month

Secondary outcomes: resolution of abnormal uterine bleeding and abdominal pain.

Results: regarding the total pregnancy rate at the end of the third month following surgery there were 15 pregnant cases out of 25 in the isthmoplasty group compared to 3 out of 25 in controls with p value of 0.0004 with a high statistically significant difference.

Regarding pain scores above 6 points there was one out of 25 in cases compared to 10 out of 25 in controls with p value 0.002.

Regarding abnormal uterine bleeding there were 2 out of 25 in cases compared to 12 out of 25 in controls with p value of 0.001 and a high statistical difference.

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Conclusion: cesarean scare defect repair significantly improve infertility and clinical pregnancy rate through laparoscopy.

Keywords: infertility, cesarean scar defect, isthmoplasty, clinical pregnancy rate.

Introduction

Infertility is a worldwide problem and one of the factors that increased infertility rate is the rise of cesarean section even in the absence of indication.

Endometrial receptivity can be adversely affected by large extent with presence of scar defect that creates a defect can adversely affect embryo implantation. (1)

Many factors during cesarean section procedure governs the healing pattern of the scar ,some factors like ;vicryl sutures, increasing the tension on sutures while knotting ,locking of the sutures ,leaving a lower segment small defect without repair .

Retroverted uterus also another factor, aiding in scar defect incidence due to traction on the lower segment at the level of the scar. (2)

Bad techniques during cesarean section repair can retard the healing of the lower segment leaving a defect in the isthmic region known also as isthmocele, the cesarean scar defect aka ithmocele can lead to abdominal pain, secondary infertility and abnormal uterine bleeding

Abnormal uterine bleeding in cases of cesarean scar defect occurs due to stagnation of the menstrual blood into the scar which can lead to abdominal pain and postmenstrual spotting (3,4)

Isthmocele incidence varies from 6 percent to 20 percent and become a problem in diagnosis and management that requires special attention.

Stagnation of menstrual blood in the cesarean scar defect can affect sperm transport or may even kill sperms, also retained blood can interfere with embryo implantation or may make the developing placenta to cover the defect leading to placenta previa and accreta spectrum with an increasing morbidity and mortality.(5)

The gold standard in the diagnosis of the scar defect aka isthmocele is by transvaginal ultrasound visualization of the defect in the lower segment then confirmed by hysteroscopic visualization.

Isthmocele diagnosed as hypo-echoic defect more than 1mm and the residual myometrial thickness can be graded as 1mm or from 3-1 mm or more than 3 mm the, residual thickness governs the route of repair; when the defect is large and the residual myometrial thickness is 1mm or below that the best correction is via laparoscopic complete resection and anatomical repair. (6)

Several modalities have been implemented for the management of isthmocele one of them is hysteroscopic resection but hysteroscopic resection pregnancy rate only 30 percent this improvement with hysteroscopy can be increased by laparoscopic repair with complete excision of the defect and DE novo repair with approximations of healthy tissue. (7)

Different techniques for management varied from hysteroscopy to laparoscopy to the conservative hormonal building up with combined pills containing high estrogen.

Vaginal repair also can be done but in a blind and incomplete way so the laparoscopic approach with complete excision of the scar and total anatomical repair is the best route.

Subjects and Methods

Study design: Prospective controlled trial comparing laparoscopic repair of isthmocele to conservative management

Objectives: present work studied efficiency of laparoscopic management of cesarean scar defect in infertile patients

Setting: laparoscopic ithmoplasty done in zinat al-Hayat hospital in Benha

Primary outcome measure; pregnancy rate

Secondary outcome measures: abdominal pain, abnormal uterine bleeding.

Sample size: 50 cases

Groups

Group one: laparoscopic ithmoplasty 25 cases

Group two: conservative ithmocele observations 25

Patients recruited from private jam clinic who complained from secondary infertility after cesarean section.

Studied subject evaluations

History: complete history of the duration of infertility, age, no of living children .the place of previous cesarean section and all details about previous sections including duration of the operation, antepartum or postpartum bleeding any blood transfusion

Complete examination general abdominal examination done

Investigations laboratory

CBC
Fasting blood sugar
TSH, t3, t4
Antinuclear antibody
Vitamin D3
Calcium

Liver function test SGPT, SGOT, bilirubin

Kidney function test urea and creatinine

Assessment of abdominal pain was done by visual analogue scale of pain and all participants given a card numerated from 0 to 10 to score the pain

Tran-vaginal scan at first visit

Thorough pelvic organ evaluation

Assessment of the ovarian volume antral follicle count and ovarian stromal flow indices

Assessment of Douglas pouch and utero-sacral ligaments

Uterine evaluation: with trans-vaginal examination after emptying bladder using sonoscape p25 (china) mid-sagittal view to visualize the site of the scar and noticing hypo-echoic defects with measurement of the residual myometrial thickness to categorize the defect

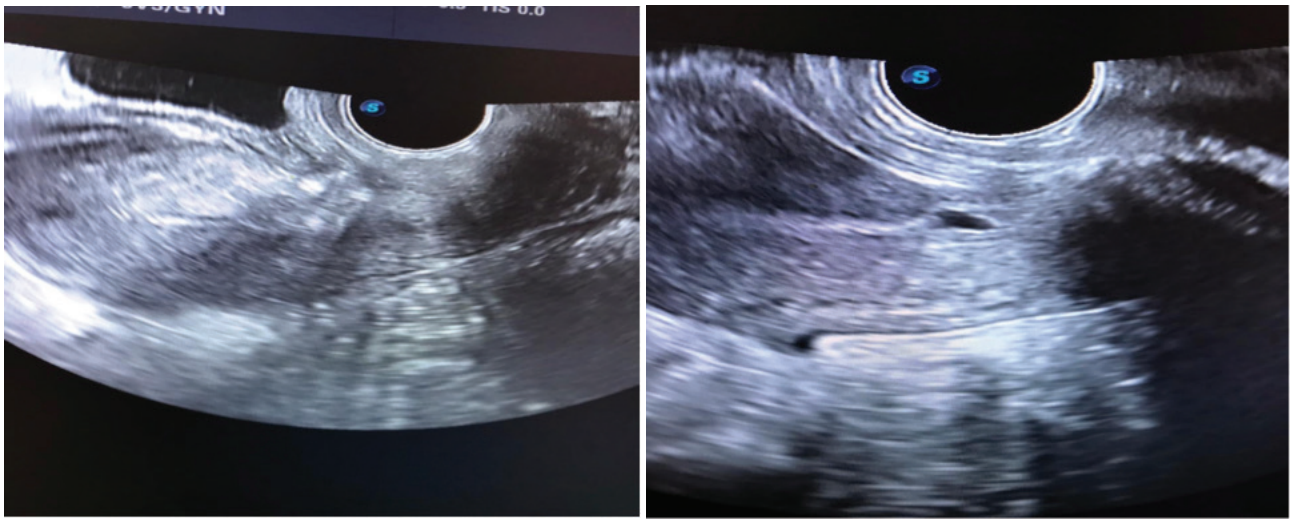


Figure 1 the ultrasound evaluation pf the scar defect before and after ithmoplasty

Standard semen analysis and it is my routine to do computer assisted semen analysis and hystero-salpingeogram done to assess tubal patency and exclude other causes

Reevaluation by ultrasound done after isthmoplasty to confirm anatomical restoration and closure of the defect

The repair

Cases with confirmed scar defect scheduled for laparoscopic isthmoplasty in Zinat al-Hayat hospital with complete preoperative assessment with examination and full laboratory investigations then after overnight fast all surgeries done in the early morning through laparoscopy combined with hysteroscopy

First hysteroscopic evaluation with telescopic sheath to visualize the tubal ostea, the endometrium, and confirming the site location and extent of the defect

Following hysteroscopic localization of the defect and evaluation of the whole uterine cavity done to ensure absence of the causes of infertility and bleeding

Laparoscopy then done and it was my routine to make the optical port two finger breadth above the umbilicus to avoid injuries of anticipated adhesions with intestine.

The two other ports inserted one for atraumatic grasper and the other for ligasure.

Thorough pelvic exploration done.

Exploration of the upper abdomen.

Most of the cases had adhesions between the scar and the anterior abdominal wall .

Adhesions cut

Uterovesical peritoneum is grasped with a-traumatic grasper and traction made to aid in easy cutting and coagulation with ligasure device

After cutting bladder reflection, dissection done with ligasure until complete exploration of the area of the scar, and this dissection of bladder flap protects bladder from accidental injuries.

The scar area perforated with a hook then debridement and excision of the entire old scar done with scissor and Maryland artery

The scar is closed carefully with Vicryl (poyglactin) absorbable sutures by needle holders with complete security of bleeding points

Final irrigation done

Complete exploration of the repaired site done to secure hemostasis.

Postoperative follow up and treatment

First month

Cases and controls left without induction but ovulation monitored by trans-vaginal ultrasound sonoscape p25

The cases monitored by ultrasound after repair to compare the picture before and after the repair

If there was a missed period pregnancy test done

Second and third month

Cases and controls induced for ovulation with Letrozole (Femara) 2.5 mg from the second day twice daily for 5 days then HMG Meriofert (IBSA) 75 unit given IM at the 3th ,5th ,and 7th day of menstrual cycle

Growing follicles monitored with vaginal ultrasound and when at least one follicle reached 18-20 mm ovulation was triggered.

Ovulation triggered with 250 μg recombinant human choriogonadotropin (Ovitrelle, Serono, Madrid, Spain)

Chemical pregnancy diagnosed afterc14 days with quantitative HCG and when pregnancy confirmed pregnancy followed by ultrasound until fetal viability of clinical pregnancy reached

Statistics

All tests were two tailed with a confidence level of 95% ($p < 0.05$).

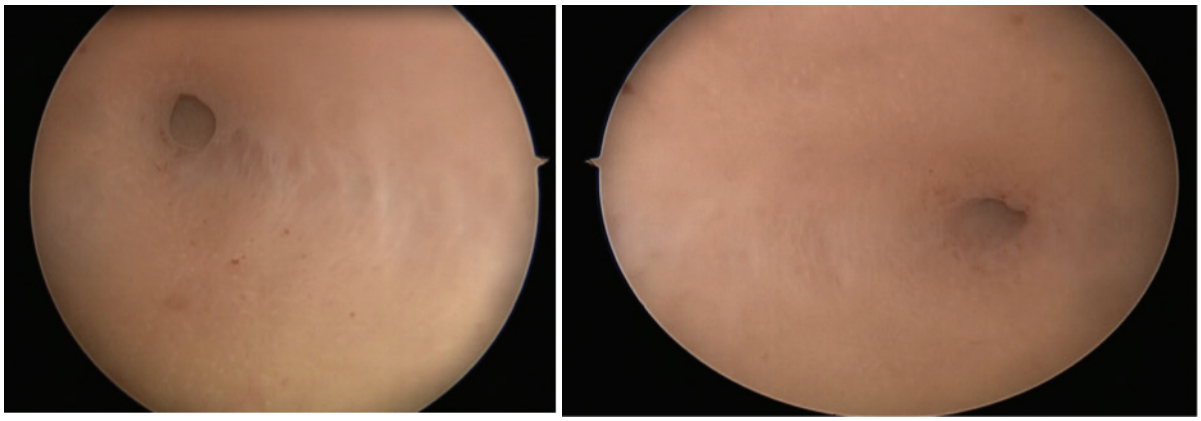
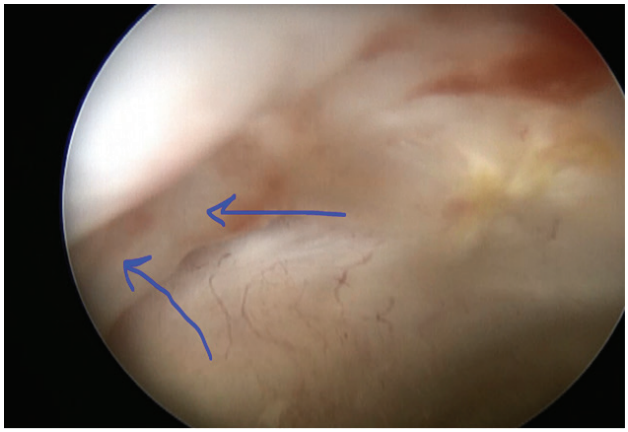
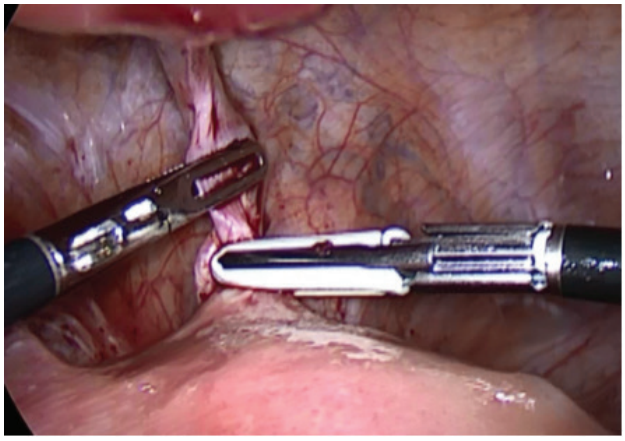


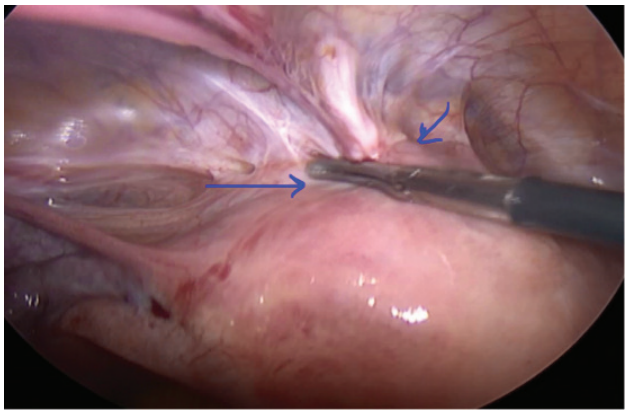
Figure2 two hysteroscopic views of both tubal Ostea sides before correction



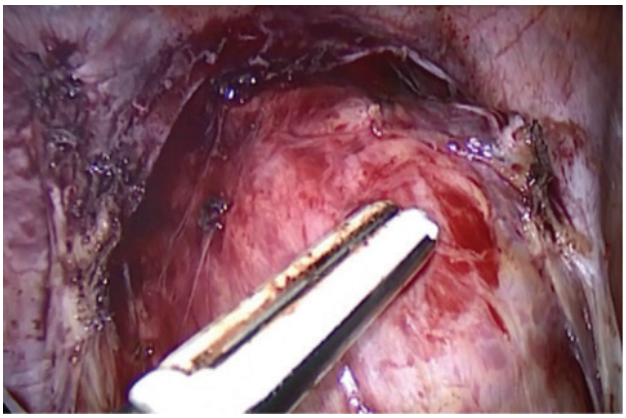
(Figure 3) Hysteroscopic localization of the scar defect arrows show the defect in muscle layer



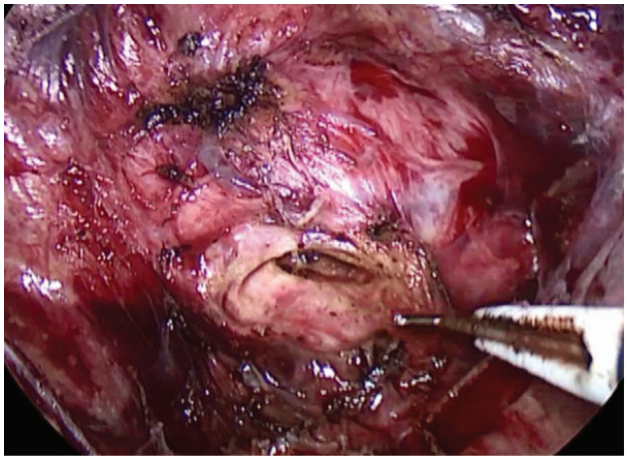
(Figure 5) Fixing peritoneal fold covering the adhesion with atraumatic grasper and cutting with ligasure



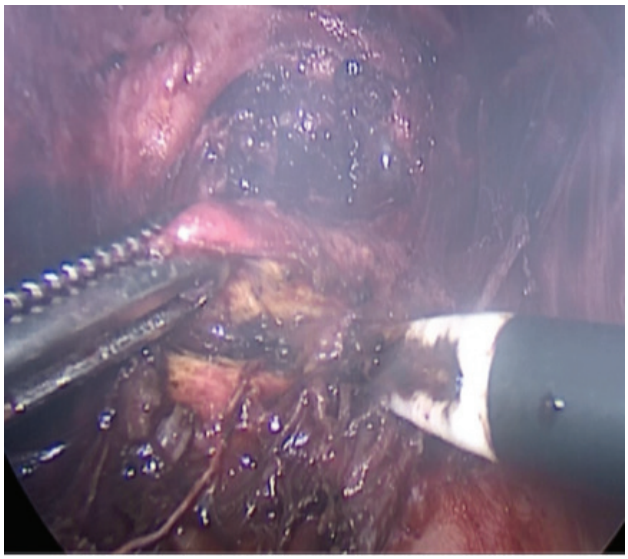
(Figure4) shows laparoscopic view of the scar site with dense adhesions between the scar and the anterior abdominal wall



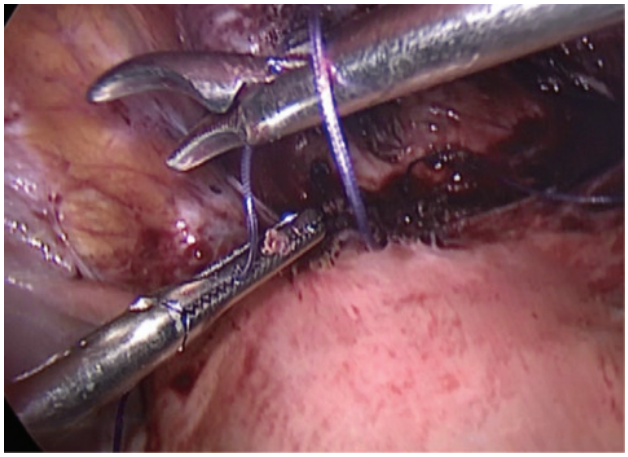
(Figure 6) Complete dissection of utero-vesical peritoneal reflection with exposure of the area of scar defect



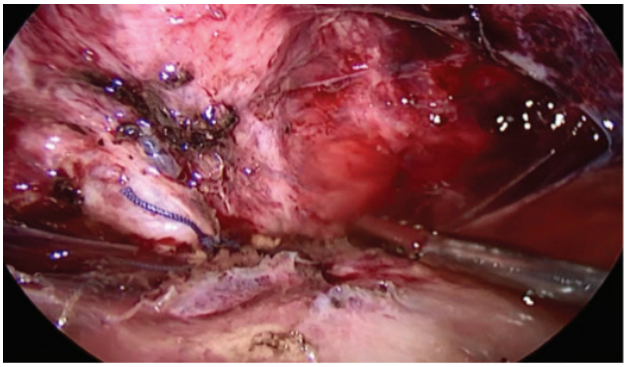
(Figure 7) The scar exposed and muscle of the scar was perforated using a hook



(Figure8) scar defect incised and cut



(figure9) The scar was sutured with absorbable sutures



Final wound irrigation

Results

First item evaluated with all participants was pain scores after doing the isthmoplasty ,regarding pain scores there were one case out of 25 compared to 10 cases out of 25 in the control that showed a high pain score above 6 with p value of 0.002 a high statistically significant difference

Regarding abnormal uterine bleeding after surgery there were only 2 cases out of 25 compared to 12 cases in the controls that showed abnormal bleeding with p value of 0.001

Regarding pregnancy in the first month of monitoring after surgery there were 5 out of 25 in the ithmoplasty group compared to 1 out of 25 in controls that showed pregnancy with p value of 0.08 a non-significant difference

Regarding pregnancy in the second and third months following isthmoplasty there were a pregnancy rate of 10 out of 25 compared to 2 out of 25 in controls with p value of 0.008 a high statistically significant difference that signified the success of scar surgery

The total pregnancy ratein cases was15 out of 25 compared to 3 in controls with P value of 0.0004 a high statistically significant difference. Table 1

Table 1 major and minor outcome measures after isthmoplasty

item	Group one laparoscopic isthmocele repair	Group two conservative management group	P value
Abdominal pain score more than 6	1 out of 25	10 out of 25	0.002
Abnormal uterine bleeding post menstrual	2	12 out of 25	0.001
Pregnancy in the first month	5 out of 25	1out of 25	0.08
Pregnancy in the second and third month	10	2	0.008
Total pregnancy rate	15	3	0.0004

Discussion

Cesarean section is a daily practice for every obstetrician, there is a rising level of non-indicated cesarean section worldwide.

High rate of cesarean sections have its own complications including placenta previa and accrete spectrum, also the new era of scar defect known by the name of uterine niche.

uterine niche or the cesarean scar defect can lead to abnormal uterine bleeding due to the accumulation of menstrual blood in the defect leading to postmenstrual spotting ,also the raw area of the scar subjected every month to the effect of menstrual blood that erodes the defect more and this ulceration add a negative impact and increase the inter-menstrual spotting.

Uterine niche can also cause infertility through impairment of implantation by continuous dripping of stagnated blood at the endometrial implantation site, uterine niche also has a negative hostile effect on sperms and sperm transport. (8)

Regional inflammatory effect around the scar defect can hinder implantation and lead to chronic endometritis with chronic pelvic pain. (9)

Scar defect us diagnosed efficiently with trans-vaginal ultrasound and diagnosis confirmed through hysteroscopy.

The presented work studied the repair effect of isthmocele on the pregnancy rate in infertile patients

Cases with diagnosed scar defect and secondary infertility scheduled for laparoscopic repair called laparoscopic isthmoplasty.

In the presented work total pregnancy rate was 15 out of 25 in cases done with laparoscopy compared to 3 out of 25 in controls with p value of 0.0004 which signified the high positive impact .

Regarding abnormal uterine bleeding there were 2 out of 25 in cases compared to 12 out of 25 in controls complained of postmenstrual spotting with p value ofv0.001 and a high statistically significant difference.

The presented work studied the surgical repair of scar defect aka (ithmoplasty) impact on pregnancy rate.

Hysteroscopic repair of cesarean scar defect may have certain complications like uterine perforation and bladder injuries.

Cesarean scar defect can be categorized by ultrasound into three classes according to the residual muscle wall thickness, when the residual myometrial thickness below 2.5 mm the risk of bladder injury during hysteroscopic repair is high.

Donney et al performed laparoscopic repair when residual myometrial thickness below 3 mm. (10)

Gubbini performed hysteroscopic ithmoplasty for 41 patients all of them achieved spontaneous pregnancy but his results need further evaluation because nothing in the universe is absolute. (11)

Conflict of interest

No conflicts of interest to declare.

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Impact of maternal weight gain during pregnancy on expected fetal weight and neonatal birth weight:A prospective cohort study

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Abstract

Objective: To determine the impact of maternal weight gain during pregnancy on expected fetal weight and neonatal birth weight.

Subjects and methods: This prospective cohort study was conducted on 159 pregnant women; 53 women with normal weight as Group (A), along with 53 overweight pregnant women as a Group (B) and 53 obese pregnant women as a Group (C) according to BMI. The maternal weight gain was calculated and correlated to expected fetal weight and fetal birth weight. The study was approved by the Ethics Committee, and all patients gave their informed consent before inclusion in the study.

Results: We found that there was a statistically positive correlation between maternal weight gain, expected fetal weight and fetal birth weight in 3 study groups. maternal weight gain was significant independent predictor of fetal weight ($p \leq 0.001$), as maternal weight gain can predictor fetal weight in group (A) 38.4% , group (B) 46.2% and group (C) 42.6% .

Conclusion: The current study has demonstrated that pregnancy weight gain was associated with a significant effect on birth weight regardless of BMI. Additionally, maternal weight gain could be considered as a significant predictor of fetal weight.

Key words: Maternal weight gain, expected fetal weight, neonatal birth weight, pregnant women, cohort study.

Introduction

Maternal weight gain shows a wide variation, even in a low-riskpregnancy. Despite this, the importance of adequate gestational weight gain (GWG) is well documented.Maternal weight gain during pregnancy has a well-established influence on birth weight and infant health outcomes. For that, prenatal care guidelines emphasize the importance of overall maternal weight gain during pregnancy and its role in perinatal health [(1)].

Maternal weight gain is affected by many factors, including

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family, physiological, psychological, behavioral, cultural, social and environmental factors.The rate of maternal weight gain per trimester also depends on a number of maternal factors and can show wide variation throughout pregnancy[2].

Birth weight is cosidered a key predictor of survival and health of infants. Infants with low birth weights (less than 2,500 g) have increased risk of hypertension, type 2 diabetes and coronary artery disease in adult life, and those with birth weights more than 4000 g have an increased risk of intrauterine death (IUFD),hypoglycemia, hypertrophic cardiomyopathy, shoulder dystocia, meconium aspiration, and neonatal hyperbilirubinemia[3].

Maternal weight gain during pregnancy is associated with high birth weight and measures of adiposity early in life. Because high birth weight predicts body mass index later in life, these findings suggest that excessive weight gain during pregnancy could increase the long-term risk of obesity-related disorders in offspring. High birth weight might also rise the risk of other diseases later in life, includingatopy, asthma, and cancer [4].

Maternal nutritional status is believed to be a reliable predictor of adverse perinatal and long-term outcomes for both mother and infant. Being overweight or obese before becoming pregnant may represent high risk factor forfetal growth disorders [5].

Therefore, it is of particular relevance to study the effects of pre-pregnancy BMI and GWG on pregnancy and the newborn, and to develop a reasonable pregnancy weight control plan. In this study, we aimed to evaluate the impact of maternal weight gainduring pregnancy on expected fetal weight and neonatal birth weight.

Patients and methods

This prospective cohort study was conducted on 159 pregnant womenduring the period from July 2020 to November 2021 at outpatient clinic of our hospital; the institutional ethical review board approved the study.

Inclusion and exclusion criteria

Women who had singleton pregnancies aged 18–35years attended for antenatal care services in outpatient clinic of our hospital were included in this study. Whereas, women with pre-existing or current medical conditions, women with history of intrauterine growth restriction (IUGR), underweight women and women with multiple pregnancy were excluded from the study

Sample size:

Sample size of 53 women one group (at least) achieve 80% power with margin of equivalence range from (-5% to 5%) with significance level 0.05%.

After enrolment, the total sample size became 159 pregnant women divided into 3 groups as seen in figure (1):

- **Group (A):** pregnant women **(n=53)** who have normal weight.
- **Group (B):** pregnant women **(n=53)** who are overweight.
- **Group (C):** pregnant women **(n=53)** who have obesity.

Ethical consideration

Written informed consent was taken from the participants after they were informed about the purposes andobjectives of the study. Confidentiality and privacy were maintained throughout the study.

Maternal data:

- Measurement of maternal pre-pregnancy weight, at 32 weeks and at full term (>36wks). Then calculation of maternal weight gain during pregnancy.
- Age, height, BMI, parity were recorded.
- The BMI is classified according to the values determined by the World Health Organization (underweight <18.5 kg/m2; normal weight, 18.5–24.9 kg/m^2;

overweight, 25–29.9 kg/m^2; and obese >30 kg/m^2).

Neonatal data:

- Measurement of expected fetal weight by ultrasound (by femur length and bi parietal diameter and abdominal circumference) at full term

Hadlock2:Log10 (weight) = 1.335 – (0.0034 X AC X FL) + (0.0316 X BPD) + (0.0457 X AC) + (0.1623 X FL).

- Measurement of actual neonatal birth weight.

Statistical analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 21). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data .The three groups were compared with ANOVA test.Pearson correlation was used to correlate continuous variables. Significant variables entered into linear regression model to predict significant determinants and to control for possible interactions and confounding effects.The results were considered significant when p value $\leq$ 0.05.

Results

The demographic characteristics showed no statistically significant difference ($P \geq 0.05$) among three groupsas regard age, parity, pre-pregnancy body BMIof the 3 study groups are shown in table (1).

However, there was a statistically significant positive difference of the mean BMI ($P \leq$ 0.01), the maternal group (A) mean BMI was (22.21±2.01)as compare to maternal group (B) mean BMI of (27.22±1.52) and group (C) mean BMI of (33.75±2.57), as we compared between three groups according to pre pregnancy BMI.The three groups according to their BMI are (normal weight, overweight, and obese).

Our analysis revealed that there was a statistically significant difference in maternal weight between the three groups in different trimester. The mean of maternal pre-pregnancy weight (C) was 86.28±9.84, group (B) was 69.73±6.34, and group (A) was 57.83±6.96. The mean of maternal weight in 32 weeks, in-group (C) was 94.07±9.73, group (B) was 77.91±7.03, and group (A) was 66.11±7.41. The mean of maternal weight at full term in-group (C) was 99.24±10.43, group (B) was 83.06±7.18and group (A) was 70.55±7.67,as seen in table(2).

The maternal weight of group (C) pre-pregnancy, 32 weeks and at full term was higher compared to the other two groups ($p \leq 0.001$).

There was no statistically significant difference between the three groups at delivery ($P \geq 0.05$)as regard maternal weight gain. The mean of maternal weight gain in-group (A) was 12.72±2.57, in group (B) was 13.32±3.18 and in group (C) was 12.96±2.68

There was no statistically significant difference in Expected fetal weight ($P \geq 0.05$), and Fetal birth weight ($P \geq 0.05$) among three group (table). However, we found that the number of LGA was more in both overweight group (17%) and obese group (13.2%) compared to normal weight group (3.8%), as seen in table (3).

The number of normal birth weight was 46 (86.8%)in group (A), 40 (75.5%) in group (B), 43 (81.1%) in group (C) , and number of large for gestational age was 2 (3.8%) in group (A), 9 (17.0%) in group (B), 7 (13.2%) in group (C), however number of small for gestational age was 5 (9.4%) in group (A), 4 (7.5%) in group (B), 3 (5.7%) in group (C).

There was a statistically positive correlation between maternal weight gain, expected fetal weight and fetal weight at birth which means

the higher the maternal weight gain, the greater fetal birth weight, as seen in table(4), figure 2,3,4.

After linear regression analysis adjusting the confounding factors, maternal weight gain was significant independent predictor of fetal weight (p≤ 0.001), as maternal weight gain can predict fetal weight in group (A) 38.4%, group (B) 46.2% and group (C) 42.6%, as seen in table (5).

Table (1): Demographic data among studied groups.

Demographic data	Group (A) (n=53)	Group (B) (n=53)	Group (C) (n=53)	Test of significance	p value
Age (years) **Mean ± SD** **Min-Max**	24.34±4.77 17-36	25.51±5.52 18-42	26.60±4.46 18-40	F=2.78	0.065
Age class **≤25 y** **>25 y**	32 (60.4%) 21 (39.6%)	31 (58.5%) 22 (41.5%)	24 (45.3%) 29 (54.7%)	$\chi 2$=2.89	0.235
Parity **Nullpara** **P1** **P2** **P≥3**	19 (35.8%) 20 (37.7%) 10 (18.9%) 4 (7.5%)	17 (32.1%) 12 (22.6%) 14 (26.4%) 10 (18.9%)	15 (28.3%) 11 (20.8%) 13 (24.5%) 14 (26.4%)	$\chi 2$=9.99	0.127
Height **Mean ± SD**	161.13±6.12	160.89±5.56	159.79±6.11	F=0.766	0.467
BMI **Mean ± SD**	22.21±2.01	27.22±1.52	33.75±2.57	F=404	≤0.001*

F: ANOVA test, χ^2 : Chi square test.

Table (2): Maternal weight and maternal weight gain of studied groups.

Maternal weight	Group (A) (n=53)	Group (B) (n=53)	Group (C) (n=53)	Test of significance	p value
Maternal pre pregnancy weight	57.83±6.96	69.73±6.34	86.28±9.84	F=174.8	≤0.001*
Maternal weight in 32 weeks	66.11±7.41	77.91±7.03	94.07±9.73	F=157.3	≤0.001*
Maternal weight at full term (>36wks)	70.55±7.67	83.06±7.18	99.24±10.43	F=149.9	≤0.001*
Maternal weight gain	12.72±2.57	13.32±3.18	12.96±2.68	F=0.611	0.544

Table (3): Fetal weight among studied groups.

Fetal weight	Group (A) (n=53)	Group (B) (n=53)	Group (C) (n=53)	Test of significance	p value
Expected fetal weight	3095.37±479.48	3180.47±432.64	3190.3±482.52	F=0.667	0.515
Fetal birth weight	3167.54±452.52	3300.26±393.18	3322.45±456.64	F=1.965	0.144

NGA (N,%) **LGA >4000 N,%)** **SGA ≤2500 (N,%)**	46 (86.8%) 2 (3.8%) 5 (9.4%)	40 (75.5%) 9 (17.0%) 4 (7.5%)	43 (81.1%) 7 (13.2%) 3 (5.7%)	$\chi 2$=5.25	0.262

Table (4): Correlation between maternal weight gain and fetal weight.

Fetal weight	Maternal weight gain					
	Group (A)		Group (B)		Group (C)	
	r	p	r	p	r	p
Expected fetal weight	0.668	≤0.001*	0.655	≤0.001*	0.628	≤0.001*
Fetal birth weight	0.620	≤0.001*	0.680	≤0.001*	0.653	≤0.001*

r: Pearson correlation

Table (5): Linear regression analysis for maternal weight gain as a predictor of fetal weight.

	Constant	Unstandardized Coefficients		P value	95% confidence interval of B		R Square
		B	Std. Error		Lower ound	Upper bound	
Group (A)	1782.6	108.8	19.3	≤0.001	70.120	147.677	38.4%
Group (B)	2182.7	83.9	12.6	≤0.001	58.437	109.349	46.2%
Group (C)	1885.4	110.8	18.0	≤0.001	74.690	147.030	42.6%

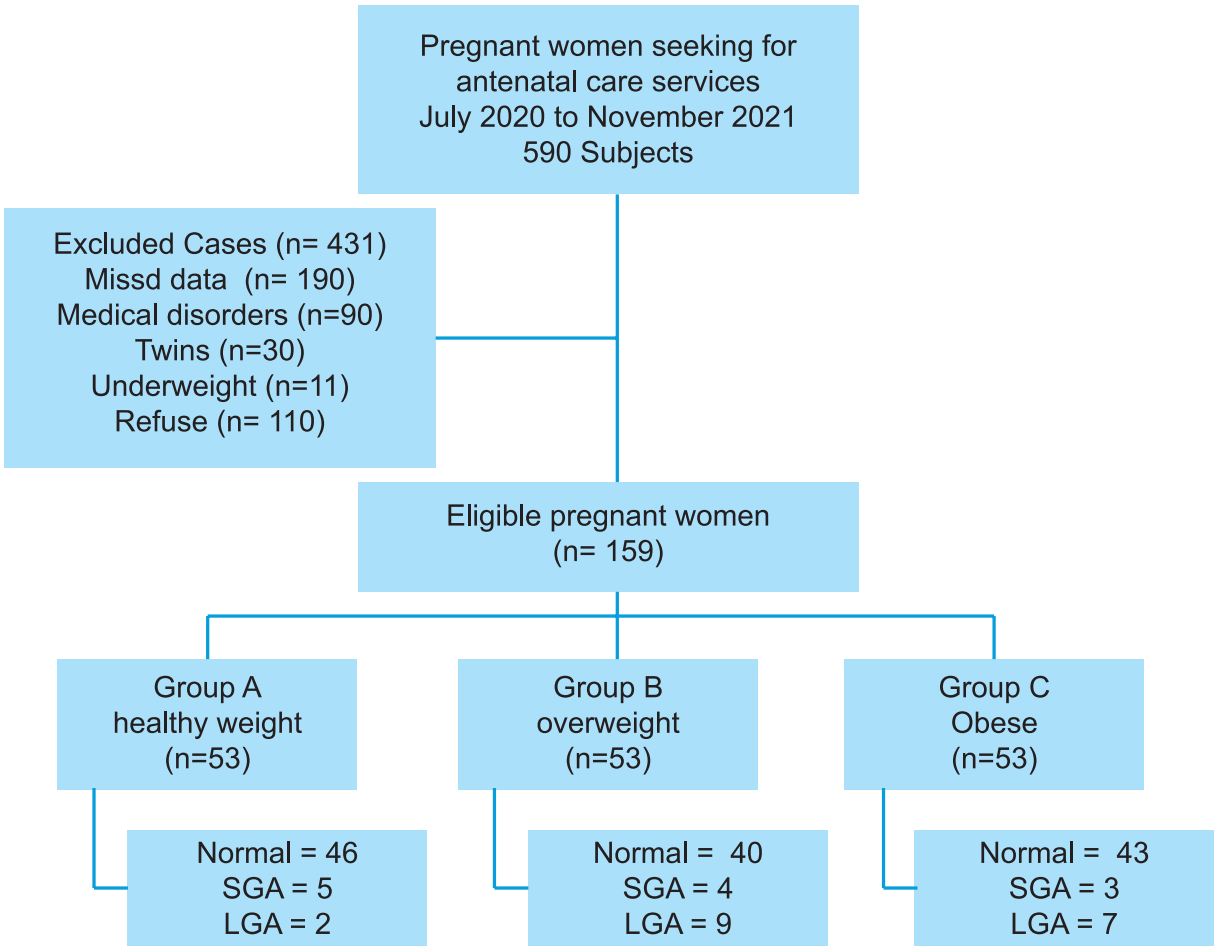

Figure (1): Flow chart of this study.

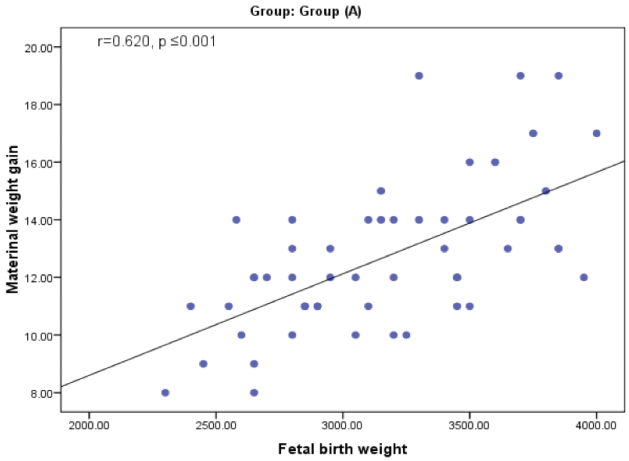

Figure (2): Scatter diagram for positive correlation between maternal weight gain and fetal birth weight in group (A).

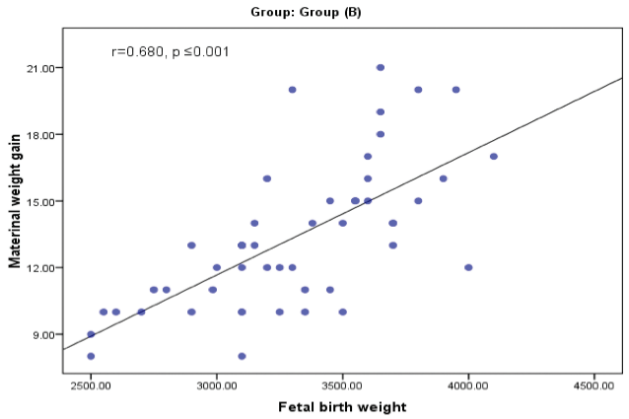

Figure (3): Scatter diagram for positive correlation between maternal weight gain and fetal birth weight in-group (B)

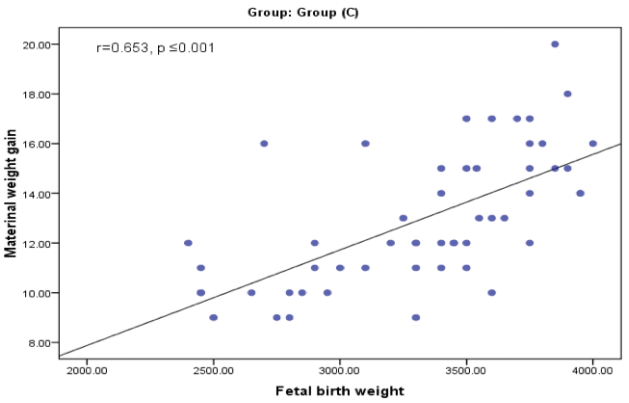

Figure (4): Scatter diagram for positive correlation between maternal weight gain and fetal birth weight in group (C)

Discussion

Maternal weight gain in pregnancy carries implications on both mother and child. Insufficient gestational weight gain has been linked to low birth weight and preterm birth, while excessive weight gain has been linked to infant macrosomia and maternal postpartum weight retention [6, 7].

This prospective cohort study was carried out on a total of 159 pregnant women aged 18–40 years to determine the impact of maternal weight gain during pregnancy on expected fetal weight and neonatal birth weight. Entire cases were further divided into three equal groups; group A which included pregnant women with normal weight, group B which included overweight pregnant women and group C which included obese pregnant women. There were no significant differences among the three studied groups regarding demographic features.

We found that there was a clear association between maternal obesity and infant size at birth. The findings were consistent with other research results [8,9,10,11].

We found that the number of LGA was more in both overweight group (17%) and obese group (13.2%) compared to normal weight group (3.8%). Similar to our results, Sun et al study strongly detected that being overweight and obese, and more gestational weight gain were important risk factors for LGA compared to pregnant women with normal BMI (5). Obesity and unacceptable weight gain during pregnancy may lead to increased concentrations of glucose, amino acids and free fatty acids in pregnant women, thereby increasing the risk of abnormal infant weight at birth [12].

This study revealed that there was a statistically positive correlation between maternal weight gain, expected fetal weight and fetal weight at birth which means the higher the maternal weight gain, the greater fetal birth weight in the context of the three studied groups separately.

In the study of Mamun et al, dedicated that excessive weight gain during pregnancy is associated with greater birth weight in the babies [13]. On the other hand, Tsai et al, found that a low birth weight was greatly associated with low weight gain (<10 kg) [14]. Tela et al, also declared that the pregnancy weight gain has a significant effect on birth weight [1].

Likewise, several studies declared that the mean BW in pregnant mothers with higher gestational weight gain was significantly greater than the mean BW in those with a lower weight gain [15, 16, 17].

These findings suggested that women can minimize their risk of neonatal morbidity and mortality by adjusting their weight prior to conception and gaining the recommended weight amount throughout the pregnancy [15].

Finally, after linear regression analysis adjusting the confounding factors, we found that the maternal weight gain was a significant independent predictor of fetal weight ($p \leq 0.001$), as maternal weight gain can predict fetal weight in group (A) 38.4%, group (B) 46.2% and group (C) 42.6%. Our results were similar to those reported by Sommer et al, who had detected that gestational weight gain is the strongest independent predictor of BW [17]. In harmony with the current study, Tela et al have reported that the pre-pregnancy BMI and GWG were statistically significant independent predictors of BW [1].

In the same line, Meinich and Trovik had displayed that; not regaining pre-pregnancy weight by week 13–18 was an independent predictor of inadequate total gestational weight gain and an independent predictor for SGA outcome, even when total pregnancy weight gain , pre-pregnancy BMI, parity, age and smoking status were adjusted [18]).

Several limitations in this study should be taken into consideration. First, the sample size may still not be large enough for stratification. Second, the pre-pregnancy weight and height were actually the weight and height may be measured during the initial prenatal examination and may therefore be biased. Third, the enrolled subjects reflect only a single Governorate, not reflect a lot of geographical regions. Moreover, there could be possible association between birth weight and other factors such as physiological, psychological, socio-cultural, and environmental factors

It is of great importance to pay attention to pre-pregnancy BMIs and GWGs to ensure adequate birth weights of newborns. Further studies have to be conducted on larger number of populations. Pregnancy weight management should be actively promoted through intensive counseling during the routine ANC contacts.

Conclusion

The current study has demonstrated that pregnancy weight gain was associated with a significant effect on birth weight regardless of BMI. Additionally, maternal weight gain could be considered as a significant predictor of fetal weight.

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Legends to tables:
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Table (3): Fetal weight among studied groups.
Table (4): Correlation between maternal weight gain and fetal weight.
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Figure (3): Scatter diagram for positive correlation between maternal weight gain and fetal birth weight in-group (B).
Figure (4): Scatter diagram for positive correlation between maternal weight gain and fetal birth weight in group (C).

List of abbreviation:
AC: Abdominal circumference
BMI: Body mass index.
BPD: Bi parietal diameter
FL: Femur length
GWG: Gestational weight gain.
IUFD: Intrauterine death.
IUGR: Intrauterine growth restriction.
LGA: Large gestational age.
NGA: Normal gestational age.
SD: Standard deviation.
SGA: Small gestational age.
SPSS: Statistical Package of Social Science.

Effect Of Hysteroscopic Correction of Symptomatic Caesarian Scar Defect in Women with An Explained Secondary Infertility: Randomized Controlled Trial

Running title:
Caesarian Scar Defect in Women with Secondary Infertility.

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Abstract

Background: One of the complications of Cesarean section, cesarean scar defect, has been shown to be associated with various gynecological and obstetric problems. Additionally, cesarean scar defect may increase the risk for complications in gynecological procedures such as intrauterine device placement, evacuation, and embryo transfer.

Objective: to investigate the effect of hysteroscopic correction of symptomatic caesarian scar defect in women with an explained secondary infertility.

Patients and methods: A prospective, randomized study was conducted on women suffered from secondary delayed pregnancy after caesarean section with a scar at the site of the caesarean wound, who attended at the Obstetrics and Gynecology department, Menoufia University Hospitals, during the period between January 2021 and April 2022.

Results: most patients in group A had positive pregnancy rate (53.33%) than patients in group B (23.33%) with a significant difference (P=0.017).

Conclusion: In women with secondary infertility and a residual myometrial thickness of less than 3 mm, hysteroscopic correction of a caesarean scar defect offers a minimally invasive method with a high success rate and no risks.

Key words: Hysteroscopic correction, cesarean scar defect, Secondary Infertility, clinical pregnancy.

INTRODUCTION

A caesarean scar defect (CSD) is a triangular, anechoic region at the caesarean scar's location. **[1]** Transvaginal sonography (TVS) can be used to identify it, although saline infusion sonohysterography (SIS) may provide a sharper picture **[2]**. Niche, isthmocele, caesarean scar defect, or pouch are all terms used to characterise uterine scarring after a caesarean operation. **[3]**

It is a reality that 20% of pregnant women have CS, and that CS rates are rising in most parts of the world. **[4]** Between 1990 and 2014, CS rates in Latin America and the Caribbean rose from 22.8 percent to 42.2 percent, in Oceania from 18.5 percent to 32.6 percent, in North America from 22.3 percent to 32.3 percent, in Europe from 11.2 percent to 25 percent, in Asia from 4.4 percent to 19.5 percent, and in Africa from 2.9 percent to 7.4 percent. **[5]** But why are the rates of CS skyrocketing? China has experienced the most rapid growth in recent decades, rising from 3% in 1988 to 39% in 2008, with an average of 34.9 percent in 2014. Egypt came in third place among international countries, with a CS rate of 51.8 percent. **[4]** The 2015 World Health Organization guidelines that CS rates > 10% are not connected with reduced maternal or newborn mortality appear to have had little effect on these high rates. **[6]** Laparoscopy, vaginal surgery, or operational hysteroscopy can all be used to resect inflammatory tissues at the location of a caesarean scar defect. **[7]** Despite the fact that caesarean scar defects are widespread, no research has looked at which cases should be considered for infertility therapy. Cesarean scar syndrome is being treated using two different surgical approaches: hysteroscopic and laparoscopic. There is, however, no evidence-based guidance for selecting the most appropriate approach. **[8]** The later in labour CS is performed, the greater the risk of developing larger CSDs, with the risks increasing considerably if labour lasts R5 hours or cervical dilation is R5 cm. The presence of intrauterine fluid at the time of ovulation may theoretically impact subsequent fertility. In addition, mucus and blood collection in the cervix, as well as a caesarean scar deformity, can impede sperm penetration and embryo implantation **[9]**.

Hysterosalpingography transvaginal sonography (TVS), saline infusion sonohysterography (SIS), hysteroscopy, and magnetic resonance imaging can all be used to detect abnormalities in the anterior uterine isthmus after CS (MRI). Hysterosalpingography, which is used to evaluate tubal factor, is sometimes used by gynecologists to detect CSDs. **[4]** The thickness of the surviving myometrium is the most useful distinguishing feature, and it can only be determined by TVS or pelvic MRI. **Junaid et al. [11]** employed hysteroscopic removal of scar tissue from the area of the caesarean scar defect and coagulation of any hypovascularized tissues in 22 patients with postmenstrual bleeding; 14 of the patients' symptoms vanished, and the other patients' symptoms significantly improved. **Vitale et al. [13]** looked explored the use of hysteroscopic roller-ball coagulation of scar tissue in 26 women who had abnormal uterine bleeding. Nine of the women suffered secondary infertility. All of their abnormal uterine bleeding stopped, and seven of the infertile ladies became pregnant. **[14]** So, the aim of the work is to investigate the effect of hysteroscopic correction of symptomatic caesarian scar defect in women with an explained secondary infertility.

PATIENTS AND METHODS

A prospective, randomized study was conducted on women suffered from secondary delayed pregnancy after caesarean section with a scar at the site of the caesarean wound, who attended at the Obstetrics and Gynecology department, Menoufia University Hospitals, during the period between January 2021 and April 2022.

Ethical consideration

Following permission from the local ethics committee, all patients who decided to participate signed an informed consent form after being told of the trial's advantages and risks. The study was approved by the Menoufia University faculty of Medicine's ethical committee.

Inclusion criteria: women ages before 35 years, who suffered from secondary delayed pregnancy after caesarean section with a scar at the site of the caesarean wound.

Exclusion criteria: women ages above 35 years, residual myometrium less than 3 mm at sonohysterography, any factor impairing fertility other than cesarean scar defect.

Patients included in this study were subjected to:

Full history taking included Personal history: Name, age, occupation and address. **Present history:** Duration of infertility, possible etiology, previous investigations and treatment if any. **Past history** of diseases or operations, blood transfusion and **family history** of a general disease. Also, **detailed obstetric history** as number of previous pregnancies and the outcome of each, and mode of delivery.

Through full examination included vital signs, weight, body mass index (BMI), pallor, cardiac examination, and presence of scars of previous operations, inspection of external genitalia, and speculum examination.

Routine infertility work up for detection of any factor of infertility if present, Saline infusion sonography was used to assess the caesarean scar defect in the sagittal plane, which revealed the widest niche and the thinnest remaining myometrium. The niche depth and residual myometrial thickness were measured.

Women included in this study were divided into two groups:

Group A (n=30): included 30 women whose scar is corrected using hysteroscopy.

Group B (n=30): included 30 women whose scars are not corrected but were given conservative treatment only.

Clinical pregnancy rates are monitored one year after hysteroscopy or not.

Surgery was planned for participants in group A during the early proliferative phase. The same operator conducted hysteroscopic niche resection on all patients under general anaesthesia. After placing the patient in a modified lithotomy position, a bladder catheter was inserted and the bladder was filled with 200 mL of normal saline, all while under the supervision of abdominal ultrasonography.

In the uterine cavity, a 24F working element with its sheath and a 4 mm 30 telescope with a hysteroscopic monopolar loop were placed.

WIEST HYSTEROMAT 3700 used glycine (1.5%) as the distending medium at an inflow pressure of 70–100 mmHg.

The distal margin of the scar defect was removed until the muscle tissue beneath was visualised, as described by **Gubbini et al.**, **[15]**, utilising a cutting monopolar loop and a pure cutting current (40 W). To promote the pouch's retraction, the bottom of the pouch was cauterised using a 3-mm rollerball and a current of 30 W. The patients were followed for a total of 12 months. Patients were contacted on a regular basis and followed up with every month.

Outcomes of the study

The primary outcome included the clinical pregnancy rate.

Secondary outcomes included duration of the procedure, amount of fluid deficit, and occurrence of any complications in group A.

Sample size calculation: Taking into account the number of pregnancies the sample size was calculated based on the previous study by **Gubbini et al. [15]** who reported pregnancy rate was 77.7%, with confidence level 95%.

The Sample plus 10% (for refusal rate and drop out) was calculated and 30 patients' women in each group needed to give 80% power of the study.

Statistical Analysis: MICROSOFT EXCEL 2019 and SPSS v. 25 (SPSS Inc., Chicago, IL, USA) were used to tabulate and statistically analyse the data on a personal computer. The following software was used for statistical analysis: Descriptive terms include percentages (%), mean, and standard deviation. Chi-Squared (X^2), and student t tests were used to compared the studied groups. $P \leq 0.05$ considered a significant level.

RESULTS

A CONSORT flow chart of the study population is shown in Figure 1. Of the 83 women admitted at the Obstetrics and Gynecology department, Menoufia University Hospitals, 6 declined consent and 9 did not meet the inclusion criteria, 68 patients were willing to participate in the study and consented for participation. But, eight patients were dropped from follow up (4 from each group). Thus, 60 women patients were analyzed, 30 in each group.

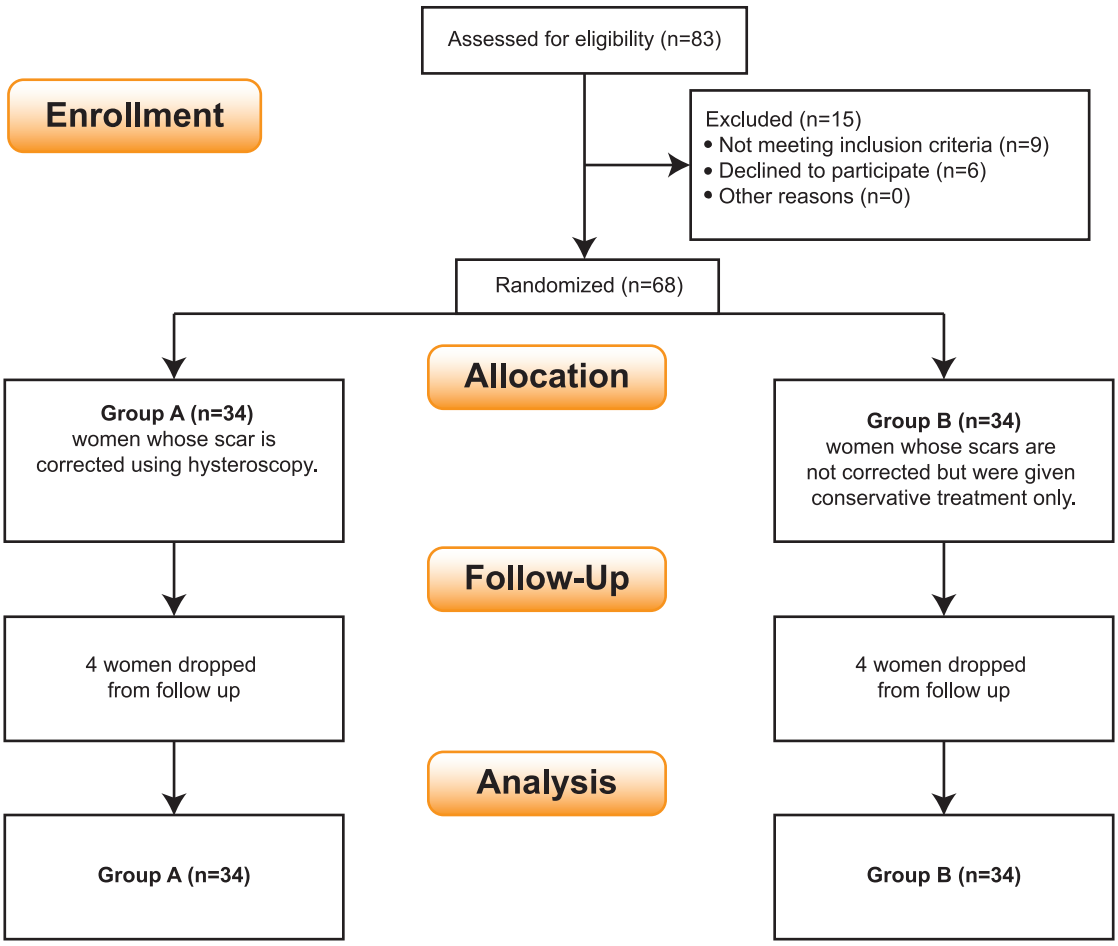

Figure 1. Flowchart of the studied participants.

Results indicated that, there were no significant differences among the studied groups regarding age, BMI, and duration of infertility ($P>0.05$). While, parity was significantly increased among group B than group A ($P=0.031$), (Table 1).

Table 1. Demographic data of the studied groups.

Variable	Group A N=30	Group B N=30	t	P-value
Age/years Mean ±SD	30.57±3.05	30.33±3.30	0.284	0.777
BMI (kg/m2) Mean ±SD	30.77±3.67	30.13±2.13	0.817	0.417
Duration of infertility/year Mean ±SD	3.10±0.995	2.80±0.76	1.312	0.195
Parity Mean ±SD	2.13±0.82	2.63±0.93	2.212	**0.031***

Group A: women whose scar is corrected using hysteroscopy.

Group B: women whose scars are not corrected but were given conservative treatment only.

In the present study, there were no significant differences among the studied groups regarding cesarean section, vaginal delivery, previous miscarriage, and branching (P>0.05). Regarding the previous obstetric history, most patients had one or two previous cesarean sections, (Table 2).

Table 2. Previous obstetric history among the studied groups.

Variable	Group A N=30		Group B N=30		Total N=60		x^2	p-value
Cesarean section:								
Once	17	56.67	11	36.67	23	46.67	4.100	0.128
Twice	11	36.67	12	40.00	23	38.33		
Thrice	2	6.67	7	23.33	9	15.00		
Vaginal Delivery:								
No	14	46.67	14	46.67	28	46.67		
Once	13	43.33	12	40.00	25	41.67	2.24	0.52
Twice	3	10.00	2	6.67	5	8.33		
Thrice	0	0.00	2	6.67	2	3.33		
Previous miscarriage:								
No	15	50.00	11	36.67	26	43.33		
Once	11	36.67	12	40.00	23	38.33	2.05	0.56
Twice	4	13.33	6	20.00	10	16.67		
Thrice	0	0.00	1	3.33	1	1.67		
Branching:								
Once	14	46.67	14	46.67	28	46.67		
Twice	11	36.67	11	36.67	22	36.67	1.11	0.774
Thrice	5	16.67	4	13.33	9	15.00		
Four times	0	0.00	1	3.33	1	1.67		

Group A: women whose scar is corrected using hysteroscopy.

Group B: women whose scars are not corrected but were given conservative treatment only.

Additionally, width and residual myometrial thickness were significantly decreased among group B than group A (P<0.05). While, depth was significantly increased among group B than group A (P<0.05), (Table 3).

Table 3. Saline infusion sonography criteria of cesarean scar defect.

Variable	Group A N=30	Group B N=30	t	P-value
Width/mm Mean ±SD	5.80±0.895	5.14±0.95	2.775	**0.007***
Depth/mm Mean ±SD	5.02±1.11	5.88±0.65	3.63	**0.001***
Residual Myometrial thickness Mean ±SD	5.83±0.77	4.82±0.78	5.051	**0.000***

Group A: women whose scar is corrected using hysteroscopy.

Group B: women whose scars are not corrected but were given conservative treatment only.

Regarding clinical pregnancy, most patients in group A had positive pregnancy rate (53.33%) than patients in group B (23.33%) with a significant difference (P=0.017).

Table 4. Clinical pregnancy between the studied groups:

Variable	Group A N=30		Group B N=30		Total N=60		x^2	p-value
Pregnancy rate								
Positive	16	53.33	7	23.33	23	38.33	5.71	0.017*
Negative	14	46.67	23	76.67	37	61.67		

Group A: women whose scar is corrected using hysteroscopy.

Group B: women whose scars are not corrected but were given conservative treatment only.

DISCUSSION

The most common obstetric surgery is a caesarean section. In developing countries, it has increased in prevalence over the last few decades, reaching 25.7%. In wealthy countries, it ranges from 16.3% to 38.2%. **[16]** Cesarean scar defect, one of the consequences of caesarean section, has been linked to a variety of gynecological and obstetric issues. Uterine rupture and ectopic caesarean scar pregnancy are relatively uncommon complications of surgical scar defects, although they can be fatal. **[17]** Postmenstrual spotting, dysmenorrhea, dyspareunia, and chronic pelvic pain are all common symptoms associated with a caesarean scar defect. **[18]** Furthermore, a caesarean scar defect can raise the risk of difficulties after gynecological treatments like IUD placement, evacuation, and embryo transfer. **[19]** So, the aim of the work is to study the effect of hysteroscopic correction of symptomatic caesarian scar defect in women with an explained secondary infertility randomized controlled trial.

The present study showed that, most patients in group A had positive pregnancy rate (53.33%) than patients in group B (23.33%) with a significant difference (P=0.017).

In the case of caesarean scar syndrome, hysteroscopic surgery is used. CSS is most commonly used to treat abnormal uterine bleeding **[20, 21]**, however numerous recent studies have shown that it can also be used to restore fertility [22,23]. Infertility can occur in women with CSS because to aberrant uterine bleeding caused by a minor haemorrhage in the CSD that prevents implantation **[24, 25]**. Gubbini et al. **[26]** examined the effect of resectoscope repair of isthmocele on 9 patients with secondary infertility and niche, and came to the same conclusion. Seven out of nine patients with secondary infertility were able to conceive. Gubbini et al., on the other hand, looked at the reproductive outcomes of 41 patients who had a cesarean-

induced isthmocele and secondary infertility. The caesarean scar defect was corrected with operative hysteroscopy. They discovered that between 12- and 24-months following arthroplasty, all patients fell pregnant on their own. Thirty-seven of the 41 patients (90.2%) had a caesarean delivery, while four patients (9.8%) suffered a spontaneous abortion in the first trimester. There were no occurrences of scar rupture reported by the authors during pregnancy.

In addition, in a study by **[28]**, the non-adjusted overall improvement was 78.83 percent among 698 patients with post-cesarean complications such as bleeding, discomfort, and secondary infertility who underwent hysteroscopy. The computed heterogeneity amongst the included trials was noted to be significant, despite the high improvement rate. However, the heterogeneity reported by **Shi et al. [29]** and **Calzolari et al. [30]** alone accounted for half of the total estimated variability. Because of the short follow-up duration, the type of data selection, and the limited sample size of patients included in that research, this is the case.

Although **de Albornoz et al. [31]** reported a 97.37 percent improvement rate, the leave-one-out sensitivity analysis revealed that the rate was not entirely driven by the high findings. The risk of bias was likewise statistically significant (p=0.001). As a result, the asymmetry in the funnel plot depicting all experiments was adjusted, and the overall improvement rate was determined to be 92.82%. **Feng et al. [32]**, on the other hand, observed an 87% reduction in AUB after hysteroscopy, but a higher rate of 100% with laparoscopy and 93% with vaginal repair. Furthermore, the same author documented a 97% pain alleviation rate with hysteroscopy and a 100% pain relief rate with laparoscopy, as well as a decrease in secondary infertility in more individuals following hysteroscopy. **[32]**.

Tanimura et al. [23] observed that endoscopic correction of a caesarean scar defect improved fertility in 22 women with secondary infertility. In four patients with residual myometrial thickness less than 2.5 mm, hysteroscopic repair was performed, whereas in the remaining 18 patients with residual myometrial thickness less than 2.5 mm, laparoscopic repair was performed. The hysteroscopic group had a 100% pregnancy rate, while the laparoscopic group had only 55.56%. Three of the four patients who received hysteroscopic surgery had full-term babies. Five of the patients who underwent laparoscopic surgery gave birth to healthy babies. There were no occurrences of uterine scar rupture documented, and all patients were delivered via caesarean section. **[23]**

Many studies have been conducted to assess the function of laparoscopic caesarean scar healing in women with secondary infertility and have indicated a significant increase in pregnancy rates. Isthmocele was detected by Hysterosalpingo Contrast Sonography (HyCoSy) and hysteroscopy in 15 patients who presented with secondary infertility following one or more caesarean sections, according to **Istvan et al., [33].** Except for one patient, who had the hysteroscopy procedure alone, all patients had hysteroscopy-guided laparoscopic arthroplasty. Within 24 months, 80% of women (n=12/15) were pregnant. Meanwhile, 11 patients (73.33%) became pregnant during the first 12 months, and one (6.67%) became pregnant within the first 24 months, out of the 15 who underwent this surgical procedure. Surprisingly, 58.33% (n=7/15) got pregnant using IVF-ET, while 41.66 percent (n=5/15) got pregnant naturally. **[33]**.

In addition, **Donnez et al. [34]** investigated the effect of laparoscopic caesarean scar healing on 18 women with infertility and residual myometrial thickness. In a cohort of 146 patients, **Zhang et al. [35]** described laparoscopic correction of a prior lower uterine section caesarean scar defect (PCSD). 32 of them wanted to start a family. In the 13–32 months following surgery, 12 of them became pregnant [35]. Furthermore, according to **Nezhat et al., [36]**, 75%

of patients who underwent laparoscopic niche correction for infertility were able to conceive. They only executed hysteroscopic repairs in women who were in discomfort or bleeding. They claimed that the laparoscopic approach is preferable for women who want to have children in the future, while the hysteroscopic approach is ideal for those who have already had children. Although, it is to be noted that they did not study the effect of hysteroscopic repair of cesarean scar defect in patients with secondary infertility, and they made their own recommendation based on the theoretical risk of rupture **[36]**.

CONCLUSION

In women with secondary infertility and a residual myometrial thickness of less than 3 mm, hysteroscopic correction of a caesarean scar defect offers a minimally invasive method with a high success rate and no risks.

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Tranexamic Acid plus Oxytocin Versus Oxytocin only in Reducing Blood loss after Cesarean Section. A Double Blinded Randomized Controlled Trial

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Abstract

Objective: to assess the efficacy of tranexamic acid in reducing blood loss after cesarean section.

Patients and methods: This was a double blinded randomized controlled trial. One hundred and thirty patients admitted for elective cesarean section were randomized into two groups to receive either tranexamic acid plus oxytocin (group T) or oxytocin only (group A) after obtaining informed consent. The primary outcome of the study was the intraoperative blood loss. Other measures of outcome were the postoperative blood loss, the need for additional uterotonics, postopertative hemoglobin and hematocrit levels, need for blood transfusion and any side effects related to tranexamic acid.

Results: tranexamic acid significantly reduced intraoperative blood loss after CS when combined with oxytocin; 246.5 ± 103.8ml in the tranexamic group versus 525.4 ± 99.4 ml in the oxytocin only group (P=<0.001). Postpartum blood loss was also reduced significantly in the tranexamic acid group; 77.7 ± 11.6 ml in the tranexamic acid group versus 103.3 ± 11.3ml in the oxytocin only group (P=<0.001). Hb 24hrs after cesarean section was significantly greater in the tranexamic group; 11.3±1.0 g/dl versus 10.7±0.9 g/dl in the oxytocin only group (p=0.001). The need for additional uterotonics was significantly reduced among the tranexamic group; 3(4.6%) versus the oxytocin only group; 12(18.5%) with p value = 0.013. Operative time was significantly shorter in the tranexamic group; 65.8±13.0 min versus the oxytocin only group; 79.1±16.3min. No significant difference was found between the two groups regarding the need for blood transfusion and there was no reported neonatal side effects.

Conclusion: tranexamic acid significantly reduced intraoperative and postoperative blood loss after cesarean section and it can be safely used for prophylaxis against postpartum hemorrhage after cesarean section in low risk patients.

Key words: tranexamic acid, cesarean section.

Introduction

Postpartum hemorrhage (PPH) is considered to be one of the leading causes of maternal morbidity and mortality in the United States and is the most common cause of maternal mortality worldwide (1). According to WHO statistics, PPH is responsible for 60% of maternal mortalities in the developing countries which accounts for more than 100,000 maternal deaths per year worldwide(2).

Primary postpartum hemorrhage is leading form of obstetric haemorrhage. The WHO defines primary PPH as blood loss of 500ml or more during the first 24hours after giving birth (3).

Medical management in the form of uterotonic drugs is the first line treatment for major PPH. When first-line treatment fails, second line therapies consist of surgical or radiological procedures. Hysterectomy is the last choice for controlling bleeding and it's a life saving procedure in severe cases(4).

Oxytocin given either by the intravenous or intramuscular route is recommended for the prophylaxis against PPH for all births. (5). In case of caesarean section, oxytocin (5 iu by slow intravenous injection) should be used to stimulate contraction of the uterus and to decrease blood loss (6)

Tranexamic acid has risen in the past years as another agent which can be used to decrease blood loss following childbirth. Small, single center, randomized, controlled trials have shown significant decrease in postpartum blood loss when prophylactic tranexamic acid is given to women undergoing elective cesarean delivery. Nevertheless, because of methodologic limitations related to blinding, outcome assessment, attrition bias, and absence of postdischarge follow-up, especially for thromboembolic events, the findings in these trials are interpreted as inconclusive, and current guidelines do not advocate routine administration of tranexamic acid after cesarean deliveries.(7)

The aim of this study is to evaluate the efficacy of tranexamic acid in reducing blood loss after cesarean section

Patients and methods

This randomized controlled study was carried out at the labor ward of Ainshams university maternity hospital during the period from August 2020 to April 2021 The study population included pregnant women with singleton fetus admitted for delivery by elective lower segment cesarean section. Age of the included participants was from 20 to 40 years of age with gestational age from 37+0 weeks to 41+0 weeks. Patients with risk factors or history of postpartum hemorrhage, medical disorders as diabetes mellitus or hypertension, contraindications or hypersensitivity to tranexamic acid and women receiving anticoagulant therapy were excluded from the study.

The study participants were divided into two groups; group(T) and group(O); Group sample sizes of at least 65 cases per group achieve 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.50 and the significance level (alpha) is 0.050 using a two-sided two sample equal-variance t-test (8). The Women who fulfilled the criteria for the study will be approached for consenting and will be given a serial number in the study, randomization will be done through a computer generated system For the sake of concealment, cards with either (T) or (O) on them will be kept in sealed envelopes with a serial number. According to the computer system an envelope will be chosen which corresponds to the number of enrollment of the women in the study and then will prepare either the TXA plus oxytocin or oxytocin only according to the card and give it to her. The mean examiner, the surgeon and the analyst will be masked to the given drug. For those in group (T), they will receive 1gm of TXA (1gm/10ml) IV just before skin incision. As soon as the umbilical cord is clamped, all women included in the study group (T) and group (O) will receive 5IU oxytocin IV bolus. Hemoglobin and Hematocrit will be withdrawn before the procedure and will be repeated 24 hours after delivery. Records of primary and secondary outcomes will be tabulated.

The primary outcome of the study was the amount of blood loss after delivery of the placenta and for 2hours after. It was estimated

by measuring the amount of blood in the suction drain, blood absorbed by soaked mops (wet weight of the used mop – dry weight) and blood absorbed by perineal sheet during vaginal toileting (wet weight – dry weight). Soaked mops and operation table perineal sheet were weighed by electronic scale before and after the surgery with one mg weight was taken as equivalent to one ml of blood (9). Other measures of outcome were the amount of blood products transfused, operative time, postoperative hospital stay and neonatal complications if existed.

The analysis will be carried out using the MedCalc 9.3 statistical software. Normal distribution of continuous variables will be assessed using the Kolmogorov-Smirnov test; the chi-square test will be used to analyze categorical variables; the Student's t test will be used for the analysis of normally distributed continuous variables; and the Mann-Whitney U test will be used for abnormally distributed variables. Relative risk with a 95% confidence interval (CI) will be calculated. P≤.05 will be indicated statistical significance.

This study will be done after approval of the ethical committee of the department of obstetrics and gynecology, Faculty of Medicine, Ain shams University. Informed consent will be taken from all participants before recruitment in the study and after explaining the purpose and procedure of the study. The investigator will obtain the written, signed informed consent of each subject before performing any study specific procedure on the subject. The investigator will retain the original signed informed consent form. All laboratory samples, evaluation forms, reports, video recordings and other record that leave the site will not include unique personal to maintain subject confidentiality. The study will be based on the investigator self-funding.

Results

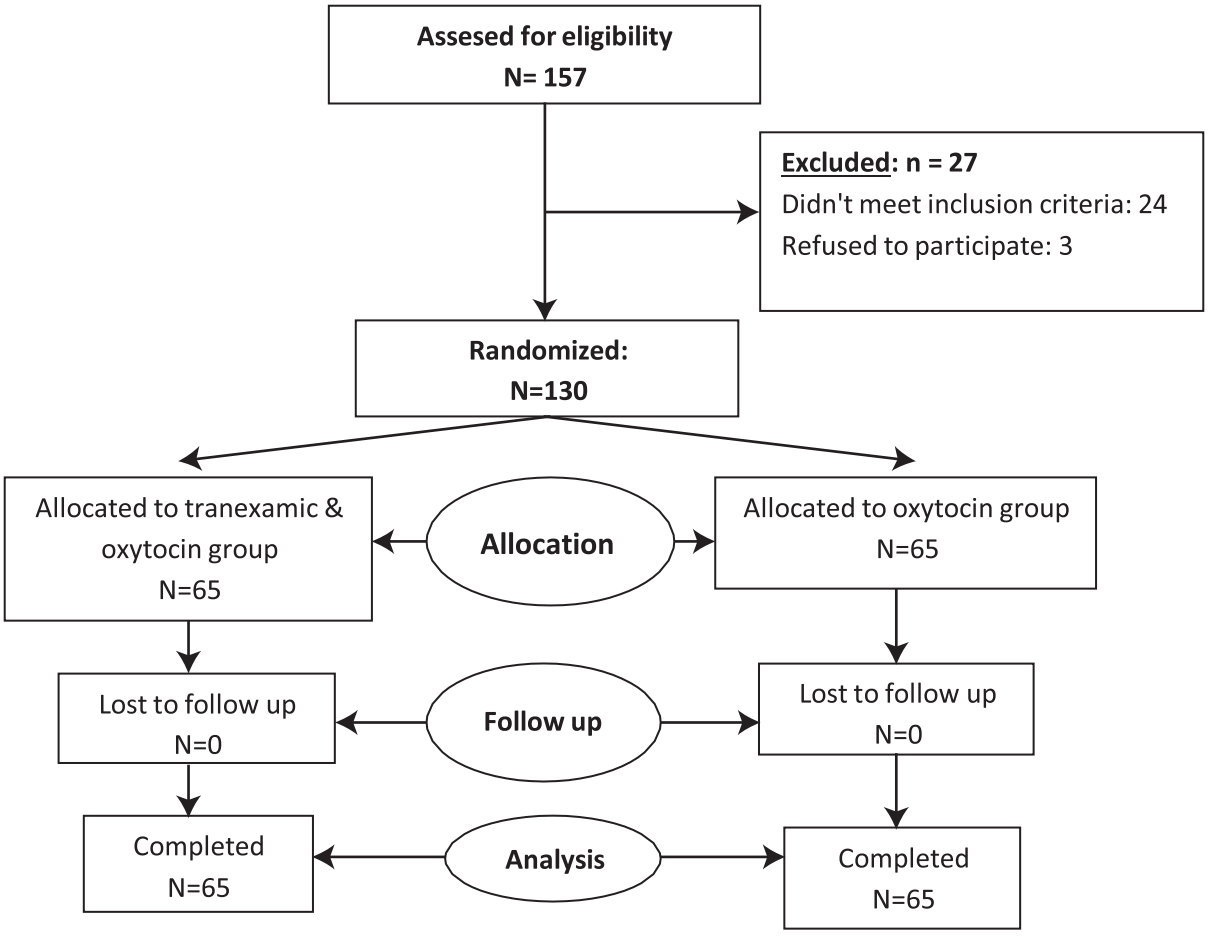

Figure 1: flow chart of the studied cases

Table 1: Demographic data among the studied groups

Items	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Age (years)	Mean±SD	29.7±5.8	29.2±6.2	^ 0.621
	Range	20.0–40.0	20.0–40.0	
BMI (Kg/m^2)	Mean±SD	29.8±2.6	29.8±2.8	^ 0.974
	Range	24.0–35.0	25.0–35.0	
Parity, (n, %)	Nulli	9 (13.8%)	10 (15.4%)	# 0.804
	Multi	56 (86.2%)	55 (84.6%)	
GA (week)	Mean±SD	38.1±0.9	38.0±1.0	^0.924
	Range	37.0–40.0	37.0–40.0	
ABO	A	33 (50.8%)	28 (43.1%)	#0.158
	B	10 (15.4%)	16 (24.6%)	
	AB	3 (4.6%)	8 (12.3%)	
	O	19 (29.2%)	13 (20.0%)	
Rh	Positive	52 (80.0%)	58 (89.2%)	#0.145
	Negative	13 (20.0%)	7 (10.8%)	
Previous cesarean section		56 (86.2%)	54 (83.1%)	#0.627

BMI: body mass index, GA: Gestational age, ^ : Independent t-test, # : Chi square test.

Table 2: intraoperative blood loss (mL) among the studied groups

Source	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Sheet	Mean±SD	180.8±74.0	275.4±122.2	**<0.001***
	Range	64.0–450.0	104.0–550.0	
Suction	Mean±SD	91.7±58.5	229.8±106.0	**0.003***
	Range	50.0–200.0	100.0–400.0	
Towel	Mean±SD	57.2±31.0	101.6±44.1	**<0.001***
	Range	11.0–165.0	20.0–234.0	
Total	Mean±SD	246.5±103.8	525.4±99.4	**<0.001***
	Range	111.0–550.0	271.0–784.0	

^ : Independent t-test, *: Significant

Table 3: Postoperative blood loss (ml) among the studied groups

Source	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Sheet	Mean±SD	77.7±11.6	103.3±11.3	<0.001*
	Range	49.0–106.0	85.0–133.0	
Drains		No intraperitoneal drains		

^ : Independent t-test, *: Significant

Table 4: Hemoglobin (gm/dl) among the studied groups

Time	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Pre-operative	**Mean±SD**	11.8±1.0	11.5±0.9	0.119
	Range	9.4–14.0	9.8–14.1	
Post-operative	**Mean±SD**	11.3±1.0	10.7±0.9	**0.001***
	Range	9.0–13.6	8.8–13.4	
Drop	**Mean±SD**	0.4±0.2	0.8±0.3	**<0.001***
	Range	0.2–1.6	0.3–1.4	

^ : Independent t-test, *: Significant

Table 5: Need for additional uterotonics and blood transfusion and neonatal side effects among the studied groups

Complications	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Uterotonics	3 (4.6%)	12 (18.5%)	**#0.013***
Blood transfusion	1 (1.5%)	2 (3.1%)	§0.999
Neonatal side effects	0 (0.0%)	0 (0.0%)	**Not applicable**

#: Chi square test. §: Fisher's Exact test. *: Significant

Table 6: operative time (minutes) among the studied groups

Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Mean±SD	65.8±13.0	79.1±16.3	<0.001*
Range	45.0–110.0	45.0–105.0	

^ : Independent t-test. *: Significant

Discussion

This was a double-blinded randomized controlled clinical trial which was conducted at the labor ward of Ain Shams University Maternity Hospital (ASUMH) during the period between November 2019 and December 2021 and it was aiming at comparing the efficacy of tranexamic acid plus oxytocin versus oxytocin alone in reducing blood loss following CS.

One hundred thirty women (130) were included in the study and they were randomized into two groups; Group (O): 65 women received oxytocin only while Group (T): 65 women received oxytocin plus tranexamic acid

Regarding the Demographic data, there was no statistically significant difference between the two groups regarding age, BMI, parity, gestational age, ABO& Rh blood groups and previous cesarean delivery.

As for Intraoperative blood loss, it was estimated by measuring the amount of blood in the suction bottle in addition to weighing the soaked towels and sheets. All measures were summated to estimate the intraoperative blood loss, there was significant difference in the between the study group and the control group favoring the study group and that difference was found in all measures; suction, sheets, towels and the total blood loss (194.6±87.2 VS 485.0±103.5). Regarding Postoperative blood loss, it was estimated by weighing the sheet which was placed beneath the patient immediately after the procedure; the sheet was weighed 2 hours after the procedure. The results showed significant statistical difference

between the two groups favoring the study group (77.7 ± 11.6 VS 103.3 ± 11.3). Our results were consistent with results obtained by Lakshmi & Abraham, who randomized their patients into two groups to receive either tranexamic acid as 20 min before skin incision in addition to 10 units of oxytocin while the other received oxytocin only. There was significant difference between the two groups regarding blood loss favoring the study group (347.17±106.6 VS 517.72±150). Moreover, blood loss over 500cc was significantly different between the study and the control group (2/60 {3.3%} VS 36/60{60%}). However, their measurements were limited to intraoperative blood loss and the postoperative period was not included (9). Our results were also similar to results by Abdelaleem et al., who conducted their study on 740 pregnant women underwent elective CS. The participants were randomized into two groups to receive either tranexamic acid or nothing before the procedure with equal dosage of oxytocin received after delivery. There was significant difference regarding total blood loss between the two groups (241.61±126.02 VS 510.7±144.52). Intraoperative blood loss and up to 2hrs post cesarean section blood loss was measured (10). The study by Movafegh et al., showed similar results as well. The study participants were randomized into two groups to receive either tranexamic acid or normal saline 20 min before procedure and the two groups received the same dosage of oxytocin after delivery of the placenta. The study showed significant difference between the study group and the control group regarding intraoperative blood loss (262.5± 39.6 mL VS 404.7±94.4 mL) and postoperative blood loss (67.1± 6.5 mL vs 141.0±33.9 mL)(11).

Regarding the Hemoglobin difference, there was no significant difference between the two groups in the levels of preoperative hemoglobin (Mean ± SD = 11.8±1 VS 11.5± 0.9 with P value 0.119) while there was statistically significant difference between the two groups regarding postoperative hemoglobin (Mean ± SD = 11.3±1 VS 10.7±0.9 with P value 0.001). Our results were consistent with that obtained by Ray et al., who showed in their study which included two groups who received either 1g intravenous (IV) tranexamic acid or placebo 20 min before beginning of spinal anesthesia and the same dose of oxytocin after delivery that post-operative fall in hemoglobin per cent was significantly more in control (0.99 g%) group than study group (0.26 g%) (p = 0.000). (Ray et al.,2016) (12). Study conducted by Senturk et al., showed similar results as well. The study included two groups who received either 20cc of IV tranexamic acid or placebo 10 minutes before the start of cesarean section and all patients received 20 IU oxytocin IV bolus form after removal of placenta. The results showed significant difference when hemoglobin loss was compared between the two groups with p value of 0.034 (13).

The Need for additional uterotonics during the procedure was also assessed in our study and it was found that the need for additional uterotonics during the procedure was significantly more in the control group (18.5% of the group) compared with that of the intervention group (4.6% of the group) with p value of 0.013. Such results were similar to that obtained by Lakshmi & Abraham as the need for additional uterotonics in the control group was significantly more compared to tranexamic acid group (15% VS 3%)(9).

Gungorduk et al., also showed similar results in their study; significant difference was found between the two groups regarding the need for additional uterotonics with 14.5% of the placebo group required additional uterotonics compared to 8.5% of the active group with p value = 0.02 (14).

Regarding the need for Blood transfusion, there was no significant difference between the two groups. Only 1 patient in the study group (1.5%) and 2 patients (3.1%) needed blood transfusion with P value 0.999. Our results were comparable to that obtained by Senturk et al., who showed no need for blood transfusion in both groups (study and control) included in their study (13). However, results obtained by Shahid & Khan were different as there was significant difference between the two groups regarding the requirement for blood transfusion; 33% of the patients in the control group required blood transfusion with only 8% in the study group. Such difference between results of their study and our study

can be attributed to certain points; the mean preoperative hemoglobin was already in the anemic range in both study and control group of the previously mentioned study (study group: 9.76

± 0.85 VS control group: 9.88 ± 1.26) with further aggravation of such anemia in the postoperative period (study group: 8.67 ± 0.715 VS control group: 8.0 ± 0.94), smaller sample size than our study and the fact that hemoglobin was withdrawn on the third postpartum day in their study which was a better reflection of the actual hemoglobin status of the patient (15).

As for the Operative time, it was significantly shorter among the tranexamic acid plus oxytocin group compared with oxytocin group (Mean ± SD = {65.8±13.0 VS 79.1±16.3}). Such difference in the operative time could be attributed to less time spent in achieving adequate hemostasis in the tranexamic group. Our results were consistent with results obtained by Lakshmi & Abraham who randomized their participants into two groups as well; one was given tranexamic acid as 1gm diluted in 100ml saline 20 min before skin incision in addition to 10 units of oxytocin while the other received oxytocin only. The operative time was significantly shorter among the tranexamic acid group (9). However, Maree and Hassein obtained different results in their study which included 100 women; one group received 10mg/kg of tranexamic acid + 5 IU bolus IV oxytocin after delivery while the other group received 20 IU infusion of oxytocin soon after delivery. There was no significant difference between the two groups regarding the operative time (Mean ± SD = {37.58±1.72 VS 37.1±2.49}). Such difference between this study and our study could be attributed to different sample size between the two studies yielding different results, higher levels of experience among the operating surgeons in the study conducted by Maree & Hassein, higher percentage of previous LSCS in our study (86.2% in the TXA group and 83.1% in the control group) compared with their study (18% in the TXA+ oxytocin and 10% in the control group) and the fact that our study was limited to elective CS while their study included emergency CS for different reasons (16).

Maternal or fetal complications related to tranexamic acid were also assessed and there were no reported complications. However, such outcome needs a much bigger sample size and it wasn't the primary concern of our study.

Our study wasn't without limitations. The major limitations of our study was the small sample size and the fact that side effects of tranexamic acid were not measured and because of its rarity, studies with much bigger sample size will be needed to detect it

Conclusion

Our study showed that tranexamic acid is an effective agent in reducing blood loss during elective cesarean section in low risk patients. It has minimal side effects and it's rarely unavailable. However, further studies are needed to evaluate its effectiveness in patients with risk factors for postpartum hemorrhage i.e high risk patients.

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Sublingual misoprostol before insertion of levonorgestrel-releasing intrauterine contraceptive device in lactating women following cesarean section

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Abstract

Background: Misoprostol is used for cervical softening before minimally invasive gynecological procedures. We aimed to assess the benefits and drawbacks of using sublingual misoprostol before inserting the levonorgestrel-releasing intrauterine contraceptive device (LNG-IUCD) in women who have never had a vaginal birth.

Methods: A clinical trial was conducted on 72 recruited women with lactational amenorrhea with no previous vaginal delivery. They were equally divided into 2 groups; group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo 2 hours before the procedure.

Results: We observed easy insertion of Mirena IUCD in women of the misoprostol group, but with no significant difference between both groups. However, the duration of IUCD insertion was significantly shorter in the misoprostol group compared to the placebo group (5.03 ± 0.74 vs. 5.58 ± 0.94 minutes, P=0.007). The VAS pain score was significantly decreased in the misoprostol group (3.33 ± 1.29 vs. 3.97 ± 1.28, P=0.038) with a higher patient satisfaction score (7.22 ± 1.38 vs. 6.28 ± 1.41, P=0.005). Regarding the side effects, women in the misoprostol group experienced more nausea/vomiting, slight hyperthermia, and uterine cramps (P= 0.018, 0.011, and 0.173, respectively).

Conclusion: Sublingual administration of misoprostol before Mirena IUCD insertion could help increase the ease of insertion with a significant decrease in the procedure time. Furthermore, it could improve patient satisfaction and decrease the pain experience.

Key words: Sublingual misoprostol, Levonorgestrel-releasing IUCD, Mirena.

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INTRODUCTION

Different contraception types have been widely used worldwide to reduce unplanned pregnancies (1). Intrauterine contraceptive device (IUCD) is one of the contraceptive

methods which is wildly used as a reversible method of contraception (2). Both types of intrauterine contraceptive devices, copper IUCD and levonorgestrel IUCD (LNG-IUCD), are equally effective, safe, and cost-effective as contraceptive methods (3). However, the LNG-IUCD has the advantage of lower risk of ectopic pregnancy (4), as well as has many non-contraceptive benefits (5). The LNG-IUCD, commercially known as Mirena, has more roles in treating menorrhagia, anemia, and dysmenorrhea (6). Despite that, it is used by 7.6% of women in developed countries and 14.5% of women in developing countries (7). This may be related to the fear of women from pain during insertion or difficulty of insertion by healthcare providers (8). Reported complications associated with IUCD insertion are 0.2% cervical perforation, 0.2% syncopal attack, and 8.8% insertion failure, which is commonly reported in women who had not delivered vaginally (9). Women delivered only by elective CS are considered nulliparous concerning IUCD insertion and are suspected of having pain during insertion (10). Many healthcare providers avoid IUCD insertion in women with previous CS due to concerns of difficult insertion and pain (11). Some studies show that the use of non-steroidal anti-inflammatory drugs (NSAIDs) before the IUCD insertion reduces the experience of pain, while other RCTs show no effect (12,13). Misoprostol is a prostaglandin E1 analogue that has different uses in Obstetrics as induction of abortion, induction of labor, and protection from postpartum hemorrhage (14). It has many uses also in gynecology in the form of preoperative priming of the cervix prior to hysteroscopy and fractional curettage in perimenopausal women (15). However, it has many side effects, such as nausea, abdominal cramps, vomiting, diarrhea, and shivering (16).

Our aim in this study was to address the benefits and drawbacks of using sublingual misoprostol before Mirena IUCD placement in previous CS patients during lactational amenorrhea.

METHODS

Study Design: Single-blinded randomized controlled clinical trial.

Setting: The study was conducted on 72 women who attended the postnatal outpatient clinic at Cairo University Hospitals, seeking IUCD for contraception from November 2020 till May 2022.

Ethical consideration: The study was approved by the Medical Research Ethics Committee of the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University. All recruited women gave their consent after properly explaining the nature of the study with the possible risks and the outcome benefits.

Inclusion criteria:

1. Age from 20 to 42 years
2. BMI less than 30 kg/m2
3. Women with lactational amenorrhea and a negative pregnancy test.
4. Women seeking IUCD insertion following the cesarean section (within six months).

Exclusion criteria:

1. Nulligravida or multigravida with normal vaginal deliveries.
2. Women with regular menses
3. Women with chronic medical disorders.
4. Women with uterine abnormalities, intrauterine adhesions, cervical stenosis, fibroids or adenomyosis.
5. Women with chronic pelvic pain, cervical infection, or spasmodic dysmenorrhea
6. Allergy to misoprostol or contraindication to levonorgestrel.

Population:

The recruited women were divided into 2 groups. Group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo 2 hours before the procedure.

Procedure:

All women were randomly allocated to both groups via a computer-generated randomization program. Basic patient characteristics were recorded for women in both groups. All women did not receive any analgesia before Mirena IUCD insertion. They underwent vaginal ultrasound before Mirena IUCD insertion to exclude any uterine or pelvic contraindication as well as to detect uterine size and axis. Women in the first group received sublingual misoprostol 400 mcg 2 hours before Mirena IUCD insertion, while women in the second group received a placebo 2 hours before the procedure. The technique of Mirena IUCD insertion was performed as prescribed by Johnson et al. (17). Women were instructed to come for follow-up after 24 hours and after 30 days.

Outcomes: Our primary outcome was to assess the difficulty of Mirena IUCD insertion, while secondary outcomes included assessment of the following:

1. Pain during insertion, according to the visual analog scale (VAS), from 0 (painless) to 10 (highest pain).
2. Duration of insertion (minutes)
3. Subjective sense of satisfaction graduated on a VAS-like scale, from 0 (totally not satisfied) to 10 (totally satisfied).
4. Side effects during IUCD insertion: bleeding, vasovagal reaction, perforation, and failed insertion.
5. Side effects after 24 hours of IUCD insertion: nausea, vomiting, cramps, and hyperthermia
6. Side effects after 30 days of IUCD insertion: displacement and expulsion

Sample size calculation: We calculated the sample size by comparing of easiness score during Mirena IUCD insertion in women with previous CS pretreated with prostaglandins versus untreated women. As reported in a previous publication (18), the mean ± SD of easiness score in the misoprostol pretreated women group was approximately 2.4 ± 1.7, while in an untreated group, it was approximately 4 ± 2.4. Accordingly, we calculated that the minimum proper sample size was 36 women in each group to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level.

Statistical analysis: Statistical analysis was performed using the SPSS software (SPSS, version 25, SPSS, Inc., IL, USA). Numerical data were presented as means± standard deviation (SD), while categorical data were presented as numbers and percentages. Statistical analysis was done using the Student's t-test test to compare numerical variables and the Chi-square test to compare the categorical variables. P-values less than 0.05 were considered statistically significant.

RESULTS

This study included 72 women with lactational amenorrhea following the cesarean section and planning to use Mirena IUCD for contraception. They were divided into two groups; group 1 received sublingual misoprostol 400 mcg 2 hours before Mirena insertion, and group 2 received a placebo two hours before the procedure. There was no significant difference between both groups regarding the demographic characteristics of women, including age, body mass index (BMI), and position of the uterus (P>0.05), as shown in **Table 1**.

Table 1: Demographic characteristics of women in both groups

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Age	27.54 ± 4.00 (21 - 35)	28.61 ± 4.21 (21 - 36)	0.273
BMI	24.39 ± 2.42 (19.5 - 29)	24.86 ± 3.02 (18.5 - 30)	0.466
Uterus position **- AVF** **- Midposition** **- RVF**	 26 (72.22%) 4 (11.11%) 6 (16.67%)	 24 (66.67%) 7 (19.44%) 5 (13.89%)	0.610

The main outcome was to assess the difficulty of insertion. We observed easy insertion of Mirena IUCD in women of the misoprostol group, but with no significant difference between both groups. However, the duration of IUCD insertion was significantly shorter in the misoprostol group compared to the placebo group (5.03 ± 0.74 vs. 5.58 ± 0.94 minutes, P=0.007) **(Table 2)**.

Regarding the secondary outcomes, pain during insertion, according to the visual analog scale (VAS), was significantly reduced in the misoprostol group compared to the placebo group (3.33 ± 1.29 vs. 3.97 ± 1.28, P=0.038). This observation was confirmed by the higher patient satisfaction score in the misoprostol group compared to the placebo group (7.22 ± 1.38 vs. 6.28 ± 1.41, P=0.005), as shown in **Table 2**.

There were some side effects observed during IUCD insertion. Most of the cases in both groups showed mild post-insertion bleeding with no significant difference (P=0.173). A mild vasovagal reaction was observed in only 4 cases in the misoprostol group and 7 cases in the placebo group, with no significant difference (P=0.326). No single case in both groups was complicated by uterine perforation **(Table 2)**.

Table 2: Outcomes during Mirena IUCD insertion

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Difficulty of insertion **- Easy** **- Difficult**	 27 (75.00%) 9 (25.00%)	 20 (55.56%) 16 (44.44%)	0.083
Duration of insertion (min)	5.03 ± 0.74 (4 - 6)	5.58 ± 0.94 (4 - 7)	0.007
Pain during insertion	3.33 ± 1.29 (2 - 7)	3.97 ± 1.28 (2 - 6)	0.038
Sense of satisfaction	7.22 ± 1.38 (5 - 9)	6.28 ± 1.41 (3 - 8)	0.005
Post insertion bleeding **- mild** **- moderate**	 33 (91.67%) 3 (8.33%)	 29 (80.56%) 7 (19.44%)	0.173
Vasovagal reaction	4 (11.11%)	7 (19.44%)	0.326
Perforation	0	0	N/A

During follow-up on the next day of IUCD insertion, women in the misoprostol group experienced more nausea/vomiting, slight hyperthermia, and uterine cramps (P= 0.018, 0.011, and 0.173, respectively). After one month, we observed IUCD displacement during the transvaginal ultrasound follow-up in only 2 cases in the placebo group. However, the rate of IUCD expulsion was 0 % in both groups, as shown in Table 3.

Table 3: Side effects of Mirena IUCD insertion after 24 hours and after 30 days

	Group 1 Misoprostol (n=36)	Group 2 Placebo (n=36)	P-Value
Nausea/Vomiting (24 hrs)	21 (58.33%)	11 (30.56%)	0.018
Cramps (24 hrs)	7 (19.44%)	3 (8.33%)	0.173
Hyperthermia (24 hrs)	6 (16.67%)	0 (0.00%)	0.011
Displacement (30 days)	0 (0.00%)	2 (5.56%)	0.162
Expulsion (30 days)	0	0	N/A

DISCUSSION

IUCD has been considered one of the most reliable contraception methods being cost-effective with a higher degree of satisfaction. The LNG-IUCD is nowadays considered the most effective IUCD, with a pregnancy rate of less than 0.5% (19). Misoprostol, a synthetic prostaglandin estrone analogue, has been used to aid cervical softening before minimally invasive gynecological procedures (20). Therefore, we aimed to discuss both benefits and drawbacks of using sublingual misoprostol before Mirena IUCD insertion in previous CS patients during lactational amenorrhea.

Our study revealed that sublingual misoprostol two hours before Mirena IUCD insertion helps increase the easiness of insertion with a significant decrease in the procedure time. In addition, women who received sublingual misoprostol before the procedure experienced less pain on the VAS scale and higher satisfaction. On the other hand, some side effects were reported 24 hours after the procedure from women who received misoprostol, such as nausea and/or vomiting, some uterine cramps, and slight hyperthermia.

In accordance with our findings, El-Garhy et al. (2020) studied the effect of sublingual misoprostol on 120 women with previous cesarean section and no prior vaginal birth. They reached the same results, although they used a higher dose of 600 mcg given two hours before IUCD insertion. They revealed that using misoprostol before IUCD insertion reduced the pain perceived by the patients but increased the incidence of mild side effects such as nausea, fever, and abdominal cramps before insertion (21).

El-Gawad et al. (2021) also studied the effect of misoprostol in 210 women delivered only by elective cesarean section but throughout the vaginal route (not sublingual) and with a different dose (400 mcg) and a different route. They revealed that using vaginal misoprostol 3 hours before IUCD insertion significantly affects the ease of insertion and reduces the pain perception by patients during the insertion (22).

Moreover, Mohammed et al. (2019) stated that vaginal or sublingual 400 µg of misoprostol administrated 4 hours before IUCD insertion facilitates IUCD insertion and reduces the pain perception by patients during the insertion. However, they preferred the vaginal route for cervical ripening as it occurs more likely with the vaginal administration of misoprostol (23).

When misoprostol is taken orally or sublingually, it reaches a peak concentration in 30 minutes and then rapidly drops. When using the vaginal method, on the other hand, the peak plasma concentration occurs after 1 hour and decreases gradually, with levels remaining high for at least 6 hours, significantly higher than when using the oral or sublingual routes (24).

On the contrary, our results did not agree with the results of Mansy (2018), as he found that using sublingual misoprostol before IUCD insertion in women with tight cervix or even in women with no previous vaginal delivery has no role in facilitating its insertion or in pain reduction during the procedure (25). Also, Elgharabawy et al. (2020) found that using sublingual misoprostol did not facilitate IUCD insertion in women with a tight cervix and did not reduce pain during the IUCD insertion (26).

The main weak points in our study are that sense of pain and satisfaction were subjective and evaluated by the patients themselves, which could be over-expressed. On the other hand, the importance of our study is that we focused only on the LNG-IUCD (Mirena), which has a slightly wider sheath than other IUCDs, making the insertion procedure more difficult and more painful.

CONCLUSION

Sublingual administration of misoprostol before Mirena IUCD insertion could help increase the ease of insertion with a significant in the procedure time. Furthermore, it could improve patient satisfaction and decrease the pain experience.

DECLARATIONS

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

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

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Deregulated Levels of Vascular Endothelial Growth Factor, Tumor Necrosis Factor-α and Total Cholesterol Early in Pregnancy may Predict Oncoming Gestational Diabetes Mellitus

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Abstract

Objectives: Evaluation of the relationship between maternal glycemia and lipidemic statuses, serum levels of vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α) at the 6th gestational week (GW) and the development of gestational diabetes mellitus (GDM) among non-diabetic pregnant women.

Patients & Methods: 169 newly pregnant women, 20 non-pregnant/non/diabetic (NP/ND) and 20 non-pregnant/diabetic (NP/D) women underwent 75-Oral glucose tolerance test (OGTT) and gave blood samples for estimation of blood levels of glycosylated hemoglobin A1c (HbA1c), plasma lipid profile and serum levels of VEGF and TNF-α at the 6th GW of the pregnant women and the 24th GW, OGTT was repeated to define GDM women.

Results: At the 24th GW, OGTT defined 37 women had GDM and 132 were non-GDM. At the 6th GW, NP/D and GDM women had significantly higher fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), and very low-density lipoprotein (VLDL) with significantly lower high-density lipoprotein (HDL-c) compared to NP/ND women, but differences were non-significant between non-GDM and NP/ND women. At-enrolment means serum levels of TNF-α were significantly lower in samples of NP/ND than in samples of women of other groups that showed non-significant differences. On contrary, at-enrolment mean serum levels of VEGF were significantly higher in NP/D and GDM women, while were non-significantly higher in non-GDM women compared to NP/ND. Moreover, at-enrolment serum VEGF levels were significantly lower in pregnant women compared to NP/D women with significantly lower levels in non-GDM than GDM women. Statistical analyses defined high at-enrolment plasma TC and serum VEGF and TNF-α as the most significant predictors for GDM during pregnancy progress. Kaplan-Meier Regression analysis showed that the risk for the development of GDM was increased by 50% at a plasma TC level of 217 mg/ml (95%CI: 215.2-218.8), serum VEGF at 137 pg/ml (95%CI: 132.2-151.8) and TNF-α level at 3.49 (95%CI: 3.35-3.97).

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Conclusion: GDM may be related to the interplay between high levels of VEGF, inflammatory cytokines, and hyperlipidemia. High blood levels of VEGF and TC can discriminate against women vulnerable to developing GDM with high sensitivity, specificity, and negative predictive values.

Keywords: Gestational diabetes mellitus, Vascular endothelial growth factor, Tumor necrosis factor-α, Lipid profile.

Introduction

Gestational diabetes mellitus (GDM) is pregnancy-induced diabetes despite being a temporary form; it is potentially associated with maternal, fetal, and neonatal complications [(1)]. Unfortunately, the incidence of GDM is increasing globally [(2)], and failure of diet and exercise as management for GDM necessities a shift to pharmacotherapy [(3)].

The progressively increasing incidence of GDM parallels the increasing incidence of obesity which was considered an epidemic [(4)]. Moreover, obesity and abdominal adiposity are two of the four components of metabolic syndrome, which is a worldwide problem, and the other two are hyperglycemia and hypertension; these components of metabolic syndrome illustrate the relation between obesity and diabetes [(5)].

Vascular endothelial growth factor (VEGF) is a 45 kDA glycoprotein, homodimeric, basic, and able to bind heparin. The VEGF family comprised several members; VEGF A to E [(6)]. VEGF is a signal protein produced by many cells to stimulate angiogenesis, especially VEGF-A, which consists of 121 amino acids and plays an important role in neoangiogenesis and its increased levels indicate the intensity of neoangiogenesis [(7)].

Tumor necrosis factor alpha (TNF-α), is a pro-inflammatory cytokine that is produced by macrophages/monocytes during acute inflammation and plays a diverse range of signaling events within cells [(8)]. TNF-α acting as a trimer exerts many of its effects by binding to cell membrane receptors to regulate a diverse range of physiological processes [(9)].

Objectives

The study tried to evaluate the relationship between maternal glycemic, angiogenic, and inflammatory statuses and the development of GDM among non-diabetic pregnant women.

Design:

Prospective comparative study

Setting

Obstetrics & Gynecology Department, Faculty of Medicine, Benha University

Ethical consideration

The was started in Nov 2021 after the preliminary approval of the study protocol by the Local Ethical Committee and the final approval was obtained after the finalization of case collection and follow-up period by RC: 5.9.2022.

Participants

All newly pregnant women who attended within the 1st six gestational weeks (GW) the outpatient clinic of Obstetrics & Gynecology at Benha University Hospital were evaluated for the presence of exclusion and inclusion criteria. Evaluation encompassed the collection of demographic data, full medical and obstetric history taking, and clinical examination. Then, all women underwent abdominal ultrasonography for assurance of the presence of a singleton fetal sac containing a viable fetus and gave blood samples for determination of their glycemic status and other investigations. All enrolled women were asked to attend the outpatient lab fasting for more than 12 hours to give a blood sample for estimation of their plasma lipid levels. The study also included 40 non-pregnant (NP) women of cross-matched age and BMI; 20 women were diabetics (NP/D) as a positive control group and 20 non-diabetic women (NP/ND) as a negative control group. Control women must be free of inclusion and exclusion criteria, and accepted to undergo a full profile of investigations.

Exclusion criteria

It included the presence of body mass index (BMI) ≥30 kg/m^2, metabolic syndrome, genetic hypercholesterolemia, and hepatic, cardiac, and vascular diseases.

Inclusion criteria

Inclusion criteria are attendance early in pregnancy within the 1st 6 GW, absence of exclusion criteria, acceptance for the study participation, and attendance at the start of the 24th GW to give blood samples for re-evaluation of glycemic status to define women who developed GDM.

Evaluation Tools:

1. **The 75-oral glucose tolerance test (OGTT):** The enrolled patients underwent the OGTT at the time of enrolment and the start of the 24th GW. Fasting blood glucose (FBG) and 2-h postprandial blood glucose (PPBG) were estimated. PPBG has to be estimated after receiving 75 g glucose by 2-h. GDM was diagnosed if the FBG and 2-h PPBG levels were ≥92 and ≥153 mg/dl, respectively [10].
2. **Estimated levels of HbA1c:** HbA1c at the cutoff point of 6% differentiates between diabetic (>6%) and non-diabetic (≤6%) states [11].

Investigations

- The 1st patients and controls' blood samples that were obtained at the time of enrolment were divided into three parts:

1. The 1st part was collected in a fluoride-containing tube (2:1=NaF: blood, by vol.) to preserve blood glucose (BG) until being sent for estimation of BG at the hospital lab by glucose oxidase method [12].
2. The 2nd part was collected in EDTA containing tube for HbA1c estimation using Latex Turbidimetry (LINEAR CHEMICALS S.L. Joaquim Costa, Montgat, Barcelona, Spain) [13].
3. The 3rd part was collected in a plain tube, allowed to clot, and centrifuged to separate serum that was collected in an Eppendorf tube and frozen to -20oC till being ELISA assayed for estimation of serum levels of tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF) using ELISA kit for estimation of human levels of these biomarkers (Abcam Inc., San Francisco, USA; catalog ab181421, ab100662, respectively) according to manufacturer instructions [14, 15].

- The 2nd patients and controls' blood samples that were obtained 12-h after enrolment were collected in EDTA containing tube for estimation of total cholesterol, low, very-low, and high-density lipoprotein cholesterol (LDL-c, VLDL-c, and HDL-c), and triglycerides (TG) using :

Study outcome

The possible relationship between the estimated parameters at enrolment time and the development of GDM at the 24th GW was evaluated.

Statistical analysis

The results were analyzed using One-way ANOVA, paired t-test, and Chi-square test (X^2 test). Regression analysis and the Receiver characteristic curve were used to determine the significant predictors as judged by the area under the curve (AUC). The suggested cutoff points using the median and quartile values were evaluated using the Kaplan-Meier regression analysis using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

During the study period, 218 women had attended the outpatient clinic within the 1st 6 GW, but 21 had BMI ≥35 kg/m2, 7 women were maintained on cholesterol adjusting therapies, 4 were hypertensive, 3 patients had a history of hepatitis, and 2 had renal manifestations, and 181 women were enrolled in the study, 12 women did not attend at the 24th GW and were excluded from the study and the data of 169 women were analyzed. At the 24th GW, lab re-evaluation detected 37 women who developed GDM (GDM group), while in 132 women 24-GW levels of BG did not reach the diagnostic level for GDM (Non-GDM group) as shown in figure 1. Enrolment data showed a non-significant difference between the women of the study groups (Table 1).

Table (1): Patients' enrolment data

Group Data	NP/ND (n=20)	NP/D (n=20)	GDM (n=132)	Non-GDM (n=37)
Age (years)	29.5±2.9	29.2±3.2	29±3.4	29±3.5
Weight (kg)	83±5.5	84.1±6.4	81.3±3.7	84.5±6
Height (cm)	168.8±4.8	169.1±5.6	169.1±3.1	168.9±2.9
BMI (kg/m^2)	29.1±1.1	29.4±2.1	28.5±1.8	29.6±1.8‡
Gravidity	1.75±0.8	1.8±0.8	1.7±0.6	1.7±0.6
Parity	1.3±0.5	1.3±0.7	0.7±0.6	0.7±0.6
Systolic BP (mmHg)	114.8±8.6	115.2±9.4	115.2±5.6	116±5.8
Diastolic BP (mmHg)	77.7±5	77.8±5.9	78±4.7	77.6±4.4

Mean and standard deviation; BMI: Body mass index; BP: Blood pressure

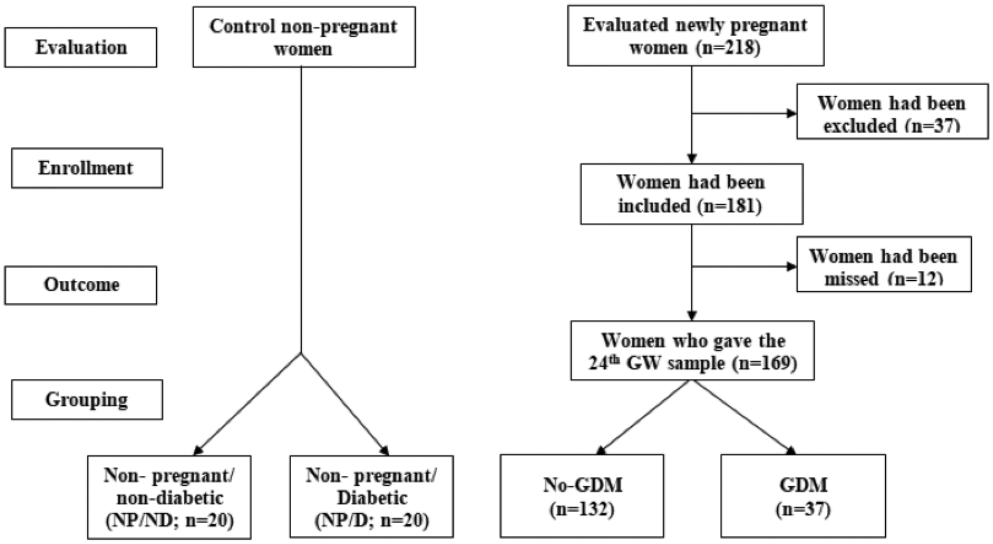

Fig. (1): Study Flow Chart

At the time of enrolment, women of NP/D and GDM had significantly (P<0.001) higher TC, TG, and VLDL with significantly lower HDL-c lipids in comparison to NP/ND women, while estimated levels of these lipids showed non-significant differences between non-GDM and NP/ND women. Plasma TC, TG, and VLDL levels were significantly higher in NP/D compared to non-GDM women, with non-significant differences concerning plasma HDL-c and LDL-c levels between women of both groups. Plasma levels of TC, TG, and VLDL estimated in women of the GDM group were significantly higher than that of the non-GDM group, with non-significant differences as regards plasma LDL-c and HDL-c. GDM women showed significantly lower plasma levels of TG compared to NP/D women (Table 2, Fig. 2).

Table (2): Lipid profile of enrolled women

Group Data	NP/ND (n=20)	NP/D (n=20)	GDM (n=132)	Non-GDM (n=37)
TC (mg/dl)	180±16.5	205.4±23.4*	179.1±20.2†	202.8±22.6*‡
TG (mg/dl)	50.2±8.8	71.3±7.4*	52±5.4†	65.2±9.2*†‡
HDL-c (mg/dl)	46±3.5	40.1±4.9*	43.1±4.7	41.5±7.3*
LDL-c (mg/dl)	65.4±8.9	68.6±19.2	64±22.2	70±25.5
VLDL (mg/dl)	18.4±6.5	25.4±7.9*	20±4.8†	26.8±4.7*‡

Mean and standard deviation; *: significant difference versus non-diabetic non-pregnant women; †: significant difference versus diabetic non-pregnant women; ‡: significant difference versus non-GDM; symbols indicate significance at P<0.001

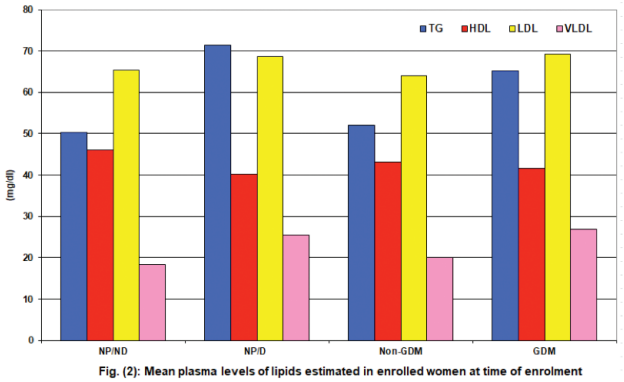

Fig. (2): Mean plasma levels of lipids estimated in enrolled women at time of enrolment

Enrolment FBG levels were significantly lower in samples of NP/ND women compared to levels estimated in samples of women of NP/D and GDM women but were non-significantly lower than levels estimated in non-GDM women. On the other hand, at-enrolment FBG levels in samples of NP/D were significantly higher than that of both groups of pregnant women with significantly higher levels in samples of GDM women. On contrary, 2-hr PPBG levels were significantly lower in NP/ND women compared to women of other groups, and in samples of pregnant women compared to in samples of NP/D with non-significant differences between pregnant women. Mean levels of FBG and 2-h PPBG estimated in 24-GW samples of non-GDM women were significantly higher than in samples of NP/ND women but were significantly lower than in samples of NP/D and GDM women. However, mean levels of FBG estimated in 24-GW samples of GDM women were significantly and non-significantly higher than in samples of NP/ND and NP/D women, respectively. On the other hand, 2-h PPBG levels in 24-GW samples were significantly higher in samples of pregnant than in samples of non-pregnant women (Fig. 3). At enrolment mean HbA1c% in NP/ND was significantly higher than that of women of other groups and that determined at 24-GW of non-GDM women but was non-significantly higher than percentage determined at 24-GW of GDM women. Mean HbA1c% in GDM at enrolment and 24-GW was significantly higher in comparison to that of non-GDM, and both were significantly higher than the HbA1c% of NP/ND women (Table 3).

Table (3): Glycemic status of studied women that was assessed at the time of enrolment and time of diagnosis of GDM for pregnant women

Group Data		NP/ND (n=20)	NP/D (n=20)	GDM (n=132)	Non-GDM (n=37)
Enrolment 75-OGTT (mg/dl)	FBG	80±4.4	89.6±5.3*	81.7±4†	84.5±3.4†‡
	2-h PPBG	98.2±5.8	134.6±8.2*	128.4±7.4*†	129.6±7*†
24-GW 75-OGTT (mg/dl)	FBG			85.6±3.5*†	90.9±6.1*‡
	2-h PPBG			122.4±9.2*†	138.7±22*†‡
HbA1c (%)	Enrolment	4.47±0.5	6.9±1.3*	4.5±0.5†	5.1±0.9*†‡
	24-GW			5.5±0.6*†	6.4±1.2*‡

Mean and standard deviation; *: significant difference versus non-diabetic non-pregnant women; †: significant difference versus diabetic non-pregnant women; ‡: significant difference versus non-GDM; symbols indicate significance at P<0.001

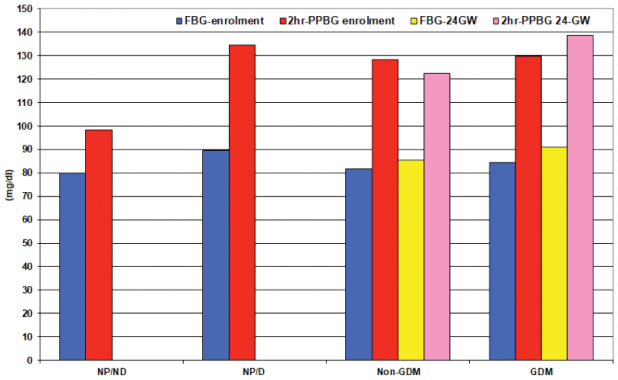

Fig. (3): Mean blood glucose measures in samples of studied women

At-enrolment means serum levels of TNF-α in a sample of NP/ND were significantly lower than in samples of women of other groups with non-significant differences between women and the later women. At-enrolment means serum levels of VEGF were significantly higher in NP/D and GDM women, while were non-significantly higher in non-GDM women compared to NP/ND. Moreover, at-enrolment serum VEGF levels were significantly lower in pregnant women compared to NP/D women with significantly lower levels in non-GDM than in GDM women (Table 4).

Table (4): Serum levels of TNF-α and VEGF estimated in enrolment samples of women of studied groups

Group Data	NP/ND (n=20)	NP/D (n=20)	GDM (n=132)	Non-GDM (n=37)
TNF-α (ng/ml)	1.9±0.46	2.67±0.79*	2.7±0.81*	3.14±0.86*
VEGF (pg/ml)	107.5±14.2	160±22.2*	100.6±20.7†	129±34.2*†‡

Mean and standard deviation; *: significant difference versus non-diabetic non-pregnant women; †: significant difference versus diabetic non-pregnant women; ‡: significant difference versus non-GDM; symbols indicate significance at P<0.001

The ROC curve analysis for the at-enrolment data as predictors for GDM development during pregnancy stratified these data as shown in table 4 and figure 4 according to the significance of the calculated area under the curve (AUC). Linear regression analysis for the variate with significant AUC defined high plasma TC and serum VEGF and TNF-α as the most significant predictors for GDM during pregnancy progress.

Table (5): Statistical analyses of enrolment data of pregnant women as predictors for the development of GDM at the 24th GW

Methods Variate	ROC Curve analysis				Regression analysis	
	AUC	SE	P	95% CI	β	P
Age (years)	0.482	0.046	0.700	0.392-0.572	0.055	0.932
BMI (kg/m^2)	0.643	0.043	0.002	0.558-0.728	0.168	0.010
plasma TC (mg/dl)	0.776	0.038	<0.001	0.701-0.852	0.338	<0.001
Serum VEGF (pg/ml)	0.731	0.042	<0.001	0.649-0.812	0.287	<0.001
Serum TNF-α (ng/ml)	0.635	0.004	0.003	0.548-0.721	0.166	0.008

ROC curve: Receiver Operating Characteristics curve; AUC: Area under the curve; CI: Confidence interval; β: Standardized coefficient; BMI: Body mass index; TC: Total cholesterol; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α

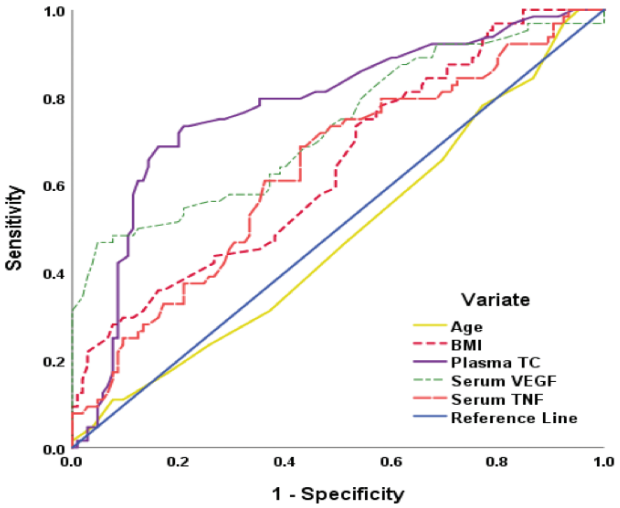

Fig. (4): ROC curve analysis for at-enrolment data for the development of GDM at the 24th GW

Kaplan-Meier Regression analysis showed that the risk for the development of GDM was increased by 50% at a plasma TC level of 217 mg/ml (95%CI: 215.2-218.8), serum VEGF at 137 pg/ml (95%CI: 132.2-151.8) and TNF-α level at 3.49 (95%CI: 3.35-3.97) as shown in figure 5a-c.

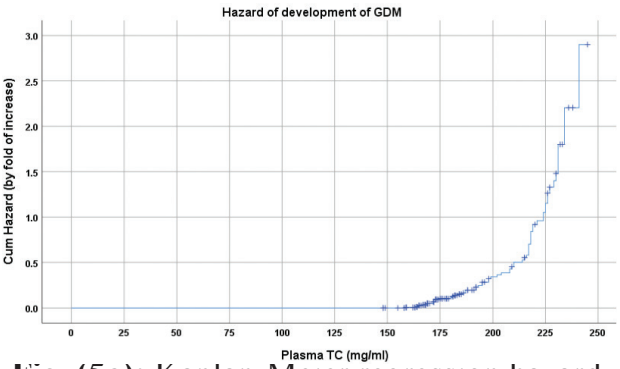

Fig. (5a): Kaplan-Meier regression hazard curve for at enrolment plasma TC for development of GDM at the 24th GW

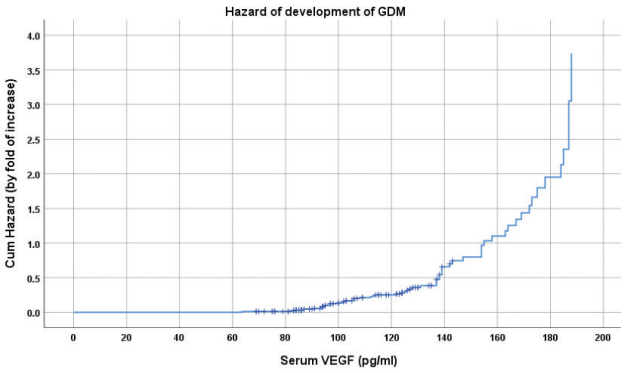

Fig. (5b): Kaplan-Meier regression hazard curve for at enrolment serum VEGF for development of GDM at the 24th GW

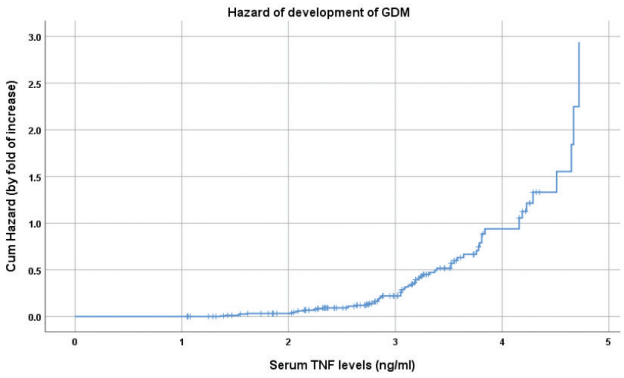

Fig. (5c): Kaplan-Meier regression hazard curve for at-enrolment serum TNF-α for development of GDM at the 24th GW

Test validity evaluation defined high serum VEGF at a cutoff point of 137 pg/ml had the highest sensitivity and negative predictive value for discriminating women liable to develop GDM during pregnancy, while high TC level at a cutoff point of 217 mg/ml had the highest specificity and both had nearly equal accuracy of prediction.

Table (6): Test validity characters of the cutoff points of the predictors for the development of GDM at the 24th GW

	Plasma TC (217 mg/ml)	Serum VEGF (137 pg/ml)	Serum TNF-α (3.49 ng/ml)
Sensitivity (%)	74.3 (95% CI: 56.7-87.5)	85.7 (95% CI: 69.7-95.2)	53.9 (95% CI: 37.2-69.9)
Specificity (%)	78.7 (95% CI: 70.4-85.6)	74.6 (95% CI: 66.4-81.7)	66.9 (95% CI: 58.1-74.9)
PPV (%)	50 (95% CI: 40.3-59.7)	46.9 (95% CI: 39-97.8)	32.8 (95% CI:25-41.7)
NPV(%)	91.4 (95% CI: 85.8-95)	95.2 (95% CI: 89.8-97.8)	82.9 (95% CI: 77.1-87.4)
Accuracy (%)	77.7 (95% CI: 70.4-84)	76.9 (95% CI: 69.8-83)	63.9 (95% CI: 56.2-71.1)

PPV: Positive Predictive Value; NPV: Negative Predictive Values; TC: Total cholesterol; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α

Discussion

The estimated glycemic parameters showed deterioration of glucose homeostasis with pregnancy as evidenced by the higher BG levels and HbA1c% at the 24th GW concerning the at-enrolment levels. These findings point to the diabetogenic phenotype of pregnancy, irrespective of reaching the diagnostic level of GDM or not, and go in hand with the previous animal models that approved the diabetogenic nature of pregnancy [16, 17].

This diabetogenic status of pregnancy was recently attributed by Amabebe & Anumba [18] to the alteration of gut microbiota which is responsible for the promotion of the metabolic changes required by the mother and fetus and in late pregnancy these microbiota shifts maternal metabolism in a diabetogenic direction, but if these alterations occurred earlier during pregnancy, the diabetogenic phenotype may develop during the second trimester resulting in GDM status.

At the 24th GW, 37 women developed GDM, while BG levels of the remaining 1325 women were under the diagnostic levels for GDM. This finding indicated the individual variations in response to the glycemic effect of pregnancy and was explained by Artunc-Ulkumen et al. [19] on genetic bases due to under-expression of the "a disintegrin and metalloproteinase with thrombospondin motifs-9" (ADAMTS-9) gene in GDM women than in non-GDM women. Recently, Lu et al. [20] detected placental methylation and expression profiles that mirror the molecular characteristics of IR and T2DM in the placentas of women who developed GDM. Moreover, Franzago et al. [21] found DNA methylation levels at CpG1 on the maternal side of the placentas were positively related to 2-h PPBG on 75-OGTT. On the other hand, Karagoz et al. [22] attributed the development of GDM to increased levels of apelin that inhibit the sodium-dependent glucose transporter leading to reduced intracellular glucose transport with subsequent hyperglycemia.

The detected lower serum levels of VEGF in samples of non-GDM women in comparison to NP/ND women indicated that normal pregnancy is associated with decreased levels of VEGF. On the other hand, in samples of GDM women, VEGF levels were higher than in NP/ND and non-GDM women, thus pointing to a possible relation between disturbed glucose homeostasis in the diabetogenic direction and increased levels of VEGF. In support of this assumption, serum VEGF levels were significantly higher in NP/D women than in women of other groups.

These findings go in hand with previous studies that reported higher levels of VEGF in GDM women than in control pregnant or non-pregnant women [23, 24]. Further, Sirico et al. [25] detected higher expression levels of VEGF in the placentas of GDM women than in controls, and the VEGF positivity was associated with the presence of GDM. In a trial to explain the pathogenesis of this relation; Dong [26] found a significant correlation between the risk of GDM and higher VEGF polymorphisms and its expression and Shi et al. [27] detected upregulated expression levels of placental receptor for advanced glycation end products and VEGF in GDM placentas. Recently, the reported relation was attributed by Zheng et al. [28] to the downregulation of expression levels of microRNA195-5P that was detected to be negatively correlated to VEGF levels in GDM mouse placental tissues.

Serum levels of TNF-α were significantly higher in pregnant and NP/D women than in NP/D women with non-significantly higher levels in GDM women than other women. These findings indicated the presence of an association between pregnancy and diabetes and this inflammatory adipocytokine, irrespective of being pathogenic or resultant relation. Similarly, multiple previous and recent studies detected higher levels of inflammatory biomarkers in GDM women than in women who had normal

pregnancies [23, 29]. A recent study attributed the relation between high blood glucose and inflammatory markers to the high incidence of small intestinal bacterial overgrowth that may increase maternal blood glucose by affecting inflammatory response [30].

At-enrolment plasma lipids at-enrolment were significantly higher in women going to have GDM than non-GDM and NP/ND women, and statistical analyses defined high TC levels as a predictor for oncoming GDM with a high specificity rate. Similarly, Cibickova et al. [31] detected high TG and non-HDL levels in women who had high BG on 75-OGTT in the 2nd trimester than in non-GDM pregnant women. Also, Yang et al. [32] detected a relationship between constituents of metabolic syndrome and pregnancy complicated by GDM and found TC levels can predict this complication. Moreover, Zhong et al. [33] using lipidomics analyses found significant associations between dysregulated lipids concentrations and maternal glucose. Multiple trials were conducted to explore the relationship between high lipid and glucose measures during pregnancy; Jiang et al. [34] detected significant downregulation of glycerolphospholipid metabolism in GDM women with a negative correlation between phosphatidyl-choline and –ethanolamine levels and maternal BG concentration, while the correlation was positive with triacylglycerol levels. Further, Luo et al. [35] reported a positive relationship between levels of several key lipid metabolites as γ-linolenic acid, and heptadecanoic acid and BG levels in GDM, while Attique et al. [36] attributed the coincidence of GDM and dyslipidemia in pregnant women to the disturbing levels of neuregulin-4.

Conclusion

GDM may be related to the interplay between high levels of VEGF, inflammatory cytokines, and hyperlipidemia. High blood levels of VEGF and TC can discriminate against women vulnerable to developing GDM with high sensitivity, specificity, and negative predictive values.

Recommendations

Estimation of blood levels of lipid and VEGF before pregnancy is recommended to be applied in health awareness programs to allow time for procedures applied to reduce these levels if were found to be high.

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Diagnostic accuracy of Trans-cerebellar diameter for estimation of gestational age and prediction of fetal weight in diabetic patients

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Ethical approval:
Study protocol was approved by the institutional board of ethics, and informed consents were obtained from all subjects included in the study.

Conflict of interest: No conflict of interest.

Financial support: No financial support.

Abstract

Objectives: To evaluate the diagnostic accuracy of TCD in prediction of gestational age and fetal weight in diabetic patients.

Subjects and methods: This prospective cross-sectional study was conducted on 84 pregnant women at third trimester of pregnancy who attended the antenatal care in the outpatient clinic at our hospital during the period from November 2019 to November 2021. Measurements of the TCD was performed and correlated with gestational age based on last normal menstrual period (LNMP)as well as estimated fetal weight. The study was approved by the Ethics Committee, and all patients gave their informed consent before inclusion in the study.

Results: The mean age± SD ratio of the study group was 29.45±6.16years. The study group included 84 consecutive diabetic pregnant women; 2 females with diabetes type A1 (2.4%), 28 females with diabetes type A2 (33.3%), 33 females with diabetes type B (39.3%), and 21 females with diabetes type C (25%)..The mean fetal TCD± SD ratio at 32-34 weeks was 40.17±2.95mm and at 37 weeks was 50.42±3.04 mm. we found that there is a statistically significant positive correlation between TCD and estimated fetal weight at 32-34 weeks ($r= 0.294$, $p= 0.007$) and at 37 weeks ($r= 0.475$, $p < 0.001$).TCD has 94.1% accuracy in detection of the actual gestational age at 32-34 weeks and 95.2% accuracy in detection of the actual gestational age at 37 weeks.

Conclusion: The current study has demonstrated that there is a statistically significant positive correlation between TCD and Estimated fetal weight at third trimester of pregnancy. TCD can be used as an accurate reliable method for the assessment of gestational age in third trimester. We recom-

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mend to conduct this study on larger sample size for further documentation of the proposed assumption.

Keywords: Trans-cerebellar diameter, Gestational age, Fetal weight, Diabetic patients.

Introduc tion

Diabetes is the most common medical problem with pregnancy. Approximately 90% of these cases are those having gestational diabetes mellitus (GDM) that affects 2–5% of all pregnancies, while preexisting type 2 diabetes accounts for 8% of such cases (1).

Poor control of preexisting (pregestational) or gestational diabetes during organogenesis period (up to about 10 wk. gestation) increases the risk of major congenital malformations and spontaneous abortion; while, poor control of diabetes later in pregnancy increases the risk of fetal macrosomia, preeclampsia, shoulder dystocia, cesarean delivery and stillbirth (2).

It has been suggested that the diabetic environment may have undesired effects on placental function and development. It is important to be precise that these effects will depend on the time period in pregnancy (3).

The fetal growth profiles leading to macrosomia in diabetic pregnancies should be known to understand the pathophysiology, because it may help to design preventive strategies, however; there is limited general information on the growth profiles in diabetic pregnancies. Previous studies in such pregnancies had indicated that fetal growth accelerates between 18 and 24 weeks' gestation (4).

The keystone in decision-making about the optimal timing of delivery in diabetes in pregnancies is the accurate knowledge of fetal gestational age (FGA), as about 10% - 45% of women do not know their last menstrual period (LMP) and at times they first attend the antenatal clinics in their last trimester of pregnancy (5). This may result in iatrogenic premature deliveries, leading to increased perinatal morbidity and mortality.

Estimation of gestational age using ultrasonographically derived fetal parameters such as Biparietal diameter (BPD) and femur length (FL) is perhaps the cornerstone in obstetrics and is an important component in the management of pregnancies (6).There are some limitations with using such parameters such as BPD and HC after 26 weeks as they may be unreliable in cases of moulding of fetal skull (7). Also, is unreliable to use femur length in calculation of gestational age in some cases like achondroplasia. A new parameter for estimation of gestational age has been developed which is trans-cerebellar diameter (TCD).

Fetal cerebellum can be detected as early as 10-11 weeks gestation by ultrasound. From the second trimester onwards, it grows in a linear correlation with gestational age. Trans-cerebellar diameter is least affected by external factors as it is surrounded by dense petrous bone which allows its use for estimating GA even in third trimester (8).

TCD is the least affected parameter in cases of growth restriction, so accurate gestational age can be predicted with it (8). TCD measurement has been evolved as a novel parameter and has been proposed to be more precise in the assessment of GA (9). This study was conducted to evaluate the accuracy of TCD over other parameters of gestational age of 30-40 weeks.

Patients and methods

This prospective cross sectional study was conducted on 84 diabetic pregnant patients between 32-34 weeks of pregnancy, during the period from November 2019 to November 2021 at outpatient clinic of our hospital; the institutional ethical review board approved the study.

The study was conducted at the outpatient clinic to determine the correlation between transverse cerebellar diameter (TCD) and gestational age in third trimester of pregnancy as well as estimated fetal weight.

Inclusion and exclusion criteria

All patients were diagnosed as controlled pre-gestational or gestational diabetes, with singleton and non-anomalous fetuses, who were sure of dates calculated by first day of last normal menstrual period. Pregnant women with anomalous fetus on ultrasound, medical disorders like hypertension, chronic renal disease, intra uterine death (IUD), multiple gestations on ultrasound, accidental hemorrhage and premature rupture of membranes were excluded from the study.

Maternal data:

- Patient's history, age, height, BMI, parity and LMP were recorded.
- Type of diabetes according to White classification(10) was recorded

Fetal data:

- Fetal measurements were done using Mindray DC-40 ultrasound equipment at 32-34 and at 37 weeks of gestation to measure fetal trans-cerebellar diameter (TCD), biparietal diameter (BPD), abdominal circumference (AC) and femur length (FL) at 32-34 and at 37 weeks of gestation.
- TCD was measured at 90 degree to the long axis of the cerebellum across its widest point, using the outer to outer method.
- Measurement of estimated fetal weight by ultrasound (by femur length, bi-parietal diameter and abdominal circumference) at 32-34 and at 37 weeks of gestation, based on
- Hadlock2:Log10 (weight) = 1.335 – (0.0034 X AC X FL) + (0.0316 X BPD) + (0.0457 X AC) + (0.1623 X FL). (11)
- Measurement of actual neonatal birth weight.

Sample size

The calculated sample size of the study will be 84 participants at 5%level of significance and 80% power of the study, using the following formula **(Daniel, 1999)**.

$$n = \frac{Z2 * P* (1-P)}{d^2}$$

Where

Z = 1.96 for 95% confidence level.
p = expected percentage of correlation between TCD and FL (94.2%).
d = precision (Margin of error) = 0.05 (15)

Ethical consideration

Written informed consents were taken from the participants after being informed about the objectives and purposes of the study. Confidentiality and privacy had been maintained throughout the study.

Statistical analysis

The collected data were analyzed using the Statistical Package of Social Science **(SPSS)** program for Windows (Standard version 21). Mean ± standard deviation was computed for demographic data, estimated fetal weight, and trans-cerebellar diameter (TCD). Association between categorical variables was tested using Chi-square test. The study groups were compared with ANOVA test. The results were considered significant when p value ≤ 0.05.

Results

This study was conducted on 84 consecutive diabetic pregnant women; 2 females with diabetes type A1 (2.4%), 28 females with diabetes type A2 (33.3%), 33 females with diabetes type B (39.3%), and 21 females with diabetes type C (25%) figure (1).

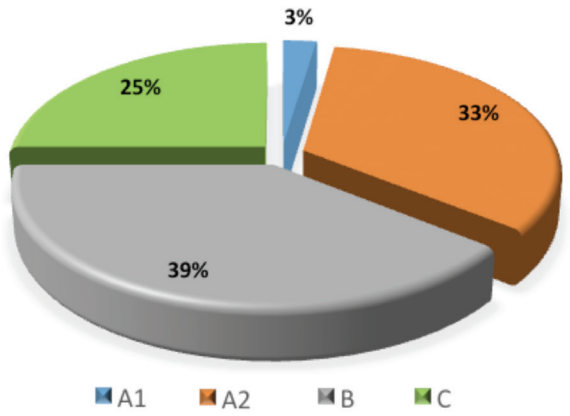

Figure (1): Type of diabetes among the studied group

The demographic characteristics showed no statistically significant difference ($P \geq 0.05$) among studygroups as regard age and parity. However;the maternal weight was a statistically significant different between study groups (P=0.001), as shown in table (1).

Table (1): Demographic data among studied groups.

	TypeA1 n=2 (2.4%)	TypeA2 n=28 (33.3%)	TypeB n=33 (39.3%)	Type C n=21 (25%)	Total n=84 (100%)	Test of significance (p value)
Maternal age (years)	22.5±3.54	28.54±6.12	28.94±5.73	32.14±6.26	29.45±6.16	0.057
Maternal weight Mean ± SD	88.5±4.95	79.96±6.54	87.61±7.45	85.90±7.06	84.65±7.70	0.001
Parity Mean ± SD	0.00±0.00	1.43±0.99	1.45±0.97	1.76±0.99	1.49±1.00	0.103

As shown in table (2) and figure (2), the mean fetal weight at 32-34 weeks was 2291.44±173.02 grams, at 37 weeks was 3117.79±460.86 grams, and at birth was 3363.3±436.39 grams with no significant difference between study groups.

Table (2): Association between type of DM and fetal weight

	TypeA1 n=2 (2.4%)	TypeA2 n=28 (33.3%)	TypeB n=33 (39.3%)	Type C n=21 (25%)	Total n=84 (100%)	Test of significance (p value)
Estimated Fetal weight at 32-34 Mean ± SD	2300± 70.71	2303.82± 169.68	2275.93± 188.37	2298.47± 166.36	2291.44± 173.025	0.933
Estimated Fetal weight at 37 Mean ± SD	2846.5± 43.13	3173.92± 430.67	3043.82± 461.65	3185.05± 514.20	3117.79± 460.86	0.500
weight at birth Mean ± SD	3325± 35.35	3425± 399.51	3310± 415.08	3367± 537.61	3359.75± 436.49	0.793

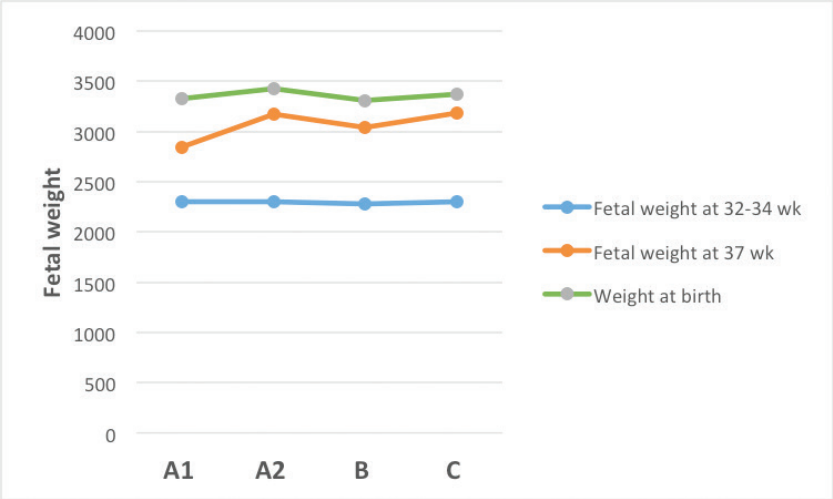

Figure (2): Association between type of DM and fetal weight

As shown in table (3), the mean TCD at 32-34 weeks was 40.17±2.95 mm and at 37 weeks was 50.42±3.04 mm with no significant difference between study groups.

Table (3): Association between type of DM and TCD

	TypeA1 n=2 (2.4%)	TypeA2 n=28 (33.3%)	TypeB n=33 (39.3%)	Type C n=21 (25%)	Total n=84 (100%)	Test of significance (p value)
TCD at 32-34 weeks Mean ± SD	38.50± 0.71	40.53± 2.50	40.48± 2.76	39.33± 3.75	40.17± 2.95	0.377
TCD at 37 weeks Mean ± SD	50.00± 0.0	51.21± 2.11	50.51± 3.17	49.24± 3.74	50.42± 3.04	0.162

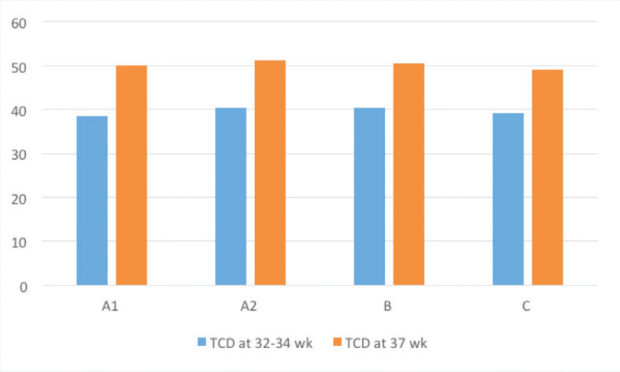

Figure (3): Association between type of DM and TCD

There was a statistically significant positive correlation between TCD and Fetal weight at 32-34 weeks (r= 0.294, p= 0.007) and at 37 weeks (r= 0.475, p < 0.001) as seen in table (4) and figure (4&5).

Table (4): Correlation between TCD at estimated fetal weight

	r	P value
TCD &EFW at 32-34 weeks	0.294	**0.007***
TCD &EFW at 37 weeks	0.475	**≤0.001***

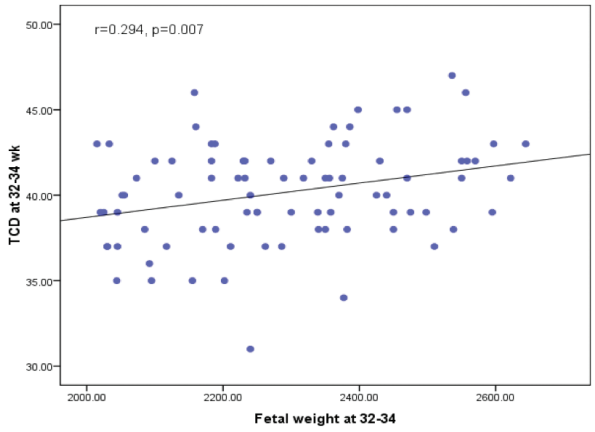

Figure (4): Scatter diagram for positive correlation between TCD at 32-34 wk and fetal weight at 32-34 wk

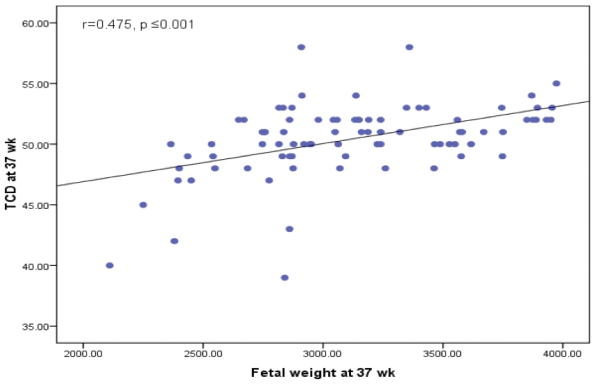

Figure (5): Scatter diagram for positive correlation between TCD at 37 wk and fetal weight at 37wk

TCD has about 94.1% accuracy in detection of the actual gestational age at 32-34 weeks, and it has about 95.2% accuracy in detection of the actual gestational age at 37 weeks.

Table (5): Diagnostic accuracy of TCD in detection of GA

	Actual GA (calculated by first date of LNMP)	Gestational age by TCD	P value
GA at 32-34 weeks True False	 84 (100%) 0 (0%)	 79 (94.1%) 5 (5.9%)	0.059
GA at 37 weeks True False	 84 (100%) 0 (0%)	 80 (95.2%) 4 (4.8%)	0.121

Fischer exact test was used

Discussion

The transverse cerebellar diameter (TCD) is considered one of the most reliable growth ultrasound parameters, especially in early gestation. The fetal cerebellum that consists of a midline part called the vermis and two lateral hemispheres displays progressive growth over the entire gestation period, thus, it can be used to predict GA during pregnancy (12).

The TCD is a reliable indicator of GA in the fetus and can be an alternative to other parameters, particularly when GA cannot be determined by routine methods of early pregnancy scanning or the date of the last menstrual cycle (13). Despite this, to the best of our knowledge, no previous studies have assessed the role of TCD in assessment of gestational age in the diabetic pregnant mothers only. For this reason, the current study was conducted to evaluate the diagnostic accuracy of trans-cerebellar diameter in prediction of gestational age and fetal weight in diabetic patients.

This study was conducted on 84 consecutive diabetic pregnant women; 2 females with diabetes type A1 (2.4%), 28 females with diabetes type A2 (33.3%), 33 females with diabetes type B (39.3%), and 21 females with diabetes type C (25%). In the current study, TCD has 94.1% accuracy in detection of the actual gestational age at 32-34 weeks and 95.2% accuracy in detection of the actual gestational age at 37 weeks.

Previous research studies that were performed on TCD measurements evaluation, clearly displayed and showed that TCD was a reliable trusted tool of measurement to calculate the fetal gestational age, it is believed to be more reliable than HC, BPD, FL and AC when the precise fetal gestational age calculation was desired. It could be even considered a dependable and reliable tool of measurement helping the settled formulas of fetal gestational age in either singleton or twin gestation (14).

In a previous study, it was found that TCD measurement had accuracy of 91.7% at 36 weeks of gestation (13). In the cross sectional study by Chavez MR et al, TCD accuracy in third trimester was found to be 94.0% which supports our study predictability (15). Dilmen et al, had studied 330 pregnant women and found a very close relation between TCD and estimated GA.(16)

Another research was applied on 50 patients from the start of the 2ndtrimester till term. TCD measurement was used to detect the gestational age. There was a significant relationship between TCD and GA, concluding that TCD is a useful and an accurate tool for GA estimation (17).

Another retrospective, cross-sectional analytic study of normally developing fetuses

and 73 fetuses with IUGR between 24 and 34 weeks gestation was done, researchers found that the TCD measurements are spared in cases of IUGR.(18).

In the current study, there is a statistically significant positive correlation between TCD and estimated fetal weight at 32-34 weeks ($r= 0.294$, $p= 0.007$) and at 37 weeks ($r= 0.475$, $p < 0.001$). Prssad and Likhitha detected a good correlation between the GA and TCD throughout the third trimester and even in the case of Intrauterine growth retardation (IUGR) (12). Akl et al. performed a research in Egypt conducted in the third trimester of 150 pregnant women to evaluate the accuracy of TCD in the assessment of GA, and concluded that TCD is a reliable tool for assessing gestational age in the third trimester of pregnancy (19).

Reddy et al. Evaluated accuracy of predicting GA using the fetal trans-cerebellar Diameter (TCD) and comparing TCD with other existing GA parameters in 15 to 40 weeks of gestation. It was shown that TCD is a reliable measure in the calculation of gestational age in the second and third trimesters, since its value is closely related to those of GA by LMP. It can be also a good predictor of gestational age compared to other parameters, especially in the third trimester (20).

The main strength point of this study is that it is the first study to assess the diagnostic accuracy of TCD in estimating the GA and determining the correlation with the fetal weight and the type of diabetes in the included cases.

The main limitation of the current study is the small sample size and being a single center study, which limit the power of the obtained results. Also, we didn't perform correlation between TCD and other sonographic fetal measurements. Further studies may be required to overcome these limitations.

Conclusion

The current study has demonstrated that there is a statistically significant positive correlation between TCD and Estimated fetal weight at third trimester of pregnancy. TCD can be used as an accurate reliable method for the assessment of gestational age in third trimester. We recommend to conduct this study on larger sample size for further documentation of the proposed assumption.

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Legends to tables:
Table (1): Demographic data among studied groups.
Table (2): Association between type of DM and fetal weight.
Table (3): Association between type of DM and TCD.
Table (4): Correlation between TCD at estimated fetal weight
Table (5): Diagnostic accuracy of TCD in detection of GA.

Legends to figures:
Figure (1): Type of diabetes among the studied group.
Figure (2): Association between type of DM and fetal weight.
Figure (3): Association between type of DM and TCD.
Figure (4): Scatter diagram for positive correlation between TCD at 32-34 wk and fetal weight at 32-34 wk.
Figure (5): Scatter diagram for positive correlation between TCD at 37 wk and fetal weight at 37 wk.

List of abbreviation:
AC: Abdominal circumference
BMI: body mass index.
BPD: Bi parietal diameter
FL: Femur length
IUGR:intrauterine growth restriction.
SD:standard deviation.
SPSS: Statistical Package of Social Science.

A Reversible Drawback Effects Of COVID 19 mRNA Vaccine On Semen Parameters Of Fertile Male

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Abstract

Objectives: To determine the impact of COVID-19 vaccine on semen parameters in an Egyptian population sample of previously proved fertile males.

Design: Prospective observational research.

Patients and methods: The study was conducted on 30 males proved to have normal semen parameters, on list of ICSI due to female factors of infertility, and received the two doses of mRNA COVID vaccine. Following the second dose of the vaccine, two samples of semen were obtained from all the subjects under the study, after 3 months and 6 months respectively . Parameters of sperm quality were examined. All semen specimens were tested throughout conformance with WHO sperm assessment guidance.

Results: The participants average age was (38.13 ± 5.27); at different period of follow up (at baseline, after 3 months and after 6 months). There was no significant difference in sperm volume among variables after 3 and 6 months (p3= 0.118). There was a significant difference in the sperm concentration between the base line and after 3 months (p1= 0.003); there was no significant difference in sperm concentration between base line and after 6 months (p2= 0.211). There was a significant difference in sperm count among variables after 3 and 6 months (p3= 0.005).

There was a significant difference in sperm progressive motility (%) between base line and after 3 months (p1= 0.007). There was no significant difference in sperm morphology (percentage) between variables after 3 and 6 months (p3= 0.096). There was significant difference in sperm DNA fragmentation (%) between base line and after 3 months (p1= 0.011). There was no significant difference in non –sperm cells /ml among variables after 3 and 6 months (p3= 0.186).

Conclusion: The sperm count and concentration, sperm motility were decreased 3 months post vaccination and return to average 6 months post vaccination. The sperm DNA fragmentation index is raised beyond limits 3 months post vaccination and return to normal limits 6 months post vaccination. The effect of mRNA vaccine on semen parameters is transient and reversible . The criteria of the sperm after obtaining the vaccine of COVID-19 were mostly within normal

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range intervals. The findings support the notion that COVID-19 vaccine is free from risk.

Keywords: COVID-19 vaccine, Sperm DNA fragmentation, Sperm parameters.

Background

The World Health Organization has announced coronavirus disease 2019 (COVID-19) as a global pandemic since March 11, 2020 .[1] The pandemic, also known as the SARS-CoV-2 pandemic, has imposed huge pressure on health care systems around the world .[2,3]

The SARS-CoV2 mainly transmits through respiratory droplets [4] and has been also observed in different biological fluids including blood, urine, and feaces .[5] Due to the blood-testis barrier (BTB), testis is partially immune to many microorganisms [6]; however, some viruses such as the mumps virus have the ability to cross the BTB and cause localized testis inflammation in forms of orchitis [8]. On the other hand, angiotensin-converting enzyme 2 (ACE2) and viral spike (S) protein, the mediators for SARS–COV-2 entrance into the target cells, mainly exist in human testis . [9,10]

Several findings indicated sexual transfer of COVID-19 infection via males; in addition to the existence of the virus in testis and semen in the acute and recovering phases. [11] SARS-CoV2 has the capacity to penetrate the male genital tract due to an incomplete blood-testis/vas deferens/epididymal barrier, particularly when there is systemic local inflammatory condition.[12] Furthermore, due to the virus's inability to reproduce inside the sex organs, it may hang most likely due to the testicle special immunity. Nonetheless, the viruses existence in sperms is not uncommon.[13,14,15] Oxidative stress and increased apoptosis are between the factors proposed to explain the negative effects of COVID-19 on the quality of sperms[16,17] , in addition to synergistic negative effects of impaired (ACE 2) signaling pathway .[18,19] Generally speaking, the COVID19 vaccine has been demonstrated to be greatly efficacious and useful for the general public. [20,21] Two widely used types of COVID -19 vaccines, Messenger RNA (mRNA) vaccine and inactivated virus vaccine. Messenger RNA vaccine is taken in two doses 28 days apart whereas the inactivated virus vaccine is given in two doses 14 days apart.[21]

The present study concerns with detection of the influence of mRNA vaccine ,after two doses ,on the different semen parameters in previously proven fertile males on waiting list of ICSI due to female factors.

Materials and method

Study setting : This prospective observational research was done at a single large reputable institution in Alexandria.

Study Design : Prospective observational research.

Study subjects : The study was conducted on 30 males proved to have normal semen parameters, on list of ICSI due to female factors of infertility ,and received the two doses of mRNA COVID vaccine.

Sample size calculation: The information was gathered and entered into the computer. The Statistical Package for Social Sciences (SPSS/version 22) software was used for statistical analysis. The F-test (ANOVA) was used, followed by a hoc test to detect the significance between the two groups. The significance level was set at 0.05.

Sampling technique : Following the second dose of the vaccine, two samples of semen were obtained from all the subjects under the study , after 3 months and 6 months respectively . Parameters of sperm quality were examined. All semen specimens were tested throughout conformance with WHO sperm assessment guidance.

All semen samples were measured for sperm volume in ml , sperm concentration / ml ,

Total sperm count in the specimen , sperm progressive motility , sperm morphology , sperm DNA fragmentation index , and non- sperm cells / ml . The WHO laboratory manual for the examination and processing of human semen , variables and Cut- off values used in the study are shown in the next table **(Table 1)**.

variable	Cut- off value
Sperm volume	< 1.5 ml
Sperm concentration	< 15 million / ml
Total Sperm count	< 39 million
Sperm progressive motility (A+B)	< 32%
Sperm morphology	< 4%
Non- Sperm cells	> 1 million / ml

Sperm DNA fragmentation index (DFI) was determined; using the following interpretation values ≤ 15% (good fertility potential) , 15-25% (average fertility potential) ,and > 25% (poor fertility potential) **(Evenson et al., 2002)** .

The values of semen parameters in the basal specimens before the vaccine and the values of semen parameters after two doses of mRNA vaccine, taken three and six months respectively, are compared to detect any significant changes caused by the effect of the vaccine.

Results

Our study population included 30 males aged between (29-46) years with a mean age of (38.13 ± 5.27) , (56.67%) were aged between (30-40) years, (36.67%) were >40 years , and (6.67%) were < 30 years. **The age of the studied subjects is depicted in Table 2 .**

Table (2): Age distribution among the studied group

Age	No	%
<30	2	6.67
30-40	17	56.67
>40	11	36.67
Range	29-46	
Mean	38.13	
SD	5.27	

At different period of follow up, sperm volume, concentration and total sperm count were described in Table (3).

The mean sperm volume at baseline was (2.88 ± 0.62); after 3 months (2.67 ± 0.57) and after 6 months (2.85 ± 0.61). There was no significant difference in sperm volume between base line and after 3 months (p1= 0.092); There was no significant difference in sperm volume among base line and after 6 months (p2= 0.439) and there was no significant difference in sperm volume among variables after 3 and 6 months (p3= 0.118).

The mean sperm concentration at baseline was (29.08 ± 5.30); after 3 months (18.6 ±3.58) and after 6 months (28.92 ± 5.12).

There was a significant difference in the sperm concentration between the base line and after 3 months (p1= 0.003); there was no significant difference in sperm concentration between base line and after 6 months (p2= 0.211) and there was a significant difference in sperm concentration between variables after 3 and 6 months (p3= 0.001). The mean sperm concentration declined

3 months post-vaccination and return to average values 6 months post-vaccination .

The mean sperm count at baseline was (71.32 ± 21.84); after 3 months (28.1 ± 8.21) and after 6 months (68.00 ± 21.64).

There was a significant difference in sperm count between base line and after 3 months (p1= 0.001) there was no significant difference in sperm count between base line and after 6 months (p2= 0.263) and there was a significant difference in sperm count among variables after 3 and 6 months (p3= 0.005). The mean sperm count declined 3 months post-vaccination and return to average values 6 months post-vaccination.

Table (3): Sperm volume, concentration and total sperm count at different period of follow up

	At base line "n=30"	**After 3 months "n=30"**	**After 6 months "n=30"**	**ANOVA P value**	**P1 P2 P3**
Sperm volume (ml)					
Range	1.8-3.9	1.6-3.7	1.8-3.9		0.092
Mean	2.88	2.67	2.85	2.01	0.439
SD	0.62	0.57	0.61	0.465 N.S.	0.118
Sperm concentration (million/ml)					
Range	20.1-37.5	12-25	19.8-36.3		0.003*
Mean	29.08	18.6	28.92	29.85	0.211
SD	5.30	3.58	5.12	0.002*	0.001*
Total sperm count (million)					
Range	41.8-103.3	24-46	41.6-107.0		0.001*
Mean	71.32	28.1	68.00	24.1	0.236
SD	21.84	8.21	21.64	0.003*	0.005*

P1 comparison between base line and after 3 months.
P2 comparison between base line and after 6 months.
P3 comparison between variables after 3 and 6 months.

Sperm progressive motility and sperm morphology at different period of follow up were described in Table (4).

The mean sperm progressive motility (%) at baseline was (46.50 ± 5.04); after 3 months (30.0± 5.21) and after 6 months (42.5 ± 5.11). There was a significant difference in sperm progressive motility (%) between base line and after 3 months (p1= 0.007); and There was a significant difference in sperm progressive movement (percentage) between variables after 3 and 6 months (p3= 0.003).

The mean sperm morphological characters (%) at baseline was (8.97 ± 1.83); after 3 months (8.29 ± 1.69) and after 6 months (8.88 ± 1.80). There was no significant difference in sperm morphological characters (percentage) among base line and after 3 months (p1= 0.071); there was no significant difference in sperm morphology (percentage) between base line and after 6 months (p2= 0.430) and there was no significant difference in sperm morphology (percentage) between variables after 3 and 6 months (p3= 0.096).

Table (4): Sperm progressive motility and sperm morphology at different period of follow up.

	At base line "n=30"	After 3 months "n=30"	After 6 months "n=30"	ANOVA P value	P1 P2 P3
Sperm progressive motility (%)					
Range	39-56	18-42	37.3-55.0		0.007*
Mean	46.50	30.0	42.5	20.1	0.278
SD	5.04	5.21	5.11	0.003*	0.003*
Sperm morphology (%)					
Range	6-12	5.5-11.0	5.8-11.6		0.071
Mean	8.97	8.29	8.88	5.21	0.430
SD	1.83	1.69	1.80	0.106	0.096

Sperm DNA fragmentation index and non –sperm cells /ml results are showed in Table(5).

The mean sperm DNA fragmentation (%) at baseline was (22.3 ± 4.5); after 3 months (31.5 ± 5.12) and after 6 months (18.2 ± 3.01). There was significant difference in sperm DNA fragmentation (%) between base line and after 3 months (p1= 0.011) and there was a significant difference in sperm DNA fragmentation (%) between base line and among variables after 3 and 6 months (p3=0.017).

There was no significant difference in non –sperm cells /ml between base line and after 3 months (p1= 0.162); there was no significant difference in non –sperm cells /ml among base line and after 6 months (p2= 0.475) and there was no significant difference in non –sperm cells /ml among variables after 3 and 6 months (p3= 0.186).

Table (5): Sperm DNA fragmentation, non –sperm cell at different period of follow up.

	At base line "n=30"	After 3 months "n=22"	After 6 months "n=19"	ANOVA P value	P1 P2 P3
Sperm DNA fragmentation (%)					
Range	16-24	20-42	17-26		0.011*
Mean	22.3	31.5	18.2	16.41	0.097
SD	4.5	5.12	3.01	0.003*	0.017*
Non-sperm cells million/ml					
Range	0.4-0.9	0.4-1.0	0.4-0.9		0.162
Mean	0.62	0.67	0.62	3.12	0.475
SD	0.17	0.19	0.18	0.167	0.186

Discussion

COVID-19 infection has been found to affect negatively the reproduction in men, whether due to local or systemic inflammatory conditions (Orvieto et al., 2021).[20] The possibilities of sexual transfer of COVID-19 and influence on the reproductive axis were discussed in many previous researches. COVID-19 infection, according to Ma et al. (2020),[17] could result in altered sex hormone production and reduced fertility. Holtmann et al. (2020)[10] postulated that disease could affect sperm production and found that medium disease lowered semen grade in a significant manner when compared to controls.

The testicles don't produce enough of the male sex hormone testosterone in men recovered from COVID-19 (Salonia et al., 2022).[24] There is small proof that various COVID-19 vaccinations affect sperm parameters or male

fertility. Evidence of (mRNA) vaccines, viral vectors vaccines' short- to medium-term protection is accumulating (Reschini et al., 2022).[22]

The present study involved (30) cases with mean age (38.13 ± 5.27); in addition, more than half of cases were aged between (30-40) years.

Similar findings were obtained in previous studies; the study by Lifshitz et al., (2022) [15] included seventy five reproductive males with an average age of (38.6 4.3).Reschini et al., (2022)[22] study included 106 people with a median age of 39 [36–42] years. The average age of participants in the Safrai et al., (2021)[23] study was 37.1 years (±6.6), and the average time from first vaccine dose to sample collection was 33.6 days (± 20.2).

In the current study, there was no significant difference in sperm quantity among variables after 3 and 6 months (p3= 0.118). The mean sperm concentration declined 3 months post-vaccination and return to average values 6 months post-vaccination . The mean sperm count declined 3 months post-vaccination and return to average values 6 months post-vaccination.

Orvieto et al., (2021)[20] investigated thirty six married people who had IVF with sequential ovulatory stimuli periods before and after obtaining the messenger RNA COVID-19 vaccine. The Infertility factors, quantity of ovarian follicles, conception fee, and semen evaluations revealed no differences. Furthermore, after vaccination, the male partner's sperm parameters remained unchanged.

According to the research results of Lifshitz et al. (2022),[15] the semen variables after the COVID-19 vaccine have been largely inside the usual WHO reference ranges and did not alter any correlative deleterious impact from COVID-19 vaccine.

Reschini et al., (2022)[22] conducted a research on the effect of COVID-19 vaccine on male fertility in a group of infertile males from Assisted Reproductive Technologies married people in Italy. The COVID-19 vaccination had no impact on fertilization rate or sperm criteria, they revealed. That was correct just after a variety of vaccines were considered (messenger RNA or viral vector).

Safrai et al., (2021)[23] explored the role of the BNT162b2 vaccine on sperm parameters. There was no significant difference in semen volume, total sperm, or movement evaluation in men experiencing childbearing therapies before and after COVID-19 vaccination.

COVID-19 vaccines had no effect on reproductive capacity in both associates' men and women trying to fall pregnant (Wesselink et al., 2022).[27] Gonzalez et al., (2021)[7] investigated sperm variables before and after concurrent administration of a COVID-19 messenger RNA vaccine. There have been no big differences in any sperm measurement in this tiny sample of healthy males.

Gonzalez et al., (2021) [7] discovered that no males had become azoospermic after receiving the vaccine, and that at follow-up, 7 of the 8 oligospermic men would have risen sperm count to normozoospermic spectrum (median concentration, 22 million/mL [IQR, 17-25.5]), whereas one person stayed oligospermic..

In the current study, the mean sperm progressive motility (%) at baseline was (46.50 ± 5.04); after 3 months (30.0± 5.21) and after 6 months (42.5 ± 5.11), and there was a significant difference in sperm progressive movement (percentage) between variables after 3 and 6 months (p3= 0.003). There was no significant difference in sperm morphology (percentage) between variables after 3 and 6 months (p3= 0.096).

After the second vaccine dose, the median sperm concentration increased significantly to 30 million/mL (IQR, 21.5-40.5; P =.02) and the median total motile sperm count to 44 million (IQR, 27.5-98; P =.001). Both sperm volume and motility risen exponentially (Vishvkarma,Voysey et al., 2021). [25,26] The

longer period of abstinence before the second sampling could explain the increase.

The impact of BNT162b messenger RNA, and the COVID-19 disease vaccine on semen quality was explored by Barda et al., (2022). [2] Total sperm concentration and as a whole motile count rose just after second vaccine compared to pre-vaccination specimens. The proportion of motile sperm no longer kept switching after the vaccine.

Our results showed The mean sperm DNA fragmentation (%) at baseline was (22.3 ± 4.5); after 3 months (31.5 ± 5.12) and after 6 months (18.2 ± 3.01) with statistically significant difference in sperm DNA fragmentation (%) between baseline and after 3 months (p1= 0.011).

Throughout furthermore to those other sperm parameters, Haghpanah et al., (2021)[8] suggested assessing the sperm deoxyribonucleic acid fragmentation index (DFI) in COVID-19 patient populations to assess male fertility. The enhanced sperm DNA fragmentation index (DFI) in COVID-19 patient populations is due to testicular inflammatory response; enhanced ROS production causes sperm deoxyribonucleic acid destruction (Anifandis et al., 2020).[1]

It could even be noted that the sperm characteristics after COVID-19 vaccination have been mostly within normal range variations. The findings back up the idea that the COVID-19 vaccine is reliable.

Our research has both advantages and disadvantages. Our study's resilience is that it is the first to offer information about the effect of COVID-19 vaccine on sperm variables in an Egyptian population. However, the sample size was small.

It is necessary to collect a larger and more diverse sample. Furthermore, because mRNA technology is increasingly being used to develop new vaccines to treat a variety of conditions of particular public health importance, the findings must be confirmed in long-term studies. Furthermore, there is a scarcity of information on patient serum hormones and clinical features that can influence sperm quality.

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