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Acknowledgments

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

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2- Books:

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

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

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Contents :

Letter from the Editor:

Dear 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. Serum AMH and AFC represent potent markers for predicting ovarian response in women with PCOS. Lidocaine didn't' add any analgesic effect over placebo. tramadol wound injection in CS is a good choice for post-operative analgesia. Vit D supplementation increases the clinical pregnancy, fertilization and implantation rates in ICSI cycles. Endometritis occurs significantly after surgical termination of first-trimester abortion. Hysteroscopic guided biopsy followed by immunohistochemistry was associated with high diagnostic accuracy for endometritis. There was no difference between the mode of delivery and successful breastfeeding. The body mass index was a significant predictor for exclusive breastfeeding. Hysteroscopic niche resection resulted in improved patients' symptoms and quality of life. Detrusor overactivity score can be utilized for selecting women with overactive bladder symptoms who would benefit from performing further urodynamic assessment. Bilateral uterine arteries ligation significantly cause reduction in the uterine volume and improve the adenomyosis symptoms and the reproductive outcome. Serum total antioxidant capacity levels are significantly lower in PCOS patients than in control patients.

Best regards.

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Diagnostic accuracy of ovarian reserve markers in the differentiation between responders and non responders after laparoscopic ovarian drilling

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Abstract

Background: Polycystic ovary syndrome results in many endocrinological derangements leading to infertility. This warrants the search for proper solutions to achieve ovulation. However, the prediction of ovarian response represents a significant challenge.

Aim: To evaluate the diagnostic accuracy of ovarian reserve markers to differentiate between responders and non-responders among women with clomiphene resistance PCOS after doing LOD.

Methods: This prospective cohort study was conducted at the obstetrics and gynecology department at Fayoum university from May 2018 to February 2020. The study recruited 50 women diagnosed with PCOS who had clomiphene citrate resistance. Transvaginal sonography was done to confirm the diagnosis of PCOS, measure the ovarian volume, and assess the mean antral follicle count (AFC) in both ovaries. A venous blood sample was obtained for AMH measurement. LOD was done early in the follicular phase under general anesthesia. Ovulation induction was prescribed using clomiphene citrate 100-150 mg from day 2 of the cycle.

Results: AMH had excellent discriminative power for response (AUC 0.995, the optimal cut-off point was 7.65 which yielded sensitivity 93.5%, specificity 100.0%, PPV 100.0% NPV 90.4% and accuracy 95.9%). AFC had good discriminative power for response (AUC 0.741, the optimal cut-off point was 16.5which yielded sensitivity 51.6%, specificity 84.2%, PPV 84.2% NPV 51.6%and accuracy 63.9%). OV had poor discriminative power (AUC 0.540, the optimal cut-off point was 13.75which yielded sensitivity 64.5%, specificity 52.6%, PPV 68.9% NPV 47.6%and accuracy 60.0%).

Conclusions: Serum AMH and AFC represent potent markers for predicting ovarian response in women with PCOS.

Keywords: PCOS; response; ovulation; AMH; AFC; ovarian volume.

Introduction

Polycystic ovary syndrome (PCOS), a common cause of female infertility, is characterized by insulin resistance and hormonal derangement (1, 2). It is diagnosed by two out of three criteria: oligo/anovulation, clinical or laboratory evidence of hyperandrogenism, and polycystic appearance of the ovaries (3). Patients present with a wide range of symptoms such as acne, hirsutism, irregular cycles, and infertility (4). Induction of ovulation is the mainstay treatment for women with infertility. Clomiphene citrate is the first-line treatment. When clomiphene resistance developed, other treatment options were introduced as the use of gonadotropins or laparoscopic ovarian drilling (LOD) (5, 6). However, the latter would impact the ovarian reserve, and the response after LOD is not guaranteed, dramatically impacting the patients psychologically (7). This study was conducted to evaluate the diagnostic accuracy of ovarian reserve markers to differentiate between responders and non-responders among women with clomiphene resistance PCOS after doing LOD.

Methods

This prospective cohort study was conducted at the obstetrics and gynecology department at Fayoum university from May 2018 to February 2020. The study recruited 50 women diagnosed with PCOS who had clomiphene citrate resistance. Clomiphene resistance was defined as the inability to detect ovulation after a daily dose of 150 mg and a thinned endometrium < 5mm for 2-3 cycles (8). All participants signed an informed written consent after explaining the aim of the study. Patients were recruited according to the following inclusion and exclusion criteria. **Inclusion criteria:** a) Age ranged from 18 – 35 y, b) PCOS according to Rotterdam criteria (3), c) clomiphene citrate resistance, d) average semen analysis, and e) normal Hysterosalpingography (HSG). **Exclusion criteria:** a) apparent cause of infertility rather than PCOS, b) hyperandrogenism due to any other endocrinal disorder, c) women refusing to participate in the study, d) the previous history of ovarian surgery, e) patients with endometriosis and/or fibroid, f) patients with chronic illness as diabetes mellitus and liver diseases, and g) hyperprolactinemia.

Women eligible for the study were subjected to detailed history and examination. Transvaginal sonography with a probe 7.5 MHz (China Philips HD11 C8-4v) was done to confirm the diagnosis of PCOS, exclude ovarian or adnexal pathology, measure the ovarian volume, and assess the mean antral follicle count (AFC) in both ovaries. Ultrasound was done two times, the first was before LOD, and the second was three months after the procedure. The same sonographer performed the ultrasound for all cases at the early follicular phase, days 3-5.

AFC is defined as counting all echo lucent rounded follicles measuring (2-10mm) present in the ovary's substance (9). The ovarian volume was evaluated with the ovary at its longitudinal axis, and the widest longitudinal and transverse diameters were measured on a frozen image. Rotation of the probe 90 degrees to get a transverse section of the ovary where the anteroposterior diameter was measured in this view. The ovarian volume was calculated using this equation: Ovarian volume = length X width X thickness X 0.5 (10).

A venous blood sample was obtained for AMH measurement. Samples were collected into EDTA-containing tubes, centrifuged for 20 min, and stored at -70 ºC. AMH was measured using an enzyme-linked immunosorbent assay technique (Immunotech, Beckman-Coulter UK Ltd, High Wycombe, Buckinghamshire, UK) following the manufacturer's protocol (11).

LOD was done early in the follicular phase under general anesthesia. Introduction of Verres needle, inflation of the abdomen,

and introduction of primary and secondary trocars were done. Fixation of one ovary away from the intestine by grasping the ovarian ligament with the traumatic grasper was done. A drilling needle was introduced and connected by monopolar current, held against the ovarian surface for 4 seconds using a power of 40 watts; four punctures were done in each ovary, putting into consideration that the puncture must be not superficial and it must go deep through the main substance of the ovary. Cooling of the ovary by lactated ringer's solution, finally removal of all instruments under vision after exclusion of any complication (12).

Follow-up of all patients was done and focused on AFC and Ovarian volume after three months from laparoscopy, AMH estimation after three months from laparoscopy, resumption of ovulation, and pregnancy rates. Ovulation induction was prescribed using clomiphene citrate 100- 150 mg from day 2 of the cycle.

Statistical analysis:

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer package version 22 (SPSS Inc, USA). The **mean, standard deviation (SD)**, and range were calculated **for quantitative data. A paired t-test** was performed to compare the **AMH, AFC**, and **Ovarian volume** values before and after the intervention. An **Independent t-test** was used to compare responders and non-responders regarding **study parameters**. Regarding Qualitative data were presented as **numbers** and **percentages**. For interpretation of results of significance tests, significance was adopted at **P< 0.05**. The receive operating characteristic **(ROC)** curve was used to determine the discrimination value of **AMH, AFC**, and **Ovarian volume** for response and to define optimal cut-points for sensitivity, specificity, and positive and negative predictive values (PPV, NPV).

Results

There were no statistically significant differences between responder and non-responder as regards age, BMI, and duration of subfertility (years) ($p > 0.05$), as shown in table (1).

ROC curves were drawn to look at maximum sensitivity and specificity for indices (AMH, AFC, and OV) before laparoscopy in the diagnosis of responder and non-responder. AMH had excellent discriminative power for response (AUC 0.995, the optimal cut-off point was 7.65which yielded sensitivity 93.5%, specificity 100.0%, PPV 100.0% NPV 90.4%and accuracy 95.9%). AFC had good discriminative power for response (AUC 0.741, the optimal cut-off point was 16.5which yielded sensitivity 51.6%, specificity 84.2%, PPV 84.2% NPV 51.6%and accuracy 63.9%). OV had poor discriminative power (AUC 0.540, the optimal cut-off point was 13.75which yielded sensitivity 64.5%, specificity 52.6%, PPV 68.9% NPV 47.6%and accuracy 60.0%) (Table 3).

Discussion

Currently, the determination of patients at risk for exaggerated response with induction of ovulation medications is essential. This is commonly performed using factors with low predictive values, such as patients' age, body weight, and the presence of polycystic ovaries (13). Accordingly, the use of robust predictive markers is essential.

There was no difference between responders and non-responders in the primary demographic data. This agreed with a previous study where there was no difference in age. BMI, years and etiology of infertility, and basal laboratory levels (14).

Our result proved that AMH had excellent discriminative power for response with an optimal cut-off point of 7.65, which yielded a sensitivity of 93.5%, specificity 100.0%,

PPV 100.0%, NPV 90.4%and accuracy of 95.9%. Another study reported a cut-off value of 3.01ng/ml; however, this was used for fertilization rate prediction in patients undergoing assisted reproduction (15). Variable results were reported regarding the AMH cut-off value for the prediction of ovarian response, together with variable sensitivity and specificity. This ranged from 3.5- 7ng/ml and 40-95% and 31- 96% respectively (16). This predictive role is rendered to producing AMH from the small and intermediate follicles representing the common follicular pool (17). Variability in the results would be rendered to different sample sizes, the nature of recruited patients, different outcomes, and different assay techniques (18).

We proved that AFC had good discriminative power for response with an optimal cut-off point of 16.5, which yielded a sensitivity of 51.6%, specificity 84.2%, PPV 84.2%, NPV 51.6%, and accuracy 63.9%. An earlier study reported similar results with an AFC of 16 had a sensitivity of 89% and a specificity of 92% (14). Variable results were reported regarding the AFC cut-off value for the prediction of ovarian response, together with variable sensitivity and specificity. This ranged from 9- 18 and 20-94% and 33- 98%, respectively (16). This difference would be rendered to their use of small AFC rather than the total AFC, which is vulnerable to inter-cycle, interobserver, and intra-observer variability (19). Additionally, 3D ultrasound yielded more validity and reliability than the 2D ultrasound used in the current study (20).

Ovarian volume had poor discriminative power with an optimal cut-off point 13.75which yielded sensitivity 64.5%, specificity 52.6%, PPV 68.9% NPV 47.6% and accuracy 60.0%. A previous study reported an insignificant difference in ovarian volume between pregnant and non-pregnant participants. It did not correlate with the number of oocytes retrieved or the AFC (21). Also, earlier studies reported that the number of oocytes retrieved decreased, and the dose of drugs used for ovulation induction increased in women with an ovarian volume <3cm3 (22, 23). Another reported an insignificant difference in the ovarian volume between responders and non-responders to clomiphene citrate and had no predictive value (24).

Strength and limitation

This study used reliable markers to predict ovarian response. However, the small sample size is a limitation. Evaluation of the predictive role of these markers in combination would be more informative. Evaluation of the predictive role of these markers in fertility rates was not done.

Conclusion

Serum AMH and AFC represent potent markers for predicting ovarian response in women with PCOS.

Conflict of interest: None.

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Table (1): Comparison between responder and non-responder as regards age, BMI, and duration of subfertility.

		Groups		Significant test	P value
		Responder N= 31	Non-Responder N= 19		
Age	Range	18-35	18-35	t = 0.021	0.718[a]
	Mean± SD	26.6±3.3	27±4.2		
BMI	Range	25-35	25-35	t = 0.684	0.497[a]
	Mean± SD	30.5±3.20	29.8±3.3		
Duration of subfertility (years)	Range	2-7	2-7	**Mann-Whitney** = 221.000	0.140[b]
	Median (IQR)	4.00 (2.00-5.00)	5.00 (3.00-7.00)		

[a] Independent T-test [b] Mann- Whitney test

Table (2): Sensitivity and Specificity of AMH, AFC, and OV level before laparoscopy in the diagnosis of responder and non-responders.

	AUC	P-value	Cut-off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
AMH	**0.995**	**<0.0001**	**7.65**	**93.5**	**100.0**	**100.0**	**90.4**	**95.9**
AFC	**0.741**	**0.005**	**16.5**	**51.6**	**84.2**	**84.2**	**51.6**	**63.9**
Ovarian volume	**0.540**	**0.639**	**13.75**	**64.5**	**52.6**	**68.9**	**47.6**	**60.0**

A prospective comparative study between tramadol, lidocaine and placebo in subcutaneous wound infiltration for postoperative pain relief in cesarean section

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Abstract

Background: As the rate of cesarean section (CS) is increasing rapidly, the need of postoperative analgesia is increasingly required. Aim: to evaluate the effect of tramadol injection at incision site before closure of the skin in patients undergoing cesarean section on post-operative pain and the need of analgesics in comparison to lidocaine.

Methods: this study was conducted in 2 hospitals in kingdom of Saudi Arabia in period of January 2021 till June 2021, ninety women undergoing cesarean section delivery were divided into 3 groups to receive tramadol, lidocaine or placebo subcutaneously before closing of skin in CS. using visual analogue scale (VAS), Pain was assessed at 6, 12 and 24 h post-operative.

Results: Pain (VAS scores) were significantly lower in the tramadol group in comparison to the other two groups at 6 h ($p<0.001$), and 12 h ($p<0.01$). VAS score at 24 h was significantly lower in the Tramadol group compared with Placebo group ($p<0.01$) and was comparable to Lidocaine group. Non statistically significant difference between VAS scores in Lidocaine group and Placebo was. Time to first analgesic demand was significantly longer in Tramadol group; 2.58±0.93 versus 2.47±0.82 versus 5.97±3.19 hours in the Placebo, Lidocaine and Tramadol group respectively, $p <0.001$.

Conclusion : local wound injection with tramadol resulted in significantly lower pain scores, But longer time to first analgesic request and lower overall cumulative 24-hour consumption of analgesics. Lidocaine didn't add any analgesic effect over placebo. tramadol wound injection in CS is a good choice for post-operative analgesia.

Keywords: Lidocaine, post cesarean section analgesia, post operative pain, tramadol.

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Introduction

Caesarean section (CS) is a major surgical procedure and it has been one of the most frequently performed operations nowadays. Although CS has some benefits, such as lowering the risk of birth injuries (e.g., asphyxia,

shoulder dystocia, fractures), it can cause moderate to severe postoperative pain. (1)

So, controlling of pain post-Cesarean section may help in rapid recovery, reduction of hospital stay and early bonding between mother and her newborn, while inadequate pain relief may prolong duration of hospitalization beside comorbidities (2)

The term "local infiltration analgesia" is used to describe the application of "high volume of diluted, long-acting local anesthetic" in tissue structures to provide analgesia. Wound infiltration with local anesthetics is used as the main anesthetic for minor surgeries, such as repair of lacerations, skin surgery and treatment of painful oral or genital lesions, but can also be used as supplement to general anesthesia in several types of surgical procedures. (3)

The aim of the current work is to evaluate the impact of tramadol infiltration at incision site before closure of the skin in patients undergoing cesarean section on post operative pain and analgesic requirements in comparison to lidocaine.

Materials and methods

This study is a prospective comparative control trial which was carried in 2 hospitals in kingdom of Saudia Arabia in period of January 2021 till June 2021. We included 90 women pregnant at term who were scheduled to deliver with elective cesarean section through Pfannenstiel incision. Women with major medical problem, bleeding disorder, drug addiction or with allergy to the drug used in the study were excluded. All women included in this study gave an informed consent after proper counseling. The study was approved by appropriate ethical committee .

Sample Size Justification

The study included all women fulfilling the inclusion and exclusion criteria who were admitted between January 2021 till June 2021 at the 2 hospitals, so 90 women were included in study.

The Ninety women undergoing cesarean section delivery under spinal anesthesia were divided into 3 groups to receive tramadol (group A), lidocaine (group B) or placebo (group C) subcutaneously before closing of skin in CS All patients had routine cesarean section then at time of skin closure, the wound was infiltrated during skin closure with 20 ml of 0.9% saline in group C (n=30), 20 ml of 1% lidocaine hydrochloride in group B (n=30) or 50mg tramadol hydrochloride diluted in 20 ml of 0.9 saline in group A (n=30).

Pain assessment was done using VAS after 6, 12 and 24 hours post-operatively. VAS is considered the gold standard tool for assessment of pain for research purpose. A paper with a 100mm horizontal straight line with 2 ends one end represents no pain and the other represents the worst pain. The patient was asked to mark on the line the pain she feels. Patients received post-operative analgesia of Diclofenac sodium 75mg intramuscular injection on demand.

Statistical analysis

Data are presented as mean, standard deviation (SD), median and range values. For parametric data, A one-way analysis of variance (ANOVA) when comparing between more than two means. Chi-square (x2) test of significance was used in order to compare proportions between qualitative parameters. The significance level will be set at $P \leq 0.05$. Statistical analysis were performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY:IBM Corp.

Results

The general characteristics, obstetric history and past medical and surgical history of the included women were comparable between the Placebo, Lidocaine and Tramadol

group. As shown in table (1), there was no statistically significant difference between the three groups as regards age, body mass index (BMI) and gestational age at delivery.

In the Placebo, Lidocaine and Tramadol group, 5 women (16.7%), 6 women (20%) and 4 women (13.3%) respectively were primigravid (p=0.691). History of previous one or more cesarean section was found in 19 women (63.3%), 17 women (56.7%) and 19 women (63.3%) among women in the Placebo, Lidocaine and Tramadol group respectively (p=0.688). (Data not tabulated).

We found that the VAS scores were significantly lower in the Tramadol group compared with the other two groups at 6 h and 12 h. While at 24 h, we found that the VAS score was significantly lower in the Tramadol group compared with the Placebo group ($p<0.001$) but was comparable to Lidocaine group. The difference in VAS scores between Lidocaine group and Placebo was statistically not significant (table 2).

We also found that time to first analgesic request was significantly longer in the Tramadol group compared with the other two groups (table 2, figure 1). While the mean time of first analgesic request in Lidocaine group compared with Placebo group revealed no statistically significant difference.

As regard the Comparison between the three groups about postoperative analgesic consumption; there were significantly fewer patients requiring diclofenac at 24 h in the Tramadol group compared with Placebo and Lidocaine group. The number of women requiring analgesia at 6h and 12 h was comparable between the three study groups (table 3). Likewise, the cumulative 24-hour consumption of diclofenac was significantly lower in the Tramadol group compared with the other two groups (figure 2).

Discussion

Our Results Interpretation and their comparison to other studies

The current study showed that VAS scores were significantly reduced with subcutaneous infiltration of tramadol compared to lidocaine and placebo at 6, 12 and 24 hours, the time to first analgesic request was significantly longer and total consumption of analgesic in 24 hours was significantly reduced with tramadol.

We also found that lidocaine did not provide good analgesic effect as the VAS scores were comparable to that of placebo throughout the postoperative period. The time to first analgesic request and total analgesic consumption of analgesics in 24 hours were comparable between lidocaine and placebo. These results disagree with Ghenaee et al. (2015) results where they studied 100 cases randomized to lidocaine 2% (4 mg/kg diluted in 30 mL of normal saline), they concluded that lidocaine 2% injection in wound of cesarean section incision has reduced the postoperative pain and decreased the need of any additional analgesia [4]

Our Results were supported by Kessous et al in their RCT which evaluated injection of 1% lidocaine solution in the incision site at cesarean deliveries and reported that there was no significant difference between lidocaine and placebo in postoperative pain scores or analgesic request. (5)

This finding is further supported in a RCT which assessed analgesic effects of tramadol versus saline infiltration subcutaneously in lower abdomen surgeries and it was reported that tramadol significantly reduces pain and opioid consumption. (6)

In our study, tramadol wound infiltration was superior to lidocaine wound infiltration, which was supported by the study of

Jabalameli et al. (2012). They compared pethidine, tramadol, bupivacaine, and placebo in the wound infiltration in total of 120 patients undergoing cesarean section [7].They found that pethidine and tramadol were superior to other compared groups in reducing postoperative pain and the need for additional analgesia in the pethidine group and tramadol group were significantly lower. These results may be explained by the long duration of action of tramadol. Sachidananda et al. (2017) found that tramadol augmented the action of bupivacaine and prolonged the pain free period and decreased the need of any extra analgesia [8].

The results of the current study disagreed with results of Jayashree et al. (2019), their study included 60 women undergoing CS under spinal anesthesia. Tramadol was compared to bupivacaine, they found that bupivacaine was better in its analgesic effect than tramadol. However, in their study, tramadol had significant pain-relieving effect and prolonged duration.[9].

Clinical Implication of our study

As Evidence revealed the high incidence of postoperative pain and its strong influence on the mother, family and medical practitioners. [10] We conclude that local wound infiltration with tramadol resulted in significantly low pain scores, longer time to first analgesic request and overall lower cumulative 24-hour consumption of analgesics. Lidocaine did not add any additional analgesic effect over placebo. Tramadol wound infiltration in cesarean section is a good choose for post-operative analgesia

Weakness and strength points of study

Main limitation of this study is inadequate number of patients as Arab women backward Islamic culture limits their participation in clinical trials, also lack of randomization in this study because there are no RCT units in private hospitals, the private patients refuse the idea of randomization and ask for best option and the hospital adminstration were not encouraging the idea stating that we are not a governmental hospital while strength point is that it is a multicenter trial that decreases the publication bias.

Recommendation for future research

Further studies are needed to evaluate the effect of bupivacaine and other narcotics injection in CS wound.

Conclusion

local wound injection with tramadol resulted in significantly lower pain scores, But longer time to first analgesic request and lower overall cumulative 24-hour consumption of analgesics. Lidocaine didn't' add any analgesic effect over placebo. tramadol wound injection in CS is a good choice for post-operative analgesia.

Ethics approval

Study approved by appropriate ethical Committee .

Consent for publication

Non applicable.

Availability and data material

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

Competing interests

The authors report there are no competing interests to declare.

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Table (1): Patients' characteristics.

	Placebo (n=30)	Lidocaine (n=30)	Tramadol (n=30)	p-value
Age (years)	31.11±4.43	30.39±4.53	30.80±4.02	0.812
BMI (kg/m^2)	28.94±4.02	27.30±3.91	28.63±3.19	0.200
Gestational age (weeks)	39.66±1.65	39.55±1.85	39.86±1.55	0.772

p-value >0.05 is insignificant

Data presented as mean ± standard deviation, analysis done using one-way analysis of variance (ANOVA), kg= kilogram, m= meter

Table (2): comparison between the studied groups as regards pain scores and time to first analgesic request

	Placebo (n=30)	Lidocaine (n=30)	Tramadol (n=30)	p-value
VAS at 6 h	3.09±1.24	3.30±1.03	2.27±0.82*	<0.001
VAS at 12 h	4.94±1.55	4.94±1.13	3.71±1.85†	0.003
VAS at 24 h	4.22±0.82	3.71±0.93	3.09±1.34‡	<0.001
TFA request, h	2.58±0.93	2.47±0.82	5.97±3.19*	<0.001

p-value <0.001 is highly significant; p-value <0.05 is significant; p-value >0.05 is insignificant

Data presented as mean ± standard deviation, analysis done using one-way analysis of variance (ANOVA), VAS= visual analogue scale, h= hour, TFA= time to first analgesic request, *P<0.001 versus Placebo group & Lidocaine group, †P<0.01 versus Placebo group & Lidocaine group, ‡P<0.001 versus Placebo group only.

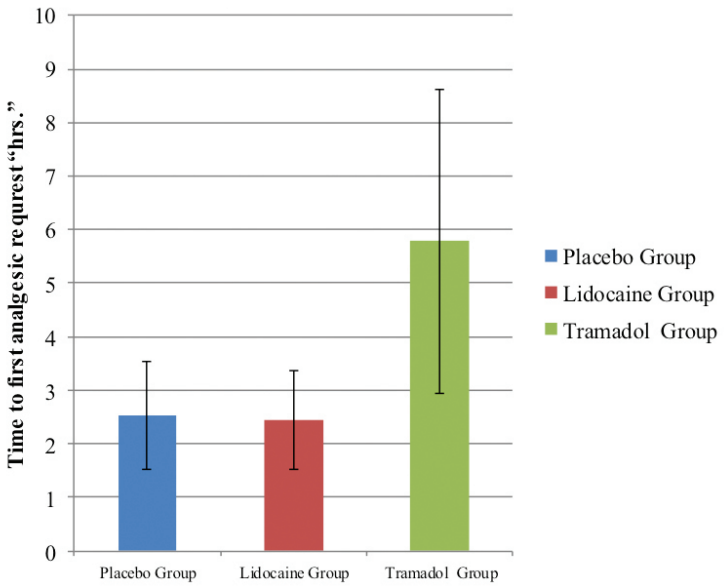

Figure (1): Mean time to first analgesic request in the three study groups. Error bars represent standard error of the mean.

Table (3): Comparison of analgesic consumption between the study groups

Diclofenac consumption	Placebo (n=30)	Lidocaine (n=30)	Tramadol (n=30)	p-value
at 6 h	6 (20.0%)	3 (10.0%)	2 (6.7%)	0.260
at 12 h	25 (83.3%)	29 (96.7%)	24 (80.0%)	0.133
at 24 h	28 (93.3%)	25 (83.3%)	15 (50.0%)	<0.001

p-value <0.001 is highly significant; p-value >0.05 is insignificant

Data presented as number (percentage), analysis done using Chi square test.

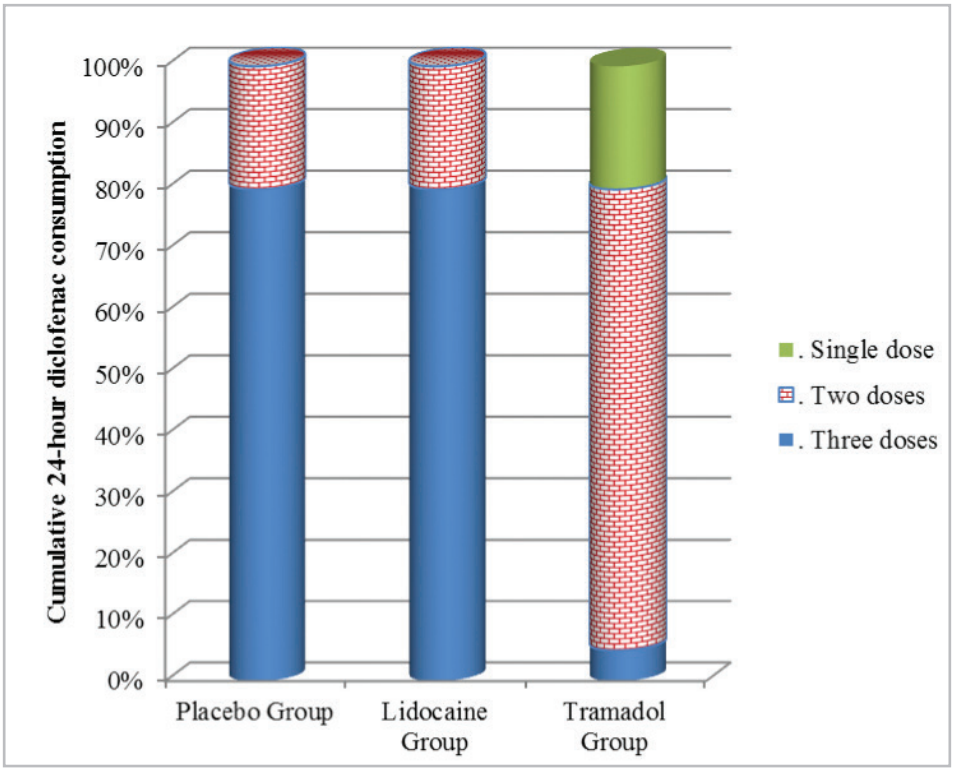

Figure (2): Cumulative 24-hour diclofenac consumption in the three study groups.

Vitamin D supplementation in vitamin deficient women undergoing ICSI cycles: Does it affect the fertility outcome? A randomized controlled trial

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Keywords: Vitamin D, Infertility, IVF, ICSI

Synopsis: Vitamin D supplementation in deficient females improves the clinical pregnancy rate vitamin D deficient females undergoing ICSI cycles

Randomized clinical trial

Abstract

Objective : to determine the effect of vitamin D (VD) supplementation on ICSI outcome in vitamin D deficient females.

Methods: A randomized controlled trial was done in IVF unit of Cairo University from July 2017 to Mach 2021. Level of VD was measured (females with level below 30 ng/ml were eligible). 400 VD deficient (or insufficient) females randomly allocated to 2 groups; VD supplementation (group 1) and non-supplemented group (group 2). Outcome data were analyzed for 187 participants in group 1 and for 186 in group 2. Regression analysis was done to calculate the Odds ratio (OR) for the primary outcome (clinical pregnancy rate, CPR) adjusting for confounders (age, BMI, type and cause of infertility). The study secondary outcome were the fertilization and the implantation rates.

Results: Group 1 had higher fertilization (86% vs 64%, difference of 18%; 95%CI; 14%, 21%, p<0.01) and implantation rates (27% vs 17%, difference 10%; 95%CI 4%, 16%, p<0.01). CPR was higher in group1 (83/187, 44% vs 63/186, 34%, difference of 10%, 95%CI; 1%, 20%; p=0.03). After adjustment, the Odds ratio for pregnancy in group 1 was 2.1 (95%CI: 2.1, 3.3, p=0.01), Conclusion: VD supplementation increases the clinical pregnancy, fertilization and implantation rates in ICSI cycles.

ClinicalTrial.gov Registration number: NCT03209856.

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Introduction

In the last decade, a large body of evidence highlighted the importance of vitamin D (VD) in female reproduction. VD has been suggested to have important roles in fertility and throughout pregnancy (1-3). However, the interest for

its possible effect on the IVF/ICSI outcome was recent (4,5).

Vitamin D receptors (VDR) mRNA was shown to be expressed not only in the calcium regulating tissues, but also in the ovary, uterus and pituitary (6). Also, 1 α hydroxylase (responsible for peripheral tissue activation of VD) was identified in the ovary and endometrium (7). This distribution of VDR and 1 α hydroxylase suggests an important role of VD in female reproduction (8). Calcitriol also enhances the release of human chorionic gonadotropin (HCG) in the syncytiotrophoblast and the expression of HOXA10 (important in endometrial growth and development essential for endometrial receptivity) (9,10).

A relation between VD deficiency and some fertility problems was suggested in the past few years. That deficiency was related to insulin resistance in polycystic ovarian syndrome (PCOS) (11). Moreover, an association between higher body mass index (BMI) and VD deficiency was shown by some investigators, (12). Therapeutic efficacy of VD supplementation was found improve insulin resistance in females with PCOS,(13).

Some recent studies have found a correlation between VD deficiency and poor IVF/ICSI outcomes (5,14). However, randomized controlled trials (RCTs) for assessment of the effect of VD supplementation on fertility outcomes in assisted reproductive techniques (ART) cycles are scarce (15).

Therefore, we aim in this study to evaluate the effect of treatment of VD deficiency (through VD supplementation for 8 weeks before the start of ICSI cycles) on fertility outcome after ICSI trials. To the best of our knowledge, this is the first big RCT addressing this issue.

Material and methods

The study was conducted in the IVF unit of department of Obstetrics and Gynecology, Cairo University from July 2017 to March 2021. Approval of the local ethical committee was taken. Informed consents were taken from participants and the ethical standards of Declaration of Helsinki were followed. The trial was registered in ClinicalTrial. gov Registry (NCT03209856) and reporting of the study conformed to CONSORT guidelines (16).

The study participants were VD deficient females undergoing ICSI trial in the age of 20 to 35 years. Serum 25 hydroxy VD (25 (OH) VD) was assessed by ELISA test (25-OH Vitamin D3/D2, ORGENTEC Diagnostika GmbH, Mainz, Germany). Accordingly if they are deficient or insufficient in VD ((25 (OH) VD < 30 ng/ml), (17)), they were eligible for the study. Patients with poor prognostic factors namely; endometriosis or previous repeated failure were excluded from the study.

The serum 25 (OH) VD was chosen for assessment of VD deficiency as the activation of VD occurs peripherally thus the serum active form (calcitriol; 1,25 dihydroxy VD) does not represent the actual VD status (18).

400 VD deficient women were randomly allocated to either one of two groups. Blocked randomization (block size of 4 and 6) was chosen with a ratio of 1:1 between the 2 groups. The decision for the participant to be in group 1 or 2 was written in sealed envelopes which were opened when the patient is eligible to participate in the study (i.e. shown to be VD deficient by serum level). The first group (Group 1; VD supplemented group) took 50,000 IU VD orally/week (17) (10,000 IU daily VD for 5 days a week) for 8 weeks before the start of ICSI cycle (Vitamin D , Solaray, Park city, UT, USA). The second group did not take VD supplementation.

Ovarian stimulation was accomplished using antagonist protocol. Follicular stimulation started on the second or third day of the cycle by daily SC 150 to 300 IU HMG (Merional, IBSA, Lugano, Switzerland). The choice

of the HMG dose was according to female age, BMI, antral follicular count (AFC) and previous response to stimulation (if present). Daily SC 0.25 mg cetrorelix (Cetrotide, Merck Serono, Darmstadt, Germany) started on the fifth day of stimulation. The first folliculometry visit was after 5 days from the start of stimulation then the visits were every other day. Ovulation trigger was done when at least 2 to 3 follicles ≥18 mm were present. Ovum pick up (OPU) was done 35-36 hours after the trigger injection. Embryo transfer was done on day 3 from OPU. If there were 4 or more top quality embryos on the third day the transfer was delayed to the fifth day (as per our IVF unit protocol). Progesterone (Cyclogest, Actavis, Barnstaple, UK) in the form 400 vaginal suppositories were taken twice daily from the evening of the day of OPU for two weeks and were continued throughout the first 10 weeks of pregnancy (if it occurred). Serum quantitative B-HCG was done 15 days from the day of ovum pick up. Clinical pregnancy was confirmed if a gestational sac was evident by transvaginal ultrasound done 4 weeks after embryo transfer.

Fertilization rate was calculated by dividing the number of 2 pronuclear fertilized oocytes by the total number of sperm injected mature ova (MII oocytes), while implantation rate is the number of gestational sacs divided by the total number of transferred embryos.

Clinical pregnancy rate is considered the primary outcome while the fertilization rate and the implantation rate are the study secondary outcome.

Sample size calculation was based on comparison of the clinical pregnancy rate (CPR) as the primary outcome between group 1 (vitamin D deficient group who took vitamin D supplementation) and group 2 (deficient group who will not take the supplementation). Previous data (19) suggested that a pregnancy rate of 41% in vitamin D deficient women following IVF/ICSI cycles. We set the clinical significant difference at 15% the alpha error at 0.05, power at 80% and dropout rate at 10% (cancelled cycles or lost for follow up). Thus we needed 200 participants in each arm. Sample size calculation was done using IBM SPSS SamplePower software, release 3.0.1 (IBM Corp., Armonk, NY, USA).

Statistical analysis: description of data was in the form of mean (SD), or count (%) according to the data type. Comparison of data between groups was done by t-test, Chi-Square and Fisher test. A logistic regression analysis was done to assess the effect of Vitamin D supplementation on CPR after adjustment for possible confounders; namely; age, BMI, type of infertility and cause of infertility. Statistical analysis was done as an intention to treat analysis. Nevertheless, it was the same as per-protocol analysis (all participants followed the allocated group). Statistical analysis was done using SPSS software, version 23 (IBM Corp., Armonk, NY, USA).

Results

Figure 1 shows the Consort flow chart of the study population. 701 females referred to IVF clinic were screened for eligibility for the study. 80 cases were excluded before testing for vitamin D status due to presence of endometriosis or repeated IVF failure. Another 176 cases were excluded after assessment of serum vitamin D for being VD sufficient. 45 females declined to participate in the study. 200 VD deficient participants were allocated to each arm of the study; group 1 (VD supplemented) and group 2 (VD non-supplemented). 13 and 14 cases were excluded in data analysis from group 1 and group 2 respectively due to cycle cancellation or patients being lost in follow up after embryo transfer (Figure 1).

The two study groups had similar clinical characteristics; namely; age, BMI, type of infertility (primary or secondary), duration of infertility and cause of infertility. They

also have similar VD level (before starting VD supplementation to group 1), (Table 1).

Regarding the ICSI cycle outcomes, group 1 had improved fertilization, implantation and pregnancy outcomes in comparison to group 2. Although, the number of retrieved oocytes were similar, the number of mature ones were higher in group 1 (6.4 ± 3.3 vs 5.6 ± 1.9, difference of 0.8, 95%CI; 0.2, 1.4, p<0.01). Similarly, group 1 had higher number of fertilized oocytes (5.3 ± 3.1 vs 3.5 ± 1.4, difference of 1.8; 95%CI; 1.3, 2.3, p<0.01) and higher fertilization rate (86% vs 64%, difference of 18%; 95%CI; 14%, 21%, p<0.01). The number of top quality embryos were also higher in group 1 (3.8 ± 2 vs 3.4 ±1.4, difference of 0.4; 95%CI; 0.1, 0.8, p=0.01). Group 1 had higher chance of day 5 embryo transfer (55% vs 40%) due to higher number of good quality embryos. In most participants of both study groups; 2 embryos were transferred (94% vs 95%). Single embryo transfer was done to the remaining participants (as they had only one transferable embryo). This is because the local protocol of the IVF unit implies 2 embryo transfer whenever possible. The implantation rate was also higher in the VD supplemented group (27% vs 17%, difference 10%; 95%CI 4%, 16%, p<0.01). (Table 2)

Clinical pregnancy rate (the study primary outcome) was higher in VD supplemented group (83/187, 44% vs 63/186, 34%, difference of 10%, 95%CI; 1%, 20%; p=0.03), (Table 2). After adjustment for possible confounders in regression analysis, the Odds ratio for pregnancy in group 1 was 2.1 (95%CI: 2.1, 3.3, p=0.01), (Table 3)

Discussion

In the present study, we evaluated the effect of VD supplementation on ICSI outcome in VD deficient females. Recently, the was increasing interest in finding correlation between VD deficiency and various infertility causes and poor pregnancy outcomes after assisted reproductive techniques (4, 14, 20). However, little is known about the effect of vitamin D supplementation on ICSI outcome (13).

In the present randomized controlled trial, clinical pregnancy rate was significantly higher in VD supplemented group. This result may be due to the positive effect of VD on various aspects of fertility at the pituitary, ovary and endometrial receptivity level (4). These effects probably explains the higher number of fertilized oocytes, higher fertilization and implantation rates.

A recent study has found similar higher pregnancy rates in PCOS females undergoing IVF cycles (after vitamin D supplementation in deficient cases) (13). To the best of our knowledge till now, this is the first big randomized controlled trial assessing the effect of VD supplementation on pregnancy outcome in females undergoing ICSI cycles.

Nevertheless, this study has its limitation. We could not assess the livebirth rate in the study groups which is the best tool for evaluation of pregnancy outcome in ICSI cycles. This limitation arise from the fact that our pregnant patients are hard to follow up. Moreover, most of our patients are from far areas. That is why if we assess the livebirth rate, the expected high dropout rate will affect the accuracy of results. So, we preferred the clinical pregnancy rate to be the primary outcome of the study.

In conclusion; VD supplementation in deficient females undergoing ICSI cycles increases the clinical pregnancy rate, fertilization rate and implantation rate. And in the view of this conclusion, Vitamin D supplementation is recommended in deficient cases to improve ICSI outcome.

Author contributions

EFO: Study design, data analysis and revision of the manuscript

SHG: Study design, conduct and revision of the manuscript

AS: Study design, conduct and revision of the manuscript

MSA: Study design, conduct and revision of the manuscript

MG: Study design, conduct, and manuscript revision

EE: Data analysis and revision of the manuscript

MFS: Study design, conduct and revision of the manuscript

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Conflict of interest

The authors report no conflicts of interest in this research.

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Table (1): Clinical and laboratory characteristics of the study groups.

Characteristic	Group 1(Vitamin D supplemented) n=187	Group 2 (non-supplemented with Vitamin D) n=186	Difference between groups (95%CI)	P-value
Age (years)	30.1 ± 4.2	29.6 ± 3.5	0.4 (-1.3, 1.2)	0.3 [a]
Body mass index	29.2 ± 5	29.6 ± 3.6	-0.4 (-1.3, 0.4)	0.3 [a]
Type of infertility			NS	0.1[b]
Primary	132 (71%)	117 (63%)		
Secondary	55 (29%)	69 (37%)		
Duration of infertility (years)	5.2 ± 2.5	4.8 ± 2.3	-0.4 (-0.1, 0.8)	0.2 [a]
Cause of infertility			NS	0.8[b]
Male	45(24%)	44 (23%)		
Ovulatory	46 (24%)	42 (22%)		
Combined factors	43 (22%)	48 (25%)		
Tubal factor	37 (20%)	35 (19%)		
Unexplained	16 (9%)	17 (9%)		
Vitamin D level (ng/ml)	13.8 ± 6	14.7 ± 6	-0.9 (-2.2, 0.4)	0.2 [a]

Values are in the form of mean ± SD, or count (percent). NS, non-significant. [a] , T-test. [b], Chi-Square test. CI; confidence interval

Table (2): ICSI cycle outcome in the study groups.

Characteristic	Group 1(Vitamin D supplemented) n=187	Group 2 (non-supplemented with Vitamin D) n=186	Difference between groups (95%CI)	P-value
Retrieved oocytes	8.7 ± 3.8	8.1 ± 1.8	0.6 (-0.01, 1.2)	0.05
Number of mature oocytes	6.4 ± 3.3	5.6 ± 1.9	0.8 (0.2, 1.4)	<0.01*
Fertilized oocytes	5.3 ± 3.1	3.5 ± 1.4	1.8 (1.3, 2.3)	<0.01*
Fertilization rate[a]	83%	64%	18% (14%, 21%)	<0.01*
Number of top quality embryos (1 and 2)	3.8 ± 2	3.4 ±1.4	0.4 (0.1, 0.8)	0.01*
Day of transfer (after ovum pickup)				
Day 5	103 (55%)	74 (40%)	15% (5%, 25%)[b]	0.01*
Day 3	84 (45%)	112 (60%)		
Embryo transfer				
2 embryos	178 (95%)	178 (95%)	NS	0.8
Single embryo	9 (5%)	8 (5%)		
Clinical pregnancy rate	83 (44%)	63 (34%)	10.5% (1%, 20.3%)	0.03*
Implantation rate[c]	27%(97/365)	17% (63/364)	10% (4%, 16%)	<0.01

Values are in the form of mean ± SD, or count (percent). NS, non-significant. CI; confidence interval. a ,fertilization rate was calculated by dividing the number of fertilized oocytes by the total number of sperm injected mature ova. b , difference was calculated in percentage of females who had day 5 transfer. c , Implantation rate is the number of gestational sacs divided by the total number of transferred embryos.

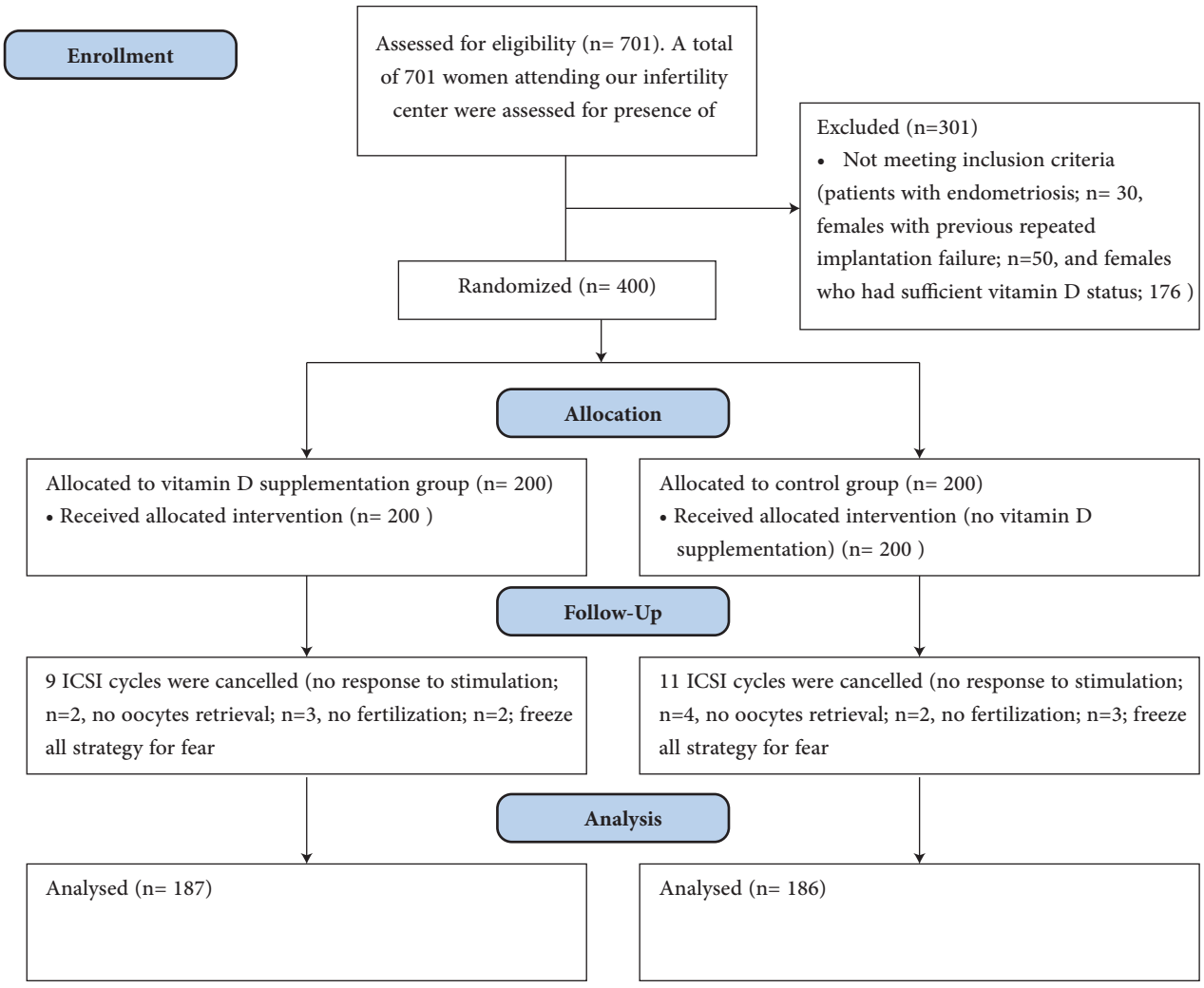
Table (3): Logistic regression for testing the effect of vitamin D supplementation on clinical pregnancy rate adjusting for possible confounders (age, BMI, type of infertility; primary or secondary and cause of infertility).

Study group	Odds ratio (95%CI)[a]	P-value
Vitamin D supplemented group versus Vitamin D non-supplemented group	2.1 (1.3 to 3.3)	0.01*

[a], the odds of having versus non-having pregnancy after ICSI cycle. * ; indicates significance. CI; confidence interval

Figures

Figure 1 Consort flow chart of the study population



Knowledge, attitude, and practice of obstetricians towards pregnancy in COVID- 19 pandemic

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Abstract

Background: COVID- 19 is a global disease declared by the WHO as a pandemic. Proper knowledge about the disease may increase the chances of protection against catching an infection.

Objective: This study aimed to evaluate the obstetricians' knowledge, attitude, and practice towards pregnancy during COVID- 19 pandemic.

Study design: This was a cross-sectional study conducted from October 2020 to March 2021. We surveyed a total of 120 obstetricians using a questionnaire that was published and distributed electronically. The questionnaire was validated statistically through principal component analysis and the calculation of Cronbach's alpha for the whole questionnaire and each section. The questionnaire included two main sectors: sector (one) inquired about the sociodemographic characteristics of the participants (age, sex, status, and years of experience); sector (two) included the physicians' knowledge, attitude, and practices towards COVID- 19 in pregnancy.

Results: The mean age of the participants was 40.73 ± 12.58. The calculated Cronbach's Alpha was more than 90% for the whole questionnaire and individually for each section. Generally, 55.64% of the participants had adequate knowledge about the COVID-19 pandemic; 76.5% had proper attitudes towards this pandemic, and 74.8% practiced with caution during this global outbreak. The full scale for knowledge, attitude, and practice was 8.8 ± 7.9, 6.27 ± 4.49, and 13.71 ± 5.99.

Conclusion: The attitude and practice of the obstetricians about COVID- 19 were encouraging; however, they need proper training to improve their knowledge. Misconceptions about this pandemic exist.

Keywords: obstetricians; knowledge; attitude; practice; COVID- 19; pregnancy.

Introduction

Coronavirus disease (COVID- 19) is a severe pandemic affecting the whole world, as declared by the WHO (1). This outbreak in a maternal and child health institute would result in catastrophic consequences (2). Health care systems across nations struggle to protect their health care workers. Multiple strategies have been adopted as rescheduling nonurgent health care services like medical appointments and surgeries. These options are not available for obstetricians. Women continue to deliver or present with life-threatening emergencies whether a pandemic is present or not. Although most of these women are not infected, their minority represent a significant risk for obstetricians (3). The lack of an evidence-based management plan for pregnant women infected with COVID- 19 increases the mental and physical stress on obstetricians (4, 5). Additionally, lack of knowledge, faulty attitudes and practices among physicians lead to increased risk of infection (6, 7). Accordingly, this study aimed at evaluating the knowledge, attitudes, and practice of the obstetricians towards the COVID- 19 pandemic.

Methods

This was a cross-sectional study conducted at the obstetrics and gynecology department at Suez Canal University hospital. The study was conducted from October 2020 to March 2021. We surveyed a total of 120 obstetricians, according to the sample size calculated before the study. They were informed that the data were confidential. The questionnaire was anonymous. Their acceptance to answer the questionnaire was considered as consent to participate in the study.

Regarding previous literature (8, 9), a questionnaire was constructed and distributed electronically to the participants. The questionnaire was tested on 10 participants and then published and distributed electronically. The questionnaire was validated statistically through principal component analysis and the calculation of Cronbach's alpha for the whole questionnaire and each section.

The questionnaire included two main sectors: sector (one) inquired about the sociodemographic characteristics of the participants (age, sex, status, place of residency training, length of practice, place of current practice); sector (two) included the physicians' knowledge (20 questions scored as 1 for correct responses and 0 for unsure or wrong ones), attitude (10 questions scored as 1 for correct responses and 0 for unsure or wrong ones), and practices (10 questions scored as 2, 1, and 0 for correct, sometimes, and wrong responses) towards COVID- 19 in pregnancy (COVID-19 incubation period, transmission, signs and symptoms, antenatal care for women not suspected or confirmed to have COVID-19, antenatal care for women with suspected or confirmed COVID –19, drug therapy for COVID-19, Obstetric medications in women with COVID-19, termination of pregnancy, postpartum care, and practices as well as attitudes of the participants to decrease the risk of infection).

Ethical approval: This study was conducted after approval of the research ethics committee of faculty of medicine, Suez Canal University, in 28/9/2020 with an approval number of #4298.

Results

The study included 120 obstetricians with a mean age of 40.73 ± 12.58. There were 69 (57.50%) and 51 (42.50%) male and female physicians, respectively. They were either residents 40 (33.33%), specialists 30 (25%), or consultants 50 (41.67%) with a mean duration of experience 14.93 ± 12.13 years.

The calculated Cronbach's Alpha was more than 90% for the whole questionnaire and individually for each section. This means that the reliability or the internal consistency of the whole questionnaire and each section

individually were excellent. Moreover, each section showed a statistically significant ANOVA. Average interitem correlations calculated were within the ideal range for all of the measurements done, which also adds to the internal consistency strength. The intraclass correlation was also more than 0.90 for the whole questionnaire and each section individually. This means excellent consistency or reproducibility of quantitative measurements made by different respondents answering the questionnaire (Table 1).

Generally, 55.64% of the participants had adequate knowledge about the COVID-19 pandemic; 76.5% had proper attitudes towards this pandemic, and 74.8% practiced with caution during this global outbreak. This resulted in a misconception rate of 31.02%.

The scale for knowledge of all participants revealed a total score of 8.8 ± 7.9 (Table 2). At the same time, the full scale for attitude was 6.27 ± 4.49 (Table 3). Finally, the full scale for practice was 13.71 ± 5.99 (Table 4).

Discussion

Since the WHO declared this global pandemic, the number of cases has been increasing worldwide. This represents a significant challenge facing health care workers. Adequate knowledge, attitude, and safe practices are crucial to guarantee safety for the health care team while managing possibly infected cases (10).

Testing the knowledge, attitude, and practices of physicians and particularly obstetricians who face emergencies requiring rapid intervention, is paramount. Lifesaving procedures cannot be delayed due to limited resources as personal protective equipment. Additionally, in limited-resource countries, women are admitted in the ward for some time depending on their relatives for food and assistance, making isolation difficult and overcoming infection control measures (11). Few studies are available about this issue, especially in Egypt.

The current study revealed that 55.64% (total score 8.8) of the participants had adequate knowledge about the COVID-19 pandemic, and 74.8% (total score 6.27) practiced with caution. An earlier study reported that 65.1% of their healthcare providers had adequate knowledge about this pandemic. Additionally, 57.5% of them adhered to safety measures during their practices (12). Other studies reported high levels of knowledge of their participants (89.51% and 82.4%) (13, 14), especially obstetricians and pediatricians (78.9%) (15). This discrepancy would be rendered to the different rates of misapprehensions about COVID- 19 - 62.5% (12) versus 31.02% in our population-. Besides, many of the topics related to pregnancy are contentious, with frequent substitutions (16, 17). Some studies reported neonatal complications (2, 18) while others did not (17, 19). Also, the difference in the training administered to the participants might have a role (12). Additionally, some studies used directed questions rather than multiple-choice ones.

A significant proportion of the physicians had positive attitudes towards this pandemic represented in applying safety precautions during this pandemic. This agreed with previous studies (14, 16, 20). This high score would be explained by the definite declaration of COVID- 19 as a pandemic when conducting these studies. Additionally, the WHO has recommended certain precautions to avoid infection that the governments and physicians practice (16). However, this would not guarantee protection because of insufficient knowledge (21).

However, this was higher than the results reported by others (57.5%, 44%) (12, 14). This difference would be related to their recruitment of healthcare workers while the current study targeted obstetricians. Also, the difference in the misconceptions plays a significant role.

Misconceptions about COVID- 19 were present in about 31.02% of the participants.

Higher results were reported in a previous study (62.5%) (12). This would be related to the presence of erroneous reports and unconfirmed results spreading so fast, confusing and misleading healthcare workers.

Strength and limitations: This was the first study to evaluate the obstetricians' knowledge, attitude, and practice towards COVID- 19 pandemic. The questionnaire was distributed electronically through groups including obstetricians and gynecologists, which obscured the number of physicians refusing to participate in the study. Also, this would limit the generalizability of the results. This was a self-administered questionnaire which might not reflect the actual practice. The source of their knowledge was not evaluated. A more significant number of participants would be more informative. We recruited obstetricians and gynecologists only. The inclusion of all healthcare workers would be more representative.

Conclusion: The knowledge, attitude, and practice of the obstetricians about COVID-19 were encouraging. Misconceptions about this pandemic exist that need proper education and training of the healthcare workers.

Conflict of interest: None.

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Table I: Reliability analysis.

Statistic	ALL	SECTION 1(Knowledge)	SECTION 2 (Attitude)	SECTION 3 (Practice)
Cronbach's alpha	97.8%	96.5%	90.5%	92.1%
Average Interitem correlation	0.451	0.423	0.446	0.551
Average Interitem covariance	0.089	0.062	0.085	0.215
Intraclass correlation coefficient	0.978	0.965	0.905	0.921
ANOVA's p-value	<0.001	<0.001	<0.001	<0.001

Table II: Descriptive statistics for the Knowledge scale.

		Agree	Not sure	disa-gree	Scale Mean ± SD
Causative organism of COVID-19 is called SARS-CoV-2 (Severe Acute Respiratory Syndrome – Coronavirus 2).		100 (83.33)	8 (6.67)	12 (10.00)	0.83 ± 0.37
Incubation period reported for SARS-CoV-2 varies between 6 and 14 days.		20 (16.67)	73 (60.83)	27 (22.50)	0.17 ± 0.37
Transmission of infection could be:	Close contact	112 (93.33)	2 (1.67)	6 (5.00)	0.93 ± 0.25
	Droplet	115 (95.83)	4 (3.33)	1 (0.83)	0.96 ± 0.2
	Airborne	66 (55.00)	31 (25.83)	23 (19.17)	0.55 ± 0.5
	Faeco-oral	39 (32.50)	29 (24.17)	52 (43.33)	0.33 ± 0.47
	Object contamination	93 (77.50)	16 (13.33)	11 (9.17)	0.78 ± 0.42
	Surface contamination	99 (82.50)	15 (12.50)	6 (5.00)	0.83 ± 0.38
Vertical transmission can occur.		44 (36.67)	42 (35.00)	34 (28.33)	0.37 ± 0.48
COVID-19 has a teratogenic effect.		5 (4.17)	58 (48.33)	57 (47.50)	0.04 ± 0.2
COVID-19 leads to increased risk of miscarriage.		47 (39.17)	55 (45.83)	18 (15.00)	0.39 ± 0.49

Adverse health outcomes due to COVID-19, include:	respiratory distress	103 (85.83)	10 (8.33)	7 (5.83)	0.86 ± 0.35
	prematurity	62 (51.67)	39 (32.50)	19 (15.83)	0.52 ± 0.5
	foetal death	38 (31.67)	53 (44.17)	29 (24.17)	0.32 ± 0.47
Pregnancy is a state of partial immunosuppression where morbidity/mortality due to COVID-19 is higher.		102 (85.00)	10 (8.33)	8 (6.67)	0.85 ± 0.36
Pregnancy is a state of partial immunosuppression where there is more vulnerability to COVID-19 infection		95 (79.17)	17 (14.17)	8 (6.67)	0.79 ± 0.41
Symptoms/signs include	dyspnea	114 (95.00)	2 (1.67)	4 (3.33)	0.95 ± 0.22
	Fever	118 (98.33)	1 (0.83)	1 (0.83)	0.98 ± 0.13
	Fatigue	117 (97.50)	0 (0.00)	3 (2.50)	0.98 ± 0.16
	dry cough	117 (97.50)	1 (0.83)	2 (1.67)	0.98 ± 0.16
	anorexia	95 (79.17)	14 (11.67)	11 (9.17)	0.79 ± 0.41
	myalgia	108 (90)	7 (5.83)	5 (4.17)	0.9 ± 0.3
	sputum production	39 (32.50)	27 (22.50)	54 (45.00)	0.33 ± 0.47
	Pneumonia	106 (88.33)	11 (9.17)	3 (2.50)	0.88 ± 0.32
	anosmia (loss of smell)	118 (98.33)	1 (0.83)	1 (0.83)	0.98 ± 0.13
	ageusia (loss of taste)	116 (96.67)	1 (0.83)	3 (2.50)	0.97 ± 0.18
Statins can be used		50 (41.67)	23 (19.17)	47 (39.16)	0.42 ± 0.5
Use of ibuprofen is encouraged		20 (16.67)	3 (2.50)	97 (80.83)	0.17 ± 0.37

There is an effective medication currently, which is safe and effective against COVID-19.	20 (16.67)	4 (3.33)	96 (80.00)	0.17 ± 0.37
Hydroxychloroquine/chloroquine can be used with the same regimen as that of non-pregnant patients	45 (37.50)	25 (20.83)	50 (41.67)	0.38 ± 0.49
Hydroxychloroquine and azithromycin can be combined in a regimen for COVID-19 in pregnant patients.	20 (16.67)	39 (32.50)	61 (50.83)	0.17 ± 0.37
Antiviral treatment is not recommended in pregnant patients.	13 (10.83)	40 (33.33)	67 (55.84)	0.11 ± 0.31
Plasma of patients who recovered from COVID-19 infection can be used and has proved promising.	96 (80.00)	0 (0.00)	24 (20.00)	0.8 ± 0.4
Antibiotics are to be used in all of COVID-19 suspected patients.	34 (28.33)	23 (19.17)	63 (52.50)	0.28 ± 0.45
Glucocorticoids are generally beneficial for COVID-19 patients.	43 (35.83)	35 (29.17)	42 (35.00)	0.36 ± 0.48
Adequate rest, hydration, nutritional support, antipyretics, and water and electrolyte balance are not supportive measures by any means.	39 (32.50)	30 (25.00)	51 (42.50)	0.33 ± 0.47

Table III: Descriptive statistics for the attitude

	Agree	Not sure	disagree	Scale Mean ± SD
Modification of antenatal care visit appointments are protective or helps in reduction of transmission of COVID-19	82 (68.33)	26 (21.67)	12 (10.00)	0.68 ± 0.47
Appointments for normal growth scans and follow-ups should be cancelled	60 (50.00)	9 (7.50)	51 (42.50)	0.5 ± 0.5
Pregnant women should be isolated	90 (75.00)	9 (7.50)	21 (17.50)	0.75 ± 0.43
Pregnant women should adapt social distancing	119 (99.17)	0 (0.00)	1 (0.83)	0.99 ± 0.09
Termination of pregnancy before viability will never be required to improve maternal conditions	70 (5.83)	3 (2.50)	47 (39.17)	0.58 ± 0.5
CT/X-ray are not allowed during pregnancy of a COVID-19 suspected subject.	29 (24.17)	9 (7.50)	82 (68.33)	0.24 ± 0.43
The usual manpower can be present in the labor ward of infected patients.	13 (10.83)	10 (8.33)	97 (80.84)	0.11 ± 0.31
COVID-19 is not an indication for cesarean delivery.	80 (66.67)	13 (10.83)	27 (22.50)	0.67 ± 0.47

General anesthesia should be avoided as much as possible.	103 (85.84)	7 (5.83)	10 (8.33)	0.86 ± 0.35
Direct breastfeeding is recommended in women infected with COVID – 19	33 (27.50)	21 (17.50)	66 (55.00)	0.28 ± 0.45
Separation of neonates from their mothers becomes essential in case of a probable COVID-19 mother.	73 (60.84)	16 (13.33)	31 (25.83)	0.61 ± 0.49

Table IV: Descriptive statistics for the practice

	Yes	Some-times	No	Scale Mean ± SD
You delay appointments till end of working day/operation room list for suspected/confirmed cases	94 (78.33)	6 (5.00)	20 (16.67)	0.62 ± 0.49
You use portable ultrasound machine	93 (77.50)	2 (1.67)	25 (20.83)	1.62 ± 0.76
While managing subjects who are COVID-19 infected, you have your full personal protective gear	108 (90)	12 (1.00)	0 (0.00)	1.57 ± 0.82
You shorten the duration of presence near to or in contact with a case	96 (80.00)	7 (5.83)	17 (14.17)	1.9 ± 0.3
You encourage home birth	22 (18.33)	12 (10.00)	86 (71.67)	1.66 ± 0.72
You delay elective caesarean section deliveries until the patient is both negative and no longer contagious.	22 (18.33)	14 (11.67)	84 (70.00)	0.47 ± 0.79
You recommend social distancing to decrease the risk of infection	114 (95.00)	4 (3.33)	2 (1.67)	0.48 ± 0.79
You reduce the number of visits to decrease the risk of infection	107 (89.17)	11 (9.17)	2 (1.67)	1.93 ± 0.31
You recommend telehealth to decrease the risk of infection	79 (65.83)	32 (26.67)	9 (7.50)	1.88 ± 0.38
You recommend antenatal vaccinations to decrease the risk of infection	37 (30.83)	43 (35.83)	40 (33.33)	1.58 ± 0.63

The effect of umbilical cord loops around the fetal neck on the modified Doppler myocardial performance index (Mod- MPI) in a sample of Egyptian population. Running Title: Effect of presence or absence of nuchal cord on Mod- MPI

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Abstract

Aim: To evaluate if there is a significant difference on the modified myocardial performance index (Mod-MPI) in cases of umbilical cord loops around the fetal neck (nuchal cord).

Methods: This was a cross-sectional study that included 60 healthy pregnancies between 28 to 35 weeks' gestation with a loop of cord around the neck (group A) and another 60 controls (group B). They were all undergoing ultrasound examination in a private clinic in Egypt from January 2021 till March 2022. Loops of cord around the neck were identified by grey scale and color Doppler. The Mod-MPI was used to assess fetal myocardial function using the Hernandez-Andrad et al. technique and the value was calculated according to Tei et al.

Results: There was no statistically significant difference between the age, BMI, nor the gestational age between both groups. However, there was a statistically significant difference regarding gravidity and parity between both groups with mean gravidity 2.13 +/- 1.41 and mean parity 0.87 +/- 1.10 for group A and mean gravidity 2.89 +/- 1.94 mean parity 1.44 +/- 1.42 (p=0.038 and 0.031) respectively. Finally, there was a statistically significant increase in the mean and standard deviation of the Mod MPI between Group A and B; 0.427 and 0.406 respectively. (p= 0.014)

Conclusion: We hope this study could provide valuable information for a comprehensive and objective evaluation of the effects nuchal cord on fetal wellbeing as well as guide intervention and provide new ways to reduce perinatal morbidity and mortality. We consider this a pilot and study and further studies with a larger sample size and follow up till delivery are required to be able to draw clearer and more solid conclusion.

Key words: Nuchal cord, Mod-MPI , fetal myocardial function.

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Introduction

Umbilical cord around the fetal neck in not uncommon occurring in up to 25% of fetuses. Most cases have no consequences and are just incidental findings. Occasionally, it may form cord knots or tight cord around the neck. In such cases intrauterine growth retardation or oligohydramnious or diminished fetal kicks and rarely intrauterine fetal demise may occur. Such effects occur as a result hemodynamic affection when a tight cord is present (1), where variable degrees of compression of the umbilical vein ends in hypoxia and acidosis. (2) Presence of two or more cord loops around the neck during labor could alter the mode of the delivery as well as the early neonatal outcome. (3) Many fetuses delivered with a tightened cord present around the neck show petechiae on the face and retinal or conjunctival hemorrhage. In other cases, there is severe respiratory distress, hypotonia, and urgent need for resuscitation. (4) There are several risk factors for occurrence of nuchal cord; it was generally noticed with multiparity and increased maternal age, and male fetuses. Additionally, it was observed with increased fetal movements and polyhydamnious or increased liquor (3).

For over twenty years, the primary tool to assess fetal cardiac function was fetal echocardiography. It is a non-invasive modality assessing cardiac anatomy as well as hemodynamics. Two-dimensional imaging, M-mode, and pulsed wave Doppler are utilized used in fetuses as well as animal models to assess both systolic and diastolic functions all through gestation (5-8).

Tei and colleagues first described the myocardial performance index (MPI) aiming to assess and evaluate cardiac functions of adults having dilated cardiomyopathy. This non-invasive index is a Doppler-derived modality and has been reported as a useful index of global cardiac function. This MPI was calculated by adding the isovolumetric relaxation time (IRT) and isovolumetric contraction time (ICT) and dividing the sum by ejection time (ET) {(IRT + ICT)/ET} (9). Later this index (MPI) was used to assess the global myocardial function of the fetus by Tsutsumi and colleagues. (8) However, there was a noticeable variation in the reference values. This was mainly as a result of absence of clear identifiable landmarks in the obtained Doppler waves used to measure these specific time intervals. As a result, the modified myocardial performance index (Mod-MPI) was devised by Hernandez-Andrade and colleagues and used the Doppler echoes of the aortic valve (AV) and the mitral valve (MV) clicks. This lead to lesser variation in addition to better inter as well as intra-observer reproducibility when compared to the standard MPI. (10) Several conditions as intrauterine growth retardation (8,11–13), gestational or pregestational diabetes (14-18), twin to twin transfusion syndrome (TTTS) (19-22), congenital heart defects (23-26), and preeclampsia (27) demonstrated the value of the MPI and its recent modification to assess cardiac performance and function. Additionally, some authors recently estimated nomograms for the Mod MPI in second and third trimester (0.408 ± 0.08). They demonstrated that the Mod MPI was not changed by the mother's age, parity, or body mass index (BMI) (28)

Putting this into perspective we aimed in this study to assess the myocardial function by measuring the Mod- MPI in the presence of one loop of umbilical cord around the fetal neck and to compare it to fetuses with no nuchal cord.

Methods

This cross-sectional study was performed in a private clinic. The study group (A) included of 60 healthy pregnant women with a single fetus between 28 and 35 weeks of gestation with a loop of cord around the fetal neck. The control group (B) similarly included 60

healthy pregnant women between 28 and 35 weeks of gestation but did not have any loops around the neck at the time of measurements of the Mod MPI. The study started from January 2021 till March 2022. We excluded fetuses with anomalies, IUGR, SGA and mothers with any known medical disorders whether pregnancy related (eg preeclampsia) or not.

Following recruitment all patients provided a written consent after a thorough explanation of the study protocol. We recorded maternal demographic characteristics, medical and obstetric history.

The ultrasound examinations were carried out by one sonographer (S.E) who had enough experience in fetal US. All measurements were double checked, and an average was obtained. Pregnancy dating was accurately estimated by fetal crown– rump length at the 11th + 0 to 13th + 6 weeks' gestation if no accurate dates were obtained. All pregnant ladies had a detailed anomaly scan that included fetal echocardiograph. The scans were conducted trans-abdominally using 2 Machines, GE Voluson P8 and GE Voluson E8 (General Electric, Chicago, IL, USA).

Any loops of the umbilical cord around the neck were detected both by grey scale and color Doppler ultrasonography. These patients were assigned to group A. Patients with no loops around the neck were assigned as group B. we examined the loops of cord in the longitudinal view of the fetus (figure 1-2) and in the transverse view of the fetal neck. The latter was found to be more accurate than longitudinal view (figure 3-5)

We followed the Giacomello classification system for cord around neck (29-30):

- type A: a nuchal loop that encircles the neck in a freely sliding pattern, where the placental end crosses over the umbilical end; this pattern can undo itself
- type B: a nuchal loop that encircles the neck in a locked pattern, where the placental end crosses under the umbilical end; this pattern locks and cannot undo itself with potential for fetal morbidity or mortality.

It was difficult to differentiate between these two classifications in our study and not all patients were classified.

We the calculated the Mod MPI for all fetuses. We used the technique devised by Hernandez-Andrad et al. as shown in figure 6 (10). The measurements were done in the absence of any fetal movements nor respiratory movements and the mother voluntarily suspended her breathing. The velocity of the Doppler sweep was the highest velocity available (15 cm/s) for clear and accurate identification of the components of the Doppler tracing. Additionally, the E/A waveform was always displayed as positive flow. The angle of insonation was maintained below 30 degrees and the thermal and mechanical indices did not exceed 1. A cross-sectional cut of the fetal thorax was obtained in the four-chamber view and an apical projection (anterior or posterior) of the heart was obtained as shown in figure 7 and 8. The Doppler sample volume was put on the lateral wall of the ascending aorta, below the aortic valve and just above the mitral valve. The Doppler trace showed a clear echo corresponding to the opening and closure of the two valves at the beginning and at the end of the E/A (mitral valve) and AF (aortic valve) waveforms. The time periods were then estimated according to : the ICT was estimated from the closure of the MV, to the opening of the AV, the ET from the opening to the closure of the AV, and the IRT from the closure of the AV to the opening of the MV (figures 6-7-8). The result for the Mod-MPI was calculated as: (ICT + IRT)/ET (9)

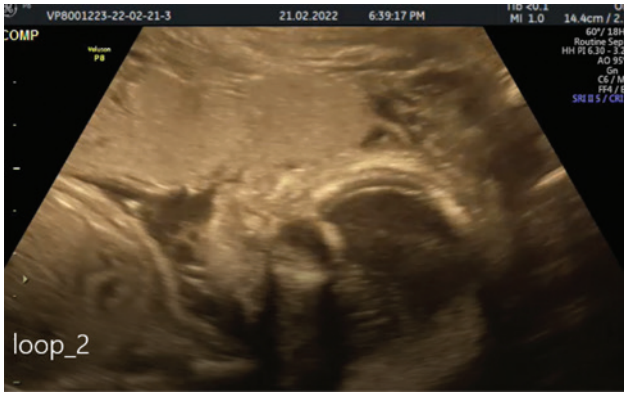

Fig 1: (Longitudinal view) A Sagittal view of the fetus with loops of cord seen below the fetal chin using gray scale image.

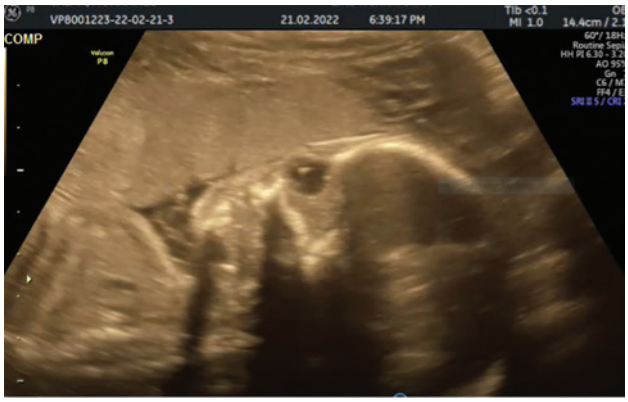

Fig 2: (Longitudinal view) A parasagittal view of the fetus with loops of cord seen below the fetal chin using gray scale image.

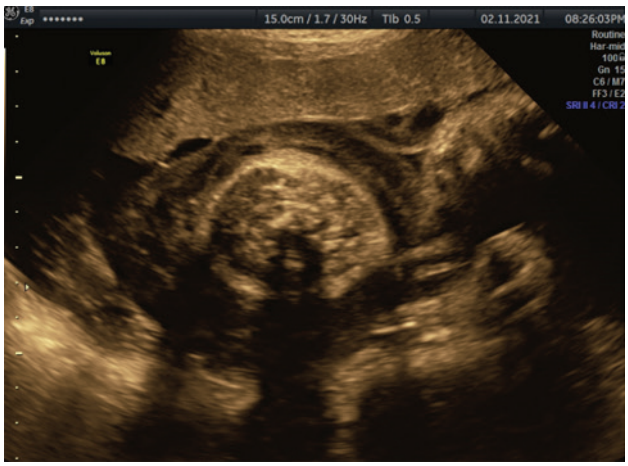

Fig 3: (Transverse view) Cut-section in the fetal neck with loop of cord seen around the fetal neck using a gray scale image.

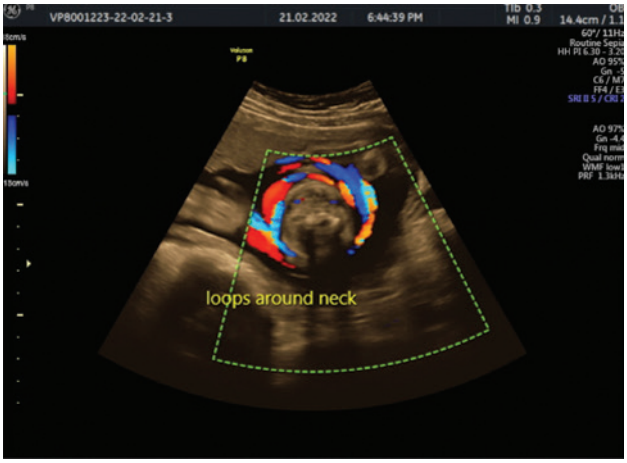

Fig. 4: (Transverse view) Cut-section in the fetal neck with loop of cord seen around the fetal neck using colour Doppler.

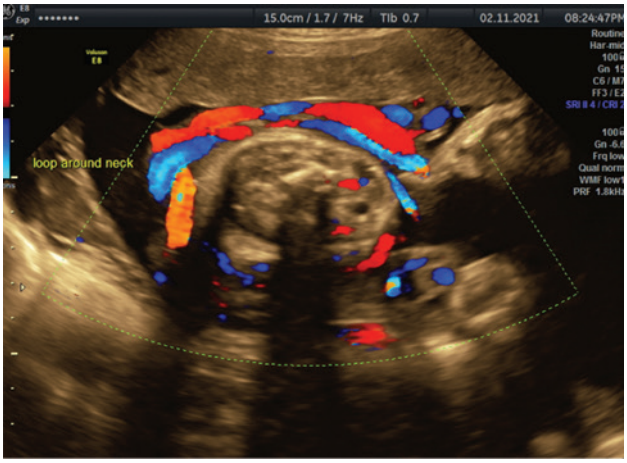

Fig. 5: (Transverse view) Cut-section in the fetal neck with loop of cord seen around the fetal neck using colour Doppler

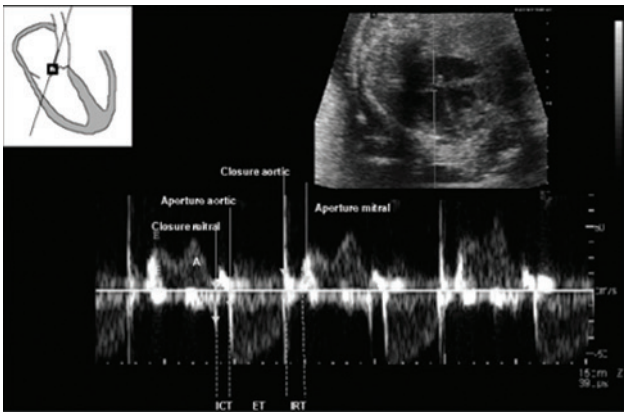

Fig 6: Doppler envelope of the modified myocardial performance index (Mod-MPI). The sample volume is located over the lateral wall of the aorta, close to the mitral valve. References for the time-period estimations are based on the echoes from the mitral and aortic valve movements. The E/A waveform is always displayed as positive flow. ET, ejection time; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time. (10)

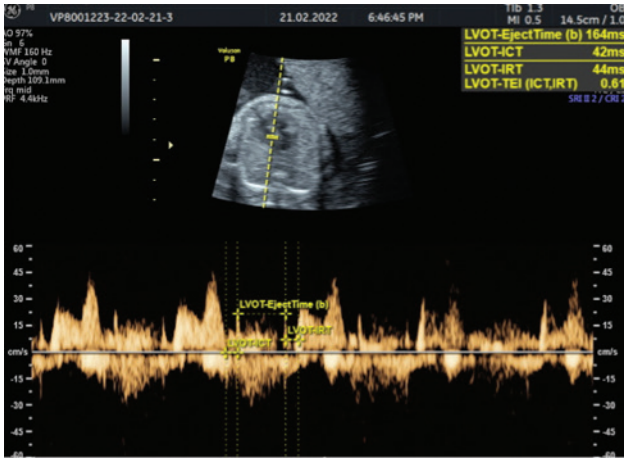

Fig 7: An example of a case with a fetal heart apical view directed upward and obtained a modified myocardial performance index.

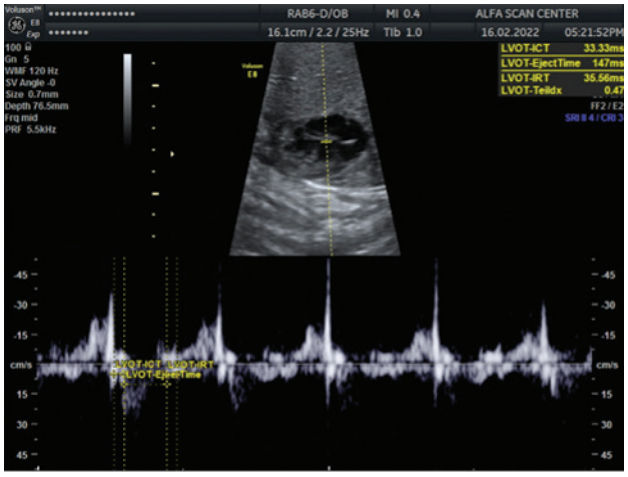

Fig 8: : An example of a case with a fetal heart apical view directed downwards and obtained a modified myocardial performance index.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical package for the social sciences- IBM® SPSS® Statistics Version 20 for Windows, IBM Corp., Armonk, NY, USA). Data was represented as mean ± standard deviation. Data was explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Data were non-normally distributed and Mann-Whitney U test was used to compare variables between the two groups. The results were considered statistically significant if the p value was less than 0.05.

Results

We approached 312 patients and collected the data of the first 60 who did not have a nuchal cord as controls (group B). Meanwhile any patient who had a loop of cord around the neck was allocated to group A. All other patients who did not have a nuchal cord after the control group was fulfilled were excluded. In our cohort the nuchal cord was identified in 19.1% of patients (60/312).

The mean age was the same across both groups being 29.9 years +/- 5.33 in group A and was 30.0 years +/- 5.72 in group B (p= 0.83). Similarly, the BMI and the gestational age at the time of the examination showed no statistically significant difference between both groups; group A mean BMI 26.8 +/- 2.85 and gestational age (GA) 31.4 +/- 1.93 while for group B mean BMI 27.5 +/- 3.47 and GA 31.1 +/- 2.16 (p=0.39 and 0.38) respectively. However, there was a statistically significant difference regarding gravidity and parity between both groups with mean gravidity 2.13 +/- 1.41 and mean parity 0.87 +/- 1.10 for group A and mean gravidity 2.89 +/- 1.94 mean parity 1.44 +/- 1.42 (p=0.038 and 0.031) respectively. Demographic data are represented in table 1.

Table 1: Demographic data of our study and control groups

	Group A	Group B	P value
Age (mean and SD)	29.9 +/- 5.33	30.0 +/- 5.72	0.83
BMI (mean and SD)	26.8 +/- 2.85	27.5 +/- 3.47	0.39
GA (mean and SD)	31.4 +/- 1.93	31.1 +/-2.16	0.38
Gravidity (mean and SD)	2.13 +/- 1.41	2.89 +/- 1.94	0.038
Parity (mean and SD)	0.87 +/- 1.10	1.44 +/- 1.42	0.031

As for the Mod MPI there was a statistically significant increase in the mean and standard deviation between Group A and B 0.406 and 0.427 respectively (p= 0.014) as shown in figure 9.

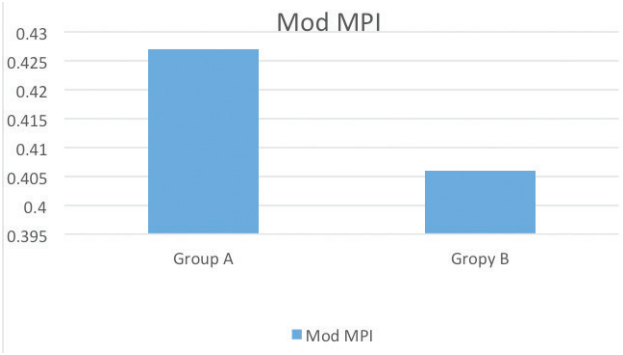

Figure 9: shows a significantly higher Mod MPI in Group A than Group B (P=0.014)

Discussion

While most nuchal cords have no or minimal adverse outcomes, some reports demonstrated poor outcomes which might be correlated with the number of cord loops around the fetal neck as well as the tightness of these loops. (4) In this study we aimed at utilizing the Mod MPI as a predictive tool for fetal hemodynamic changes which might be associated with significant undesirable consequences. We considered this a pilot study just to check if there would be a change in the Mod MPI when nuchal cords are present not knowing whether this will influence the neonatal outcome or not.

In our study we found that nuchal cords were common in women with lower parity rather than higher parities. This is contrary to what a recent study showed in 2021 were women of higher parity had more frequent loops of cord around the neck. (3) This team studied 250 patients and found that only 50 patients 20% were nullipara and the remaining 80% (200 patients) were multipara. We assume such a difference in to be related to sample size and GA at detection as they had a mean GA of 38.24 +/- 1.2 which is higher than our cohort's GA. However, we agree with their detection rate of nuchal cord, 18.8% vs 19.1% in our study. We also agreed with authors from other countries who have demonstrated similar incidence of nuchal cord 65 out of 350 or 18.6% (31) and 100 out of 506 or 19.8% (32). Other reports have shown an incidence of up to 25% (1).

We have found no correlation for the presence of a nuchal cord with the age of the patient, BMI or GA at the time of examination. This agrees with most other authors (3, 31,32) who also found no relation with these demographic parameters.

To date, there are only a few studies describing cardiac parameters of fetuses with loops of cord around neck. A former study suggested that the incidence of IUFD caused by nuchal cord is higher than without a nuchal cord. (33) Therefore, prompt, and correct assessment of the fetal hemodynamics and cardiac functions cannot be ignored in those fetuses. In 2012 Zuo and colleague utilized "velocity vector imaging" (VVI) to detect myocardial strain in such fetuses. They studied 35 patients and concluded that (VVI) might respond to changes in cardiac function in such fetuses. (1) However, (VVI) is a very demanding 2-dimensional image, that needs clear image acquisition to clearly identify

endocardial borders, in addition to a small fetal heart volume and shadowing from the ribs and spines. (34,35)

In 2020, Seif et al., made a gestational age-based reference for the Mod MPI in the Egyptian population working on 1021 fetuses. (28) We agreed with their reference ranges whether in patients with or without nuchal cords. Other authors, however, reported a wider variation of reference ranges which might be attributed to different sample sizes and a wider range of gestational ages. (34)

In our study we have detected that the Mod MPI significantly increased in fetuses with a nuchal cord. Additionally, it was previously reported that it increased under different pathological conditions, as when there is an increase in the afterload due to increased placental resistance. (36) Our results also agree with Api et al., who detected an increase in the Mod MPI in fetuses of preeclamptic mothers. (37)

By this we can assume that Mod MPI increase might be a marker for cardiac strain in such fetuses. Whether this will affect the outcome or not is not known yet and this is a main limitation of the study as we did not follow up these fetuses. Other limitations include small sample size and imperfect classification of the nuchal cord in all the patients. However, we consider our strength to be proper assessment of this index by an experienced sonographer.

We hope this study could provide valuable information for a comprehensive and objective evaluation of the effects of nuchal cord on fetuses, as well as guide interventions and provide new ways to reduce perinatal morbidity and mortality. We consider this a pilot and study and further studies with a larger sample size and more follow up are required to be able to draw clearer and more solid conclusion.

Conflicts of interest: The authors have nothing to declare.

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Subclinical endometritis after first-trimester abortion

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Abstract

Background: Endometritis is a severe complication occurring after the termination of pregnancy. It occurred at variable rates after first-trimester abortion. Variable diagnostic methods with variable accuracies are reported.

Aim: to detect endometritis after medical and surgical termination of first-trimester abortion using different diagnostic methods.

Methods: This cross-sectional study was conducted at the obstetrics and gynecology department at Fayoum university from May 2018 to February 2020. The study recruited 100 women divided into two groups. Groups A and B included fifty patients who had medical and surgical evacuation of first-trimester abortion, a history of unexplained delayed conception for at least one year, and recurrent miscarriage. Recruited women were subjected to history taking, laboratory investigation, pelvic examination, trans-vaginal ultrasonography, and endometrial sampling. An office hysteroscopy was arranged during the follicular phase of the menstrual cycle. This was followed by two endometrial samples using the Pipelle (Pipelle de Cornier, CCD).

Results: There was an insignificant difference between group A and group B regarding H&E examination by Hysteroscopy and Pipelle and immunostaining examination by Pipelle (P-value > 0.05);. At the same time, it points to a statistically significant difference between group A and group B regarding Immunostaining examination by Hysteroscopy (P-value =0.029). Endometritis was more significantly evident in Immunostaining examination by hysteroscopy in group B than in group A (40% vs. 20%, respectively). The diagnostic accuracy of Immunostaining examination by hysteroscopy was significant (P-value = 0.028).

Conclusion: Endometritis occurs significantly after surgical termination of first-trimester abortion. Hysteroscopic guided biopsy followed by immunohistochemistry was associated with high diagnostic accuracy for endometritis.

Key words: endometritis; abortion; immunostaining; hysteroscopy.

Introduction

Endometritis is defined as inflammation of the endometrium, which lines the uterine cavity. It is considered a pelvic inflammatory disease (1). It occurs due to ascending infection from the genital tract; however, after pregnancy, it occurs due to retained products of conception (RPC) (2). After an abortion, the risk increases due to cervical opening, fetal tissue and blood clots, and uterine instrumentation (3).

First-trimester abortion could be managed surgically or medically. Surgical termination would be associated with infection, uterine perforation, and Asherman syndrome, while; medical termination was associated with avoiding surgical intervention, failed evacuation, and increased bleeding (4). The development of intrauterine synechia was related to endometritis (5). Other reported changes included polyp formation and vascular changes created by endometritis, and as a result, endometrial receptivity was impaired (6). The diagnosis was confirmed by plasma cell infiltration in endometrial biopsies (7). The diagnosis was further confirmed by immunohistochemical staining of endometrial samples (8). Given that endometritis would lead to infertility (9), the current study evaluated endometritis after two first-trimester pregnancy termination methods.

Methods

This cross-sectional study was conducted at the obstetrics and gynecology department at Fayoum university from May 2018 to February 2020. The study recruited 100 women divided into two groups. Group A included fifty patients who had medical evacuation by misoprostol due to a first-trimester abortion, a history of unexplained delayed conception for at least one year, and/or recurrent miscarriage following the medical evacuation. Group B involved fifty patients who had surgical evacuation due to first-trimester abortion and had a history of unexplained delayed conception and/or recurrent miscarriage.

Women aged ≥40 years, with infertility related to a known cause, with recurrent miscarriage due to a known cause, with oxytocin-induced first-trimester abortion, with a history of second-trimester abortion, and those refusing to participate in the study were excluded.

Recruited women were subjected to: -

- History taking included name, age, residence (urban or rural), gravidity, parity, the number of miscarriages, history of evacuation of the products of conception, and method of evacuation, whether medically by misoprostol or surgically by dilatation and evacuation.
- Laboratory investigation: qualitative beta-human chorionic gonadotrophin (B-HCG) to exclude ongoing pregnancy.
- Pelvic examination to detect the position and size of the uterus, vaginal abnormalities, pelvic infection, and cervical polyps.
- Transvaginal ultrasonography (TVS) to exclude organic causes of abortion and delayed conception.
- Endometrial sampling: First, an office hysteroscopy was arranged during the follicular phase of the menstrual cycle (days 6–12), getting a panoramic view of the uterine cavity, the endometrium, and tubal ostia. This was followed by two endometrial samples using the Pipelle (Pipelle de Cornier, CCD). The samples were collected in two separate tubes filled with formalin and normal saline NaCl 0.9% with a ratio of 1:10, respectively.

All specimens were submitted to the same laboratory and analyzed by the same pathologist, utterly ignorant of the hysteroscopic results.

Formalin-fixed biopsies were embedded in paraffin-forming blocks. Each block was sliced into two four-micron sections, one of which was stained with Haematoxylin and Eosin for standard histological inspection. The other was immunostained for Syndecan-1 (CD138) to show plasmacytes.

Pathological diagnostic criteria for chronic endometritis

- For HE-stained specimens: At least five typical plasma cells were visible in the endometrial stroma for the diagnosis of chronic endometritis (10).
- For Immunohistochemically stained specimens: in each 400 x magnification field, five or more typical plasma cells were observed in the endometrial stroma for the diagnosis of chronic endometritis (11).

Statistical analysis

Data were coded and entered using SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the non-parametric Mann-Whitney test. For comparing categorical data, Chi-square ($\chi 2$) test was performed. The exact test was used when the expected frequency was less than 5. P value was considered significant when < 0.05. ROC curve was constructed with the area under curve analysis performed to detect the best cutoff value.

Results

One hundred and nine women were eligible for the study. Nine patients refused to participate in the study, leaving 100 women for the final analysis. Patients were allocated into two groups according to their history of evacuation of first-trimester abortion, with 50 patients in each group.

There was no statistically significant difference between both groups regarding age, gravidity, parity, and residence. (P-value > 0.05) (Table I).

Table (II) showed an insignificant difference between group A and group B regarding H&E examination by Hysteroscopy and Pipelle and immunostain examination by Pipelle (P-value > 0.05);. At the same time, it points to a statistically significant difference between group A and group B regarding Immunostain examination by Hysteroscopy (P-value =0.029). Endometritis was more significantly evident in Immunostaining examination by hysteroscopy in group B than in group A (40% vs. 20%, respectively).

There was an insignificant difference between Hysteroscopy and Pipelle regarding H&E examination and Immunostaining examination in both groups (P-value > 0.05 each)

The diagnostic accuracy of Immunostaining examination by hysteroscopy was significant (P-value = 0.028). Sensitivity, specificity, -ve prediction, +ve prediction, accuracy, and the likelihood ratio of Immunostaining examination by hysteroscopy are 40, 80, 66.7, 57.1, 63.14%, and 4.83, respectively (Table III).

Discussion

Endometritis occurred in a higher proportion after surgical evacuation of pregnancy rather than a medical evacuation. The difference was insignificant, but when hysteroscopy and Syndecan-1 were utilized in combination, 40% of cases were detected. This agreed with previous study results using the same diagnosis technique (12). An earlier study reported lower infection rates after medical termination of first-trimester abortion (13), which further decreased after adopting the oral route of misoprostol administration (14). This would be rendered to the vaginal

flora gaining access to the uterine cavity. Additionally, uterine instrumentation increased this risk (15).

The current study adopted the threshold of at least five plasma cells for the diagnosis of endometritis according to previously published studies (16, 17). Different endometritis rates were reported previously, which was rendered to the different diagnostic methods, which only depended on histological detection of plasma cells (18).

Endometritis was better demonstrated with combined hysteroscopy and immunohistochemistry. It also demonstrated better diagnostic accuracy than other tools, which was different from other studies (9, 19) due to different sample sizes, surgical experience, and ethnicity. This was attributed to the increased false negative rates by the Pipelle biopsy as it is a blind technique for obtaining tissue that might miss small polyps. Additionally, these micropolyps are exposed to destruction and crushing during tissue preparation (20). Besides, endometritis might be localized, which enables better detection and evaluation using hysteroscopic guided biopsies (21). Also, tissue preparation may affect the detection of plasma cells leading to missed diagnosis (22). Earlier studies confirmed the superiority of immunohistochemistry in the diagnosis of endometritis over traditional H&E stain (8, 12).

Strength and limitations of the study

The role of hysteroscopy was highlighted as a diagnostic tool. We used a diagnostic marker of high accuracy (CD138) to diagnose inflammation. However, The small sample size of our study was apparent, and maybe the etiology of some contradicting results.

Conclusion

Endometritis occurs remarkably after surgical termination of first-trimester abortion. Hysteroscopic guided biopsy followed by immunohistochemistry was associated with high diagnostic accuracy for endometritis.

Conflict of interest: None.

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Table I: Distribution of demographic data of the studied groups.

	Medical evacuation (N= 50)	Surgical evacuation (N=50)	P value
Age (years) (median, range)	30.00 (25.75-38.00)	28.00 (23.00-35.25)	0.235
Gravidity (median, range)	4.00 (3.00-5.00)	3.00 (2.00-6.00)	0.930
Parity (median, range)	3.00 (2.00-3.25)	2.00 (1.00-4.00)	0.131
Rural residence N (%)	36 (72.0%)	35 (70.0%)	0.826
Urban residence N (%)	14 (28.0%)	15 (30.0%)	

Table II: Comparison between group A and group B regarding H&E examination by Hysteroscopy and Pipelle and Immunostain examination by Hysteroscopy and Pipelle

		Group A	Group B	P-value
		N (%)	N (%)	
H&E examination by hysteroscopy	**-ve**	43 (86%)	36 (72%)	0.086
	+ve (Endometritis)	7 (14%)	14 (28%)	
H&E examination by Pipelle	**-ve**	46 (92%)	40 (80%)	0.084
	+ve (Endometritis)	4 (8%)	10 (20%)	
Immunostain examination by hysteroscopy	**-ve**	40 (80%)	30 (60%)	**0.029**
	+ve (Endometritis)	10 (20%)	20 (40%)	
Immunostain examination by Pipelle	**-ve**	44 (88%)	38 (76%)	0.118
	+ve (Endometritis)	6 (12%)	12 (24%)	

Table III: Diagnostic accuracy of the different methods used

	Sensitivity	Specificity	-VE prediction	+VE prediction	Accuracy	Likelihood Ratio	
						Value	P-value
H&E examination By Hysteroscopy	28.00	86.00	66.7	54.4	58.21%	3.00	0.083
Immunostain examination by Hysteroscopy	40.00	80.00	66.7	57.1	63.14%	4.83	**0.028**
H&E examination by Pipelle	20.00	92.00	71.4	53.5	56.40%	3.076	0.079
Immunostain examination by Pipelle	24.00	88.00	66.7	53.7	56.39	2.47	0.115

Association between the mode of delivery and breastfeeding

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Abstract

Background: The rising rate of cesarean section is noticed all over the world. Cesarean delivery is associated with multiple adverse effects. Its association with successful breastfeeding has been questioned.

Objective: To evaluate the association between breastfeeding and the mode of delivery.

Study design: This was a cross-sectional study conducted from January 2021 to December 2021 at a tertiary hospital's obstetrics and gynecology department. We recruited women with a firstborn child aged 18- 45 years and had their delivery 1.5 to 2 years ago. Data were obtained about age, weight, height, occupation, level of education, duration of exclusive breastfeeding, total duration of breastfeeding, and need for supplementary formula. Data about the mode of delivery - vaginal, elective CS, CS after labor pains- were also obtained.

Results: There were 21, 49, and 19 women in the vaginal delivery, elective CS, and emergency CS groups, respectively. The mean age of the studied population was 25.51 ± 3.6. The duration of breastfeeding was prolonged with vaginal delivery (13.6 ± 7.1 months) yet, statistically insignificant (p-value 0.412). Exclusive breastfeeding was maintained with vaginal delivery (80.9%) followed by elective CS delivery (71.4%), but the difference was insignificant (p-value 0.455). Lower body mass index predicted successful breastfeeding significantly (p-value 0.021).

Conclusion: There was no difference between the mode of delivery and successful breastfeeding. The body mass index was a significant predictor for exclusive breastfeeding.

Key words: breastfeeding; cesarean section; vaginal delivery.

Introduction

Breastfeeding is beneficial to the mother and the baby; however, the rate of exclusive breastfeeding is declining (1, 2). The mode of delivery influences breastfeeding adversely, particularly cesarean delivery. The mode of delivery is decided by the combined opinions of the obstetricians and the parturient herself (3). The

association between breastfeeding and the mode of delivery is not well established, with data documenting no association (4, 5) while others reported negative association (6). With the rising rates of cesarean deliveries, far from the recommended rates by the WHO (7), it is crucial to understand the relationship between breastfeeding and the mode of delivery. This would be helpful while counseling women requesting elective cesarean delivery. This study aimed to explore the association between the mode of delivery and breastfeeding in nulliparous women.

Methods

This was a cross-sectional study conducted from January 2021 to December 2021 at the obstetrics and gynecology department of a tertiary hospital. The study was conducted after the approval of the research ethics committee. Written informed consent was obtained from all participants before enrollment in the study.

We recruited women according to inclusion and exclusion criteria as follows:

- **Inclusion criteria:** a) age range from 18- 45 years, b) primiparous women, c) delivery from 1.5 to 2 years ago, and d) women delivering vaginally, elective cesarean section (CS), and CS after labor pains.
- **Exclusion criteria:** a) women who refused to participate in the study, b) women who refused to breastfeed their infants, c) history of chronic illness, d) history of a breast mass or surgery requiring cessation of breastfeeding, e) smoking, and f) complications after delivery –PPH, puerperal infection, prolonged hospital admission, and tears or infected wounds.

Eligible women were interviewed, and data were obtained about age, weight, height, occupation, level of education, duration of exclusive breastfeeding, total duration of breastfeeding, and need for supplementary formula. Data about the mode of delivery – vaginal, elective CS, CS after labor pains- were obtained. We recruited eligible women over one year.

Ethical approval: This study was conducted after approval of the research ethics committee of faculty of medicine, Suez Canal University, in 28/12/2020 with an approval number of 4397#.

Results

One hundred and one women were eligible for the study. Twelve women refused to participate in the study leaving 89 women participating in the study. There were 21, 49, and 19 women in the vaginal delivery, elective CS, and emergency CS groups. The mean age of the studied population was 25.51 ± 3.6, with younger women having vaginal delivery than their peers. The majority of CS was among housewives and highly educated women (75.5% and 81.6 %, respectively) (Table 1).

The duration of breastfeeding was prolonged with vaginal delivery (13.6 ± 7.1 months) however; the difference was insignificant (p-value 0.412). Exclusive breastfeeding was maintained with vaginal delivery (80.9%) followed by elective CS delivery (71.4%), yet the difference was insignificant (p-value 0.455) (Table 2).

Logistic regression analysis revealed that lower BMI was a significant predictor for successful breastfeeding (p value 0.012) (Table 3).

Discussion

Cesarean delivery rates were increased among women of advanced ages, highly educated women, and housewives. This agreed with the results of a previous study in which CS was increased among older women and high school graduates (3, 8). It has been

reported that CS rates increase with age and family income. This would be explained by preferring birth in private hospitals with higher CS rates than governmental ones (9). However, there is a discrepancy in CS rates, which may be related to cultural and social factors that affect women's decisions regarding the mode of delivery (3).

The duration of breastfeeding and exclusive breastfeeding was prolonged with vaginal delivery, although insignificant. This agreed with the results reported in a previous study where no association was found between the duration of breastfeeding and exclusive breastfeeding between women delivered vaginally or by CS (3). In the meantime, previous studies reported that exclusive breastfeeding was significantly lower among women delivered by CS (10, 11, and 12). Additionally, vaginal delivery failed to predicted successful breastfeeding. This was in agreement with the results reported by Kiani et al., where breastfeeding did not differ according to the mode of delivery (13). However, another study reported that CS was associated with breastfeeding for one month (14). Also, women who delivered by VBAC had successful breastfeeding than those delivered by repeated CS (15).

Additionally, higher education was associated with breastfeeding for less than one month. This was documented in the current study as well. This was rendered to maternal awareness of the benefits of breastfeeding and the ability to decide to breastfeed. Those women would be employed in a full-time job which hinders breastfeeding (14). This would be explained by the negative maternal feelings associated with CS as a surgical intervention precluding the duration of breastfeeding (14). Successful breastfeeding is affected by the delay in skin-to-skin contact between the mother and the neonate, as the neonate is transferred to a nursing unit allowing the mother to rest and recover after delivery (10). Also, there might be antepartum or intrapartum fetal complications that lead to delayed breastfeeding (3). This would lead to early interruption of breastfeeding before six weeks of delivery (16).

Additionally, the increased rates of CS above the recommended rates by the WHO contribute significantly to failed breastfeeding (10). Prescription of post-cesarean delivery antibiotics is a routine practice in our country. Women may delay breastfeeding initiation for fear of transmission of the antibiotic to their infants (17). The amount of breast milk is scarce in the first five days after cesarean delivery contributing to an additional obstacle for breastfeeding initiation (18).

Lower BMI was a significant predictor of successful breastfeeding. This was in accordance with a previous systematic review where obese women were less able to initiate breastfeeding or to maintain exclusive breastfeeding for a long period (19). Failure to initiate breastfeeding was explained by the storage of progesterone in fat cells which affects the production of lactogenesis II (20). Also, obese women have large breasts which might impact the ability of the neonate to suckle adequately (21). As obesity might be associated with other comorbidities, this would impact successful breastfeeding (22). In addition, obese women had lower confidence in their ability to provide adequate milk, less satisfaction towards body image, and lack of intention towards prolonged breastfeeding (23, 24).

Strength and limitations

This study recruited a small number of primiparous women. This was within two years of delivery to avoid recall bias. Few women were still breastfeeding their infants, contributing a little to the proper estimation of breastfeeding duration. Not all of them had their delivery in the institute, causing a lack of information about elective or emergency CS practiced in private hospitals, which might affect the mothers' decision regarding breastfeeding.

Conclusion

There was no difference between the mode of delivery and successful breastfeeding. The body mass index was a significant predictor for exclusive breastfeeding.

Conflict of interest: None.

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Table 1: Patient demographic data

Variables	Variables	Mode of delivery			P value
		Vaginal delivery (21)	Elective CS (49)	Emergency CS (19)	
Occupation N (%)	House wife	17 (80.9%)	37 (75.5%)	17 (89.5%)	0.432
	Working	4 (19%)	12 (24.5%)	2 (10.5%)	
Education N (%)	None	5 (23.8%)	0 (0%)	1(5.3%)	0.008
	Middle	2 (9.5%)	9 (18.4%)	4 (21.1%)	
	High	14 (66.7%)	40 (81.6%)	14 (73.6%)	
Age (Years) (Mean ± SD)		24.3 ± 3.8	25.9 ± 3.9	26.4 ± 3.3	0.196
BMI		26.4 ± 5.2	27.1 ± 4.7	25.1 ± 3.2	0.300

Table 2: Duration of breastfeeding among the studied population

Variable	Vaginal delivery (21)	Elective CS (49)	Emergency CS (19)	P value
Duration in months (mean ± SD)	13.6 ± 7.1	10.9 ± 7.5	11.8 ± 9.0	0.412
Exclusive breastfeeding N (%)	17 (80.9%)	35 (71.4%)	12 (63.2%)	0.455
Need for supplementation	6 (28.6%)	15 (30.6%)	7 (36.8%)	0.838

Table 3: Logistic regression analysis for the predictors of successful breastfeeding

Parameter	β	P value	95% CI
Housewife	-0.319	0.595	0.224- 2.358
None educated	1.718	0.114	-0.151- 0.180
Middle education	-1.941	0.071	0.017- 1.184
Vaginal delivery	-1.639	0.069	0.033- 1.133
Elective CS	-0.391	0.522	0.358- 0.980
Age	0.011	0.419	0.204- 2.239
BMI	-0.027	0.012	-0.048- -0.006

A randomized double-blinded clinical trial to explore the clinical outcome of self-administered vaginal isonicotinic acid hydrazide (INH) administration 12 hours before hysterosalpingography in primarily infertile patients

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Abstract

Objective: The purpose of this study was to assess the clinical outcomes of using a combination of oral Ketoprofen and vaginal isonicotinic acid hydrazide (INH) for pain management during hysterosalpingography (HSG) vs using solely oral Ketoprofen.

Methods: The randomized controlled study was conducted between August 2020 and September 2021. Infertile women scheduled for HSG were randomized (1:1) to Ketoprofen with or without INH. All women received oral 150 mg Ketoprofen plus 900 mg vaginal INH or placebo tablets 12 hours before the procedure. The primary outcome was the participant's self-rated pain perception utilizing a 10-cm Visual Analogue Scale (VAS). During speculum insertion, cervical tenaculum application, dye injection, and 5 and 30 minutes following the procedure, the participants' self-rated pain was assessed using a 10-cm VAS.

Results: A total of 200 women participated (100 in each group). Oral Ketoprofen combined with vaginal INH substantially lowers the major VAS pain ratings during dye injection (4.23 ± 0.89 vs. 6.18 ± 0.90), 5-minute post-procedure (3.05 ± 0.95 vs. 5.81 ± 0.91), and 30-minute post-procedure (2.14 ± 0.74 vs. 4.69 ± 0.80), with p 0.01 at all phases. After using a speculum or tenaculum, there were no significant differences in VAS values. In terms of side effects, there was no significant difference between the study groups.

Conclusion: Adjuvant vaginal INH to oral Ketoprofen 12 hours before HSG may be considerably more effective than Ketoprofen alone in reducing the caused pain score during and 30 minutes after the HSG procedure.

Key words: Hysterosalpingography; INH, NSAIDs; infertile; pain.

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Introduction

Infertility is described as a couple's failure to conceive after 12 months of unprotected sexual intercourse (1). Tubal abnormalities are estimated to be the cause of infertility in 30–40% of infertile people, hence tubal patency testing is crucial in their identification (2).

A radiographic evaluation of a women's genital tract is called hysterosalpingography (HSG). Examinable areas include the cervical canal, endometrial cavity, tubal lumen, and peri adnexal region. The National Institute for Health and Care Excellence suggests using HSG to check for tubal occlusion as part of a baseline infertility workup (3).

During cervical instrumentation, dye injection into the uterus, which produces distension, or peritoneal irritation owing to tubal leak, women may experience substantial pain (5).

Women's pain during HSG is essential since it may affect their compliance, decreasing the procedure's value. The greatest effective technique for pain mitigation during HSG is debatable in the literature. (6)

Nulliparity, a history of dysmenorrhea, anxiety, and a high degree of predicted pain are all risk factors that may enhance the amount of pain experienced (4, 5). Nonsteroidal anti-inflammatory medicines, topical anesthetic gel or spray, paracervical block, nitrous gas, misoprostol, and conscious sedation have all been used to alleviate pain during HSG, with mixed success. (7).

There are multiple randomized comparison trials for pain reduction utilizing HSG, according to a recent Cochrane systematic review. Despite the fact that the results of this systematic review reveal that only topical anesthetics provide significant pain relief, the authors recommend that large randomized controlled trials be conducted to investigate the effect of combining multiple analgesic classes on HSG-related pain (8).

Because the synthesis of prostaglandins from cervical manipulation and uterine distension can cause pain during HSG, a prostaglandin-synthetase inhibitor looks to be a promising pain-relieving method. NSAID given one hour before hysteroscopy will have the most analgesic impact throughout the procedure. After one 50 mg Diclofenac pill, mean peak plasma concentrations took 20–60 minutes to reach (9).

Oral non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be ineffective in reducing pain during HSG or within 30 minutes in a variety of trials, with variable results. (10,11).

Cervical ripening can be caused by the nitric oxide donors isosorbide mononitrate and glyceryl trinitrate. Nitric oxide donors may be a better choice than prostaglandins for cervical ripening. (12)

Isonicotinic acid hydrazide (INH) is an anti-tuberculosis medication that helps the cervical ripening process. In term pregnancies, it was proven to be just as effective as misoprostol (13). According to some studies, the effect of INH on cervical ripening may be due in part to nitric oxide (NO) production in the cervix. INH injection has previously been shown to cause a significant increase in NO levels in rat red blood cells (RBCs), and it has been suggested that NO plays a critical role in the pathophysiology of INH-induced oxidative stress in RBCs (14).

The purpose of this study was to assess the clinical outcomes of using a combination of oral Ketoprofen and vaginal isonicotinic acid hydrazide (INH) for pain management during HSG vs using solely oral Ketoprofen.

Materials and Methods

A randomized, double-blind controlled study (ClinicalTrials.gov identifier NCT04500470; registered on August 3, 2020) was conducted at a tertiary university hospital between August 1, 2020, and September 30, 2021.

The hospital's Institutional Research Ethics Committee accepted the study's protocol (Aswu/352/3/19). Patients were counseled and signed a written informed consent form before enrolling in the study.

Eligible Participants

Women who visited our infertility department and underwent HSG for a primary infertility workup were asked to participate in the study. We included infertile women, aged 19–42 years old, who did not receive any analgesics in the 48 h before HSG.

The study excluded women having a history of cervical surgery, acute pelvic inflammatory illness, secondary infertility, NSAID contraindications, unexplained irregular uterine bleeding, or acute cervicitis. The study excluded women with persistent pelvic pain, irregular uterine bleeding, or a history of cervical surgery. Women who had an allergy to INH or had a medical condition that made it impossible for them to use it were also excluded, as did those who refused to take part in the trial.

Participants who qualified were divided into one of two groups. Group I women received 3 tablets (900 mg) of vaginal INH 12 hours before the procedure. Group II women received 1 placebo tablet to INH. All patients received 150 mg of Ketoprofen 1 hour before the procedure.

Randomization

Participants were randomly assigned to receive INH or a placebo vaginal tablet in a 1:1 ratio. A statistician who was not engaged in the study in any way created a computer-generated randomization table and placed the allocation data in serially numbered sealed envelopes. Each envelope contained a card indicating the sort of intervention. Only a study researcher opened the envelopes in the order of women's attendance. Allocation could not be modified once it had been completed.

All women were randomly allocated to one of two groups: (INH, group) received three 300 mg INH tablets virginally 12 hours before HSG, or (Placebo group) got three placebo tablets of the same size, color, and shape as INH tablets. The Faculty of Pharmacy's Pharmaceuticals department pharmacist made the placebo pills. The same pharmacist placed all the study drugs into unlabeled sterile boxes, so neither the physicians nor the ladies knew what they were getting (double-blind study).

Intervention

One of the study researchers approached all included women and collected their demographic characteristics: age, parity, residence, educational level, duration of infertility, history of dysmenorrhea or chronic pelvic pain, and history of previous HSG. He next gave the subjects an explanation of the common 10-cm visual analog scale (VAS) for pain assessment. (15). A VAS scale was used to measure the intensity of the pain (0 being no pain and 10 being the worst agony possible). Finally, he instructed the women to take the Ketoprofen oral tablet one hour before HSG and insert place the INH or placebo tablets as high as feasible in the vaginal canal 12 hours before their HSG appointment.

All of the female patients had HSG as an outpatient procedure while in the follicular phase of their menstrual cycle. A single experienced radiologist performed the HSG. On a fluoroscopic table, women were positioned in the dorsal lithotomy position. The radiologist inserted a sterile speculum into the vagina and used povidone-iodine to clean the cervix. A Rubin's cannula was then introduced into the cervical canal after the anterior lip of the cervix was gripped with a tenaculum. A 15 ml water-soluble contrast dye (Sodium amidotrizoate and meglumine at 76% Urografin® Bayer Hispania SL; Barcelona; Spain) was injected over 20

seconds into the uterine cavity.

Radiographic images were taken in the anteroposterior view when the uterine cavity was filled with the dye. All equipment was then taken away, and the women were given a 30-minute observation period within the clinic. The woman was asked to assess the level of discomfort during the operation using the same 10-point VAS on multiple sheets of paper by the research assistant who was standing next to her. Six different times during the procedure—baseline (expected pain), after speculum installation, after tenaculum implantation, after dye injection, and 5 and 30 minutes later—participants were asked to assess their level of discomfort.30 minutes after the surgery, all women were questioned about whether they needed any extra analgesics.

Ibuprofen 400 mg was made accessible to women as extra analgesia if necessary because it was widely available in our clinic. All women were asked to report any side effects occurring during the procedure and 30 min after HSG, such as syncope, dizziness, nausea, or vomiting.

Study Outcome

The main endpoint was the variation in mean pain score throughout the procedure. The number of women who required extra analgesics, the difference in the mean pain scores at 5 and 30 minutes after HSG, and the adverse effects of the study drugs were the secondary endpoints.

Sample size

Sample size calculation was based on the VAS score during the most painful step of the HSG procedure as reported by a randomized clinical trial (16). The most painful mean VAS score was 4.9 with a standard deviation (SD = 2.7) in the placebo group. We considered a 25% reduction to an overall VAS score of 3.7 (SD = 2) in the active treatment group would be significant. Considering an alpha error of 0.05, a statistical power of 85%, and a 10% rate of loss to follow-up. A sample size of at least 100 women in each group would be required.

Statistical Analysis

SPSS software, version 21, from Chicago, Illinois, USA, was used to analyze all data. When necessary, Fisher's exact test and the Chi-square test were utilized to compare groups. Quantitative data were described as means (SD) or medians, after testing for normality by the Kolmogorov-Smirnov test. In normally distributed variables, independent samples t-test was used for comparison between groups. P ≤0.05" was statistically significant.

Results

A total of 220 women were approached to take part in the study. Four women experienced irregular uterine bleeding, and eight women had already had intravenous analgesics prior to HSG, thus they were disqualified. In addition, eight women rejected to take part in the research. The remaining 200 women were divided into two groups at random (Fig. 1, the study flowchart).

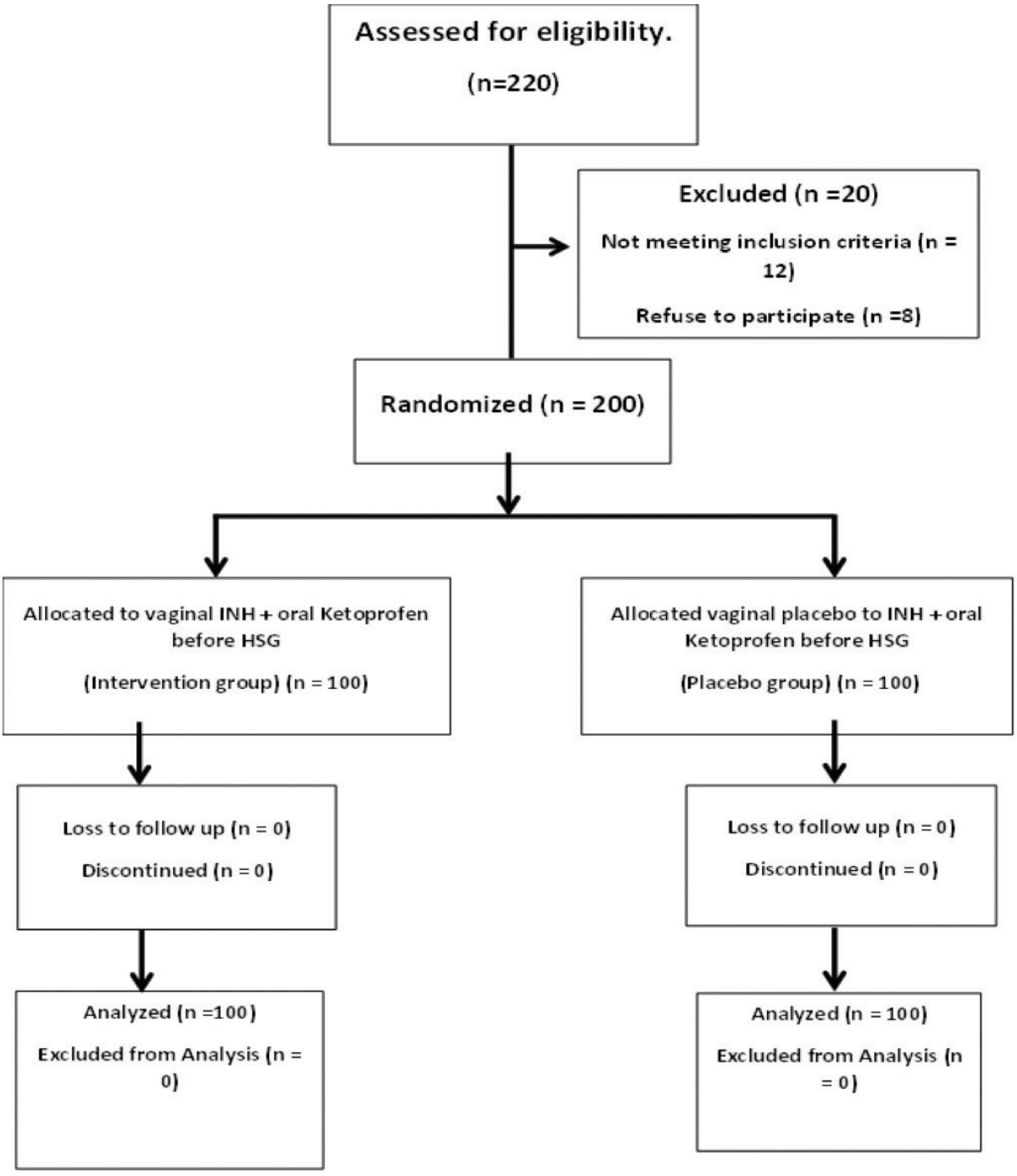
There was no significant difference between the two groups' baseline characteristics, such as age, BMI, length of infertility, place of residence, and educational level. (Table 1).

The pain score for each group was determined using a visual analog scale (VAS). There was no significant difference in pain score between the two groups during speculum and tenaculum application (p=0.7, p=0.7). However, in comparison to the placebo group, there was a substantial reduction in pain score during dye injection, 5- and 30-minutes following injection in the INH group, (P<0.001). In addition, women in the INH Group were more satisfied than those in the placebo group(P<0.001).

In comparison to the INH group, the addition of extra analgesic resulted in a substantial rise in the placebo group. P=0.013; however, there was no significant difference in the mean procedure duration between the two groups, p=0.719 (Table 2).

In terms of HSG result diagnosis, there were no significant differences between the two groups, (P = 0.9). (Table-3)

There was no significant difference between the research groups in terms of adverse effects. (Table-4)



Discussion

This is the first randomized, double-blind, placebo-controlled study in women with primary infertility to test the effectiveness of vaginal INH with oral Ketoprofen against oral Ketoprofen alone in lowering pain during and after HSG.

Adjuvant 900 mg vaginal INH utility 12 hours before HSG to 150 mg oral Ketoprofen one hour before HSG considerably reduced the caused pain scores during and 30 minutes after the HSG treatment as compared with Ketoprofen alone.

HSG is a valuable diagnostic method in the study of infertility. One of the most serious concerns with this therapy is difficulty reaching the interior cervical os. When there is significant cervical stenosis, an immature cervix, or severe anteflexion or retroflexion, cervical trauma or uterine perforation are more likely (17). Traditional cervical dilatation with Hegar's dilators may not be feasible in certain patients with very tight cervices or cervical abnormalities, regardless of parity (18). Furthermore, uterine sounding might be a challenge or a failure in particular disciplines. As a result, cervical softening is critical to the success of the procedure.

INH is a cervical ripening therapy that is still relatively new. According to the findings of a study conducted by Highlight et al. (19), vaginal INH is an effective medication for cervical ripening prior to labor induction in term pregnancies. When it comes to cervical dilatation, INH acts similarly to NO donors. According to the findings of several studies (20), INH impacts cervical dilatation via NO production.

The minimal clinically significant difference (MCSD) in VAS pain score was defined by Todd et al. (21) as the quantitative change in VAS pain score that is connected to the patient's subjective judgment of a little less or a little more discomfort. MCSD in acute pain ranged from 13 to 20 mm (22), (23), and changes in VAS pain score of less than 13 mm may be of low clinical relevance (24).

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

In a study by Moore (25), pain sources during HSG were described as cervical instrumentation, pain secondary to uterine distention with contrast medium, and pain due to peritoneal irritation because of contrast leakage into the peritoneal cavity.

We hypothesized that cervical priming using INH as adjunctive to ketoprofen may decrease the filling pressure of the uterus with contrast media and decrease pain; our results indicated that INH reduces the VAS outcomes compared to those of the group that does not use INH.

The pain score in the area of dye injection was higher than 30 minutes following the procedure in both groups, according to the findings of this study. According to other research, the most painful element of the HSG process was injecting the dye into the uterine cavity (2, 18,).

Women who underwent vaginal INH were more satisfied than women in the placebo group when questioned about their satisfaction with the HSG procedure. There were no significant differences in side effects or procedure-related complications between the two groups. Many studies use our dose for cervical ripening, and they did not encounter any adverse drug reactions in either group specialty headache (19,26)

One study indicates that the mechanism(s) of action of INH may be similar to nitric oxide (NO) donors but without their frequent adverse effects, such as headache or hypotension.

The subjective assessment of pain in our study was limited by the fact that it might be influenced by patient characteristics or anxiety levels. Randomization and adequate

research design, however, were able to overcome this issue.

The randomized, double-blind, placebo-controlled design of our study is one of its strongest features. The ladies and the HSG radiologist were blinded, and sufficient sample size was acquired. In addition, we employed validated pain measures and evaluated women's satisfaction, which was not done in many previous studies. Finally, the trial was carried out at the same hospital with a single radiologist to exclude any inter-assessor variability in pain VAS assessment.

Conclusion

Adjuvant vaginal INH to oral Ketoprofen 12 hours before HSG may be considerably more effective than Ketoprofen alone in reducing the caused pain score during and 30 minutes after the HSG procedure.

Ethics declarations

Ethics approval and consent to part manuscript preparation icipate

Approval of the western Municipality and Faculty of Medicine was obtained. The ethical review board approved the study by a grant number of (Aswu/209/7/20) from Aswan university Review Board and Ethics Committee. ClinicalTrials.gov identifier NCT04500470; registered on August 3, 2020.

Every patient enrolled in the study counselled about the intervention and written informed consent was taken from each woman before performing any intervention.

Consent for publication

Not applicable

Availability of data and material

The data was obtained from case records of outpatient clinic in our department.

Competing interests

The authors declare that they have no competing interests.

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There was no funding received from the institution.

Authors' contributions

All authors agree to be accountable for all aspects of the work. NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation: HM manuscript preparation, AT: manuscript preparation. HM: manuscript preparation, design preparation

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Figure legends

Figure 1: Consort flowchart showing enrollment of participants.

Table (1): Base line Characteristics in the study groups: -

Parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Age (year)	29.4±3.3	29.1 ±2.7	T=0.9, p=0.4
BMI	27 ±2.2	27.3 ± 2	T= 1.2, p= 0.2
Anticipated pain score	5.5 ± 1	5.5 ± 1.1	T=0.3 p=0.8
Duration of infertility (year)	4 ±1.3	4.04 ±1.3	T=0.3 p= 0.8
Residence (%): Urban Rural	 31 (31) 69 (69)	 37 (41) 63 (63)	Chi-squared test=0.8 P=0.4
Education level (%) Primary Secondary high	 35 (35) 42 (42) 23 (23)	 31 (31) 44 (44) 25 (25)	Chi-squared test=0.4 P=0.8
Position of uterus (%): AVF RVF Mid position	 70 (70) 22 (22) 8 (8)	 72 (72) 21 (21) 7 (7)	Chi-squared test=0.1 P=0.9

BMI (body mass index),

Variables are presented as mean and standard deviation, and number (percentage).

Table (2): The study outcomes in the study groups: -

Parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Duration of the procedure	12.9±1.3	12.8±1.7	T=0.3, p=0.7
VAS at speculum placement	3.01 ± 0.8	3 ± 0.9	T=0.3, p=0.7
VAS at tenaculum placement	4.02 ± 0.8	4.01 ± 0.9	T=0.1, p=0.9
VAS during dye injection	4.04 ± 0.8	6 ± 1.04	T=14.7, p < 0.001*
VAS 5 minutes post injection	3 ± 0.8	5 ± 0.9	T=17.4, p < 0.001*
VAS 30 minutes post injection	1.9 ± 0.7	4.1 ± 0.8	T= 19.6, p < 0.001*
Women satisfaction score	6.6 ± 1.1	4.4 ± 1.2	T= 13.5, p < 0.001*
Need for additional analgesia (%)	12 (12)	28 (28)	Chi-squared test=8 p= 0.005*

VAS (visual analogue scale). *Statistically Significant Difference

Variables are presented as mean and standard deviation, and number (percentage).

Table (3): Diagnosis of HSG (hysterosalpingogram) in the study groups: -

parameters	INH Group (n = 100)	Placebo Group (n = 100)	Test of significance
Diagnosis of HSG (%)			
Normal	53 (53)	50 (50)	Monte Carlo test
Uterine adhesion	1 (1)	2 (2)	
Uterine anomalies	6 (6)	7 (7)	P = 0.9
Unilateral tubal block	13 (13)	14 (14)	
Bilateral tubal block	9 (9)	8 (8)	
Peri tubal adhesion	18 (18)	19 (19)	

Variables are presented as number (percentage).

Table (4): Side effects in the study groups: -

parameters	INH Group (n = 100)	Placebo Group (n = 100)	Significance
Tenaculum site bleeding (%)	8 (8)	9 (9)	Chi-squared test=0.1, p= 0.8
Headache (%)	17 (17)	14 (14)	Chi-squared test=0.3, p= 0.6
Fever (%)	0	1 (1)	----
Chills (%)	0	0	----
Nausea (%)	3 (3)	5 (5)	Fisher s exact test, p= 0.7
Vomiting (%)	0	0	----
Diarrhea (%)	0	0	----

Measuring the effectiveness of hysteroscopic resection of symptomatic cesarean scar defects and its effect on quality of life

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Abstract

Background: Cesarean section (CS) delivery increased to represent more than one third of all deliveries. CS related complications include CS scar defects that result in abnormal uterine bleeding which affect female sexual function and women's quality of life.

Aim: To evaluate the effectiveness of hysteroscopic resection of cesarean scar defects in symptomatic women.

Materials and methods: A randomized clinical trial conducted in the obstetrics and gynecology department of a tertiary hospital. Patients were recruited according to inclusion and exclusion criteria. 70 Patients were allocated into two groups: a study group who had hysteroscopic resection of the scar defect and a control group who were managed expectantly. Patients were assessed for postmenstrual spotting amount and duration. Evaluation of spotting related discomfort and dysmenorrhea was done using a visual analogue scale. Quality of life was evaluated using the Arabic validated SF 36 quality of life questionnaire. Patient satisfaction was measured using a five- point Likert scale.

Results: There was a statistically significant difference between both groups regarding the total number of spotting days post-procedure. The visual analogue scale decreased from 8.37 ± 1.57 and 2.69 ± 1.57 to 3.31 ± 1.76 and 1.43 ± 1.01 for discomfort and dysmenorrhea respectively in the study group. The study group showed significantly increased scores of each component of the quality-of-life questionnaire . Patients' satisfaction was significantly increased in the study group than the control one. The overall satisfaction rate was 74.28%.

Conclusion: Hysteroscopic niche resection resulted in improved patients' symptoms and quality of life.

Key words: niche; resection; postmenstrual bleeding; hysteroscopy.

Synopsis: Caesarean scar defect result in postmenstrual bleeding affecting women's quality of life. Hysteroscopic niche resection considered to be an effective and safe approach for treatment of women with symptomatic niche.

Introduction

Globally, there is an increase in the rate of cesarean section (CS) reaching about 1/3 of all deliveries (1). This attracted the attention towards CS related complications and its effects on women's health (2). Monteguado et al., first described a CS scar defect presented as an anechoic area at the site of the scar and was called "niche" (3). It occurred at an incidence of 24- 69% of cases with previous CS delivery as evaluated by transvaginal ultrasound (4). This resulted in a range of symptoms including pelvic pain, dysmenorrhea, postmenstrual bleeding, and infertility. This was collectively called cesarean scar syndrome (5). About one-third of women with niche complain of abnormal uterine bleeding either in the form of prolonged menstruation or postmenstrual spotting (PS) (6). Hysterectomy was the done to treat such symptoms; however, this is not suitable form women desiring fertility. This led to the adoption of less invasive procedures with the aim to drain menstrual blood and to decrease local production of blood by vessel coagulation. This would be performed laparoscopic resection, hysteroscopic resection or through vaginal repair (7-9). Hysteroscopic resection is less invasive with promising results however it requires sufficing residual myometrium to avoid bladder injury (10). Previous studies reported on symptom improvement (PS) with no data about quality- of- life using validated tools (6, 7, 8, 10). The current study aimed at assessing the effect of hysteroscopic niche resection versus no treatment on patients' symptoms (postmenstrual spotting, pain, and bleeding related discomfort), quality of life, and patient's satisfaction.

Materials and methods

The study was a randomized controlled clinical trial conducted at the Obstetrics and Gynaecology department at a tertiary Hospital from May 2020 to September 2021. The medical ethical committee of the Faculty of Medicine approved the study before commencement and informed consents were obtained from all enrolled patients.

Women were recruited according to predetermined inclusion and exclusion criteria. **Inclusion criteria:** a) age ranged from 18- 45 years, b) previous CS delivery, c) history of postmenstrual spotting (defined as two or more days of intermenstrual spotting or two or more days of brownish discharge at the end of menstrual bleeding when the total period of menstrual bleeding exceeds 7 days) (10) and dysmenorrhea, d) persistent spotting for at least three consecutive months after the last caesarean section, and e) fit for hysteroscopic surgery. **Exclusion criteria:** a) Pregnancy, b) Suspected malignancies, c) Absence of cyclic bleeding periods caused by a levonorgestrel intrauterine device (IUD), continuous oral contraceptives or gonadotropin-releasing hormone (GnRH) agonists, d) Contraindications for spinal or general anesthesia, e) Atypical endometrial cells or cervical dysplasia in cervical cytology, f) Uterine or cervical polyps, g) Submucous fibroids, h) evidence of cervical or pelvic infection, i) communicating hydrosalpinx, j) An irregular cycle (defined as less than 21 days or more than 35 days in duration or where the cycle length varied from month to month by more than 4 days) (11), and k) history of coagulopathy.

Randomization was factorial and balanced in a 1:1 manner using a computer-generated randomization list, allocating patients into two groups using opaque sealed envelopes that the senior researcher opened after patients' evaluation for eligibility. Each group matched the same baseline characteristics, including women's socio-demographic characteristics (age group, education, occupation, and residency). The control group included **35 women** who were managed expectantly. The study group included 35 women who hysteroscopic resection of the niche. Patients and researchers were aware

of group allocation, but outcome assessors and data analysts were kept blinded.

Eligible women for the study were subjected to the following:

- **History taking** to obtain their socio-demographic characteristics (age, education, occupation, parity, and residency, along with their Menstrual history, Obstetric history, Past History of surgical operations, Operative details of previous cesarean section and Past history of medical disorders.
- **Clinical examination** (Height measurement while the woman is standing, bared foot, the measurements rounded to the nearest 0.5 cm. Weight measurement using a scale. Women were requested to take off any heavy clothing. Weight rounded to the nearest 0.5 Kg. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Women's BMI was classified according to WHO classification (12).
- **Transvaginal ultrasound evaluation**: for diagnosis of niche, by using a Mindray ultrasound machine, model DC-30, 240-270V 50/60Hz, 630VA (Mindray, china). Patients were examined at the end of their menstrual cycle (between day 5 to day 7). The patients were asked to empty the urinary bladder just before the procedure and was put in the lithotomy position. The transducer tip was covered with gel and introduced into protective rubber sheet (condom). The probe tip was covered with a small amount of gel and was gently inserted into the vagina. Niche was defined as a triangular anechoic area at the site of the scar with a depth of at least 2 mm (3).
- The degree of dysmenorrhea and discomfort were determined using a visual analogue scale (VAS). The VAS is a unidirectional measure of the intensity of pain. It is composed of a horizontal scale, 10 cm in length. It is anchored by two verbal pain extremes. An extreme was represented by "no pain" (scored as 0) and the other extreme was represented by "the worst pain ever" (scored as 10). The patients were told to place a mark on the scale that represents the extent of pain they suffer. The score was determined by measuring the distance between the "no pain" extreme and the mark determined by the patient. This gave a range of scores from 0- 100. A higher score indicated a severe pain (13).
- menstrual changes were reported as a) vaginal spotting defined as very slight bleeding that needs no sanitary protection, b) heavy bleeding defined as bleeding that needs sanitary protection, and c) bleeding/ spotting episode defined as one or more successive days with reported blood loss. The number of bleeding/ spotting days, and number of bleeding/ spotting episodes were reported (14). Bleeding was evaluated using a bleeding diary given to each participant after enrollment. Women were instructed to mark a sign ○ for spotting and a sign ● for bleeding days. The usual menstrual bleeding was marked as /. Women were asked to use disposable normal pads and to report the number of pads each day. Heavy menstrual bleeding was defined as increased menstrual blood loss affecting women's physical, social, emotional, and/ or quality of life (15).
- Quality of life was evaluated using the Arabic validated SF-36 health survey questionnaire (16). It yields an 8-scale profile of functional health and well-being scores: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), mental health (MH), and one single item scale on health transition. Score ranges from 0 to 100, with higher score indicating higher level of function

and/or better health and lower score indicating lower level of function and/or bad health (17).

- Participants received preoperative preparation including vaginal administration of 2 tablets misoprostol (Misotac, Segma pharmaceuticals, Egypt) 3 hours before surgery to soften the cervix.
- Hysteroscopy was performed only in the study group following these steps: a) Under spinal anesthesia, patients were placed in the lithotomy position and the vulva was sterilized, b) Painting and draping of towels with support of both legs, c) Bladder evacuation through urethral metal catheter, d) Examination under general anesthesia (EUA) to determine position of uterus (AVF or RVF) and bimanual examination of adnexa, e) Holding the cervix by multi toothed volsullum, and f) Introduction of the hysteroscope. In cases with insufficient dilatation, mechanical dilatation using Hegar dilator was done.
- The endocervical canal was seen then the uterine cavity was visualized, both tubal ostia were seen then the scar defect can be seen & visualized. Operative hysteroscopy was performed using a 9-mm resectoscope (Karl Storz), unipolar electrical current, and sorbitol-mannitol solution as a medium of distension. We performed a resection of the inferior edge of the defect using a cutting loop and pure cutting current to remove the flap of fibrotic tissue. Complete removal of the scar tissue was done using a resectoscopic loop until the muscular tissue below was evident. The base of the pouch was treated by electrocauterization with a roller-ball 3- mm. The operation was conducted under visual examination (7, 18).
- After the surgery, participants were observed in the inpatient ward for 2 hours to avoid surgical complications or those associated with anesthesia. Participants were evaluated at the outpatient clinic at 3 months after the surgery for assessing improvement of symptoms. Quality of life was evaluated again after surgery.
- Patient satisfaction was measured using a Likert scale from 1 to 5, corresponding to extremely dissatisfied, dissatisfied, neutral, satisfied and extremely satisfied.
- The control group was instructed to follow an expectant management which entailed continuing any medication used to control the symptoms (hemostatic drugs) for three months. Then, quality of life and patient satisfaction were evaluated.

Primary outcome measure was the effectiveness of hysteroscopic resection of niche compared to expectant management in the form of postmenstrual bleeding episodes and its duration. Secondary outcome measures were evaluation of the quality of life and patient satisfaction.

Ethical approval: This study was conducted after approval of the research ethics committee of the faculty of medicine, Suez Canal University, on 19th September 2018 with a number of 3578#.

Sample size

Sample size was calculated according to the following equation (19)

$$n = \left[\frac{Z_{\alpha/2} + Z_{\beta}}{P_1 - P_2}\right]^2 (p_1 q_1 + p_2 q_2)$$

Where:

- n= sample size
- Z α/2 = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)
- Zβ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)
- P1 = Prevalence/proportion of prolonged postmenstrual bleeding after operation = 33.3% (20)

- P2 = Prevalence/proportion of success of procedure = 66.67% (20)
- q = 1-p

According to the previous equation, the sample size was equal to 35 subjects after the addition of a 10% drop-out rate for each group, giving a total sample size of 70 subjects.

Statistical analysis: The data were coded, organized and the final study results was stated using the SPSS (statistical package for social sciences) version 20 and data was presented through tables. As appropriate numerical data was expressed as mean with or without SD and categorical data was expressed as number %. Student T test was used to test statistical significance of continuous variable between two groups, while chi-square test was used for categorical variables. Statistical significance was considered at P-value < 0.05 and highly significance at P-value < 0.01.

Results

Seventy- six women were eligible for the study. Six women refused to participate leaving a total of 70 women allocated to the study and control group (Figure 1).

Table 1 showed that there were no statistically significant differences between the means of the study groups' ages, body mass indices, parities, previous CSs and times since last CSs. Smoking, Parity and previous CS frequency distributions did not show statistically significant differences between the study groups.

Of note, all cases in the study group still had postmenstrual bleeding/spotting after the procedure. There was a statistically significant decrease between both control and study groups regarding total number of spotting days post-procedure (p value < 0.001) (Table 2).

The VAS score decreased from 8.37 ± 1.57 and 2.69 ± 1.57 to 3.31 ± 1.76 and 1.43 ± 1.01 for discomfort and dysmenorrhea respectively in the study group (p value <0.001 and 0.001, respectively) (Table 3).

The study group showed significantly increased scores of each component of the quality-of-life questionnaire as well as the total score after the operation (Table 4). Patients' satisfaction was significantly increased in the study group than the control one (2.8 ± 0.53 and 1.57 ± 0.61, respectively, p value <0.001). The overall satisfaction rate was 74.28%.

Discussion

Postmenstrual bleeding was present in both groups with durations reaching 9 days. This was explained by several causes such as accumulated menstrual blood in the caesarean scar defect with intermittent discharge after cessation of menstruation, failure to drain menstrual blood adequately because of fibrotic tissue presence below the scar defect, and the formation of new fragile vessels causing in situ accumulation of blood (7, 21). Hysteroscopic resection of the niche resulted in improved patients' symptoms (postmenstrual bleeding, pain, and discomfort). This agreed with the results reported previously (7, 10, 18, and 22). This would be rendered to resection of the lower margin of the niche and cauterization of the bleeding fragile vessels in its base improving menstrual blood drainage and decreasing formation of blood after the menstruation stops.

Pain and discomfort were decreased significantly after niche resection. Another study reported a significant reduction in suprapubic pelvic pain (23). According to a previously published systematic review (6), pain resolved in 97% of patients after hysteroscopic- resection (23, 24, 25); however, methods of pain assessment were not mentioned. Discomfort was not decreased significantly in another study (10). This was explained by persistent postmenstrual

bleeding despite the decrease in its duration.

The overall satisfaction rate was 74.28%. This agreed with the results reported previously where 79.66% of the participants reported a satisfactory symptom relief (26) while another one reported increased satisfaction from 2.10 ± 1.05 to 3.53 ± 1.41 ($p<0.01$) (27). A systematic review reported a satisfaction rate of 87% due to relief of bleeding symptoms (6). This study reported a significant improvement in all aspects of the quality- of- life questionnaire as well as the total score. However; this was not evaluated using a validated tool in previous studies (6). A study reported on the QOL after hysteroscopic resection of the niche declared no improvement in the QOL among the study and control groups (10). This would be rendered to the ultrasound findings after the operation where the depth of the niche and the myometrial thickness showed no difference between both groups and within the two groups compared to baseline data. Also, 55% of women allocated in the intervention group had their operation 2- 3 months after allocation. This would result in improper evaluation of the data obtained at 3 months later. Additionally, the duration of bleeding in the control group was prolonged (10 days) with marked improvement with medical treatment which would underestimate the effect of their study.

Strength and limitations

This study evaluated the QOL after surgery using a validated tool. The small sample size is a limitation. Long term follow up would be more conclusive. We did not recruit women with infertility. Postoperative ultrasound evaluation of the scar defect was not done. Blinding was not possible for the patients and the surgeons. We recruited patients with small niche and residual myometrium > 3 mm which might limit the generalizability of results.

Conclusion

Hysteroscopic resection of cesarean scar defects resulted in improved patients' symptoms as well as their QOL.

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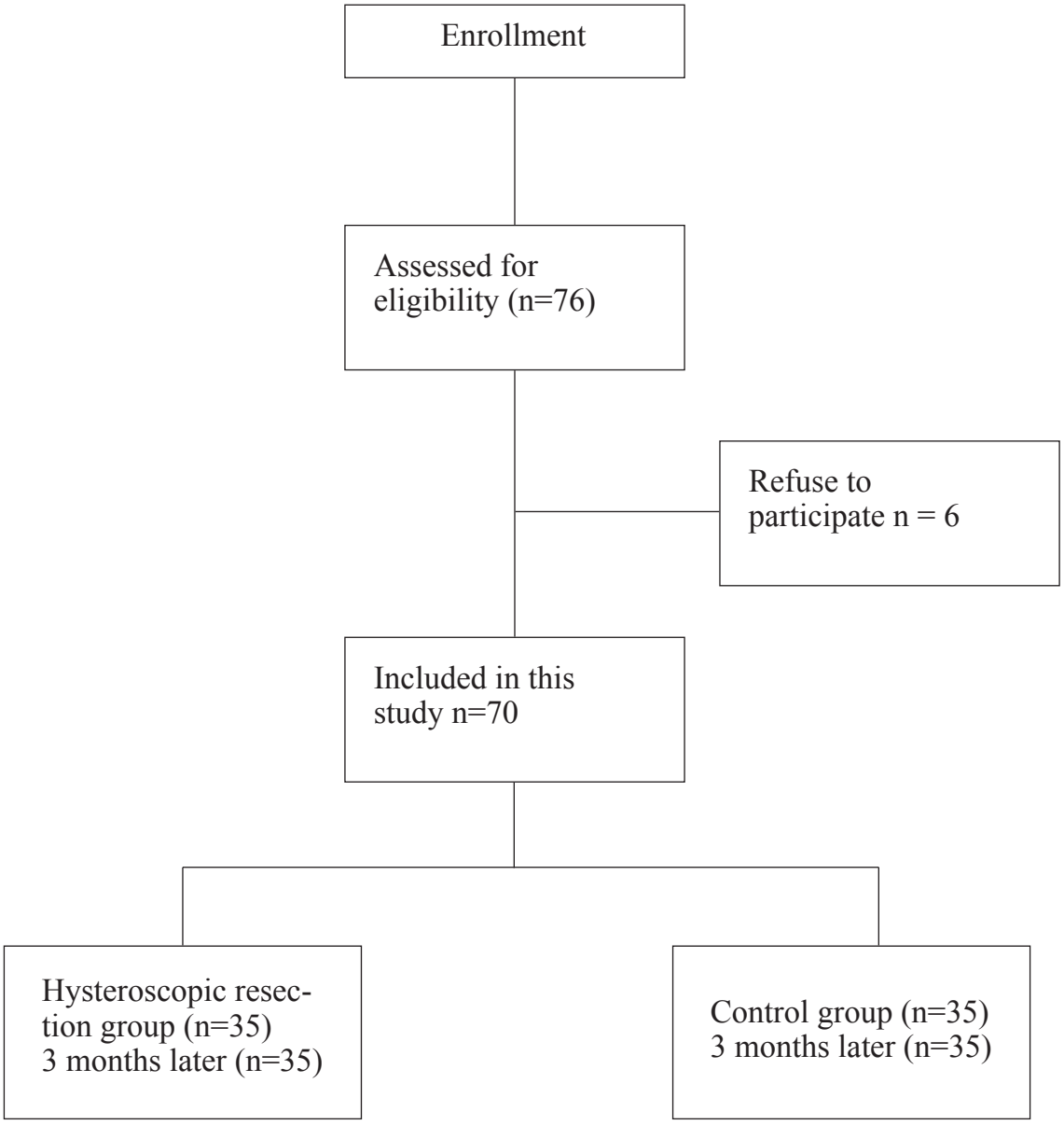
Figure 1: flow diagram of the study



A Novel Simple Clinical Scoring System to Guide the Utilization of Urodynamic Studies in Women with Overactive Bladder Symptoms: A retrospective Observational study

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Keywords: Urinary incontinence, overactive bladder, urodynamic studies, detrusor overactivity

Synopsis: We are suggesting a new clinical score that can be of value in the clinical evaluation of women with Overactive bladder symptoms.

Abstract

Background: To present a simple clinical scoring system that can be utilized in selecting women with overactive bladder symptoms who would benefit from further urodynamic assessment.

Materials and Methods: This was a retrospective study done at a tertiary centre. Filed data of 210 women with OAB symptoms who presented at urinary incontinence clinic were analyzed. Women were grouped into those with detrusor overactivity (DO) and those without DO according to filling cystometry. The variables which were independently associated with DO were used to create a score that can be used for selecting women for further urodynamics assessment.

Results: Women with DO had significantly higher incidence of nocturia (92% vs 62%, p <0.001) urgency (86% vs 66%, p=0.002) and frequency (76% vs 51%, p=0.001). The detrusor overactivity score was calculated by adding the value of the corresponding symptom as follows: nocturia = 3, urgency = 2, frequency = 1. The sensitivity and specificity were 83% and 52% respectively at a cut-off value of 4. Women with a score ≥4 are expected to have DO when assessed by further urodynamic studies.

Conclusion: Detrusor overactivity score can be utilized for selecting women with OAB symptoms who would benefit from performing further urodynamic assessment.

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BACKGROUND

The International continence society (ICS) defined detrusor overactivity (DO) as a urodynamic observation of spontaneous or provoked involuntary detrusor muscles contractions during the bladder filling phase (1). The accepted definition of overactive bladder syndrome (OAB) is "the storage symptoms of urgency with or without urgency incontinence, usually with frequency and nocturia" (2). DO has been reported to be detected in 22-58.4% of women with these symptoms (3)(4).

For assessment of a patient with urinary incontinence (UI), work-up involves history, examination, urine analysis and residual volume assessment (5). Additionally, exacerbating factors, the effect on the woman's quality of life and her desire for treatment should be addressed (6). After this comprehensive assessment, a provisional diagnosis is usually reached, and the most suitable treatment plan is selected (5).

Moreover, urodynamic studies (UDS) are used to objectively diagnose and demonstrate urinary incontinence. They are recommended when the results may change management, following treatment failure, or as part of both short and long-term surveillance programs (5).

The cost-effectiveness of UDS has been evaluated in cases with stress urinary incontinence (SUI) where the treatment is mainly surgical. Reduction in the need for surgery after testing has been found more or less effective (7). However, in OAB where therapy is mainly medical using usually non-expensive drugs, performing UDS is not usually justified before initiating treatment. Also, it has been documented that UDS may have a poor agreement with the patient's symptoms. So, in certain situations, the patient may undergo this invasive investigation without added benefit to the plan of treatment. Thus, in this study, we evaluated different clinical parameters and compared them to the UDS aiming to develop a simple clinical score that can help to select patients who would get the benefit of further UDS assessment.

MATERIALS AND METHODS

This is a retrospective study. We collected filed data of women who were referred to the Women Urinary Incontinence Clinic at Cairo University Hospital during the period from January 2018 to December 2020. The study was approved by the scientific and ethics committee of the Obstetrics and Gynecology department of Cairo university teaching hospitals (approval number O20005). All methods were carried out in accordance with relevant guidelines and regulations. The scientific and ethics committee has waived informed consent due to the retrospective nature of the study.

We collected the data of adult women who had OAB symptoms, namely frequency, urgency, urge incontinence or nocturia. We excluded cases with urinary tract infections, urinary lithiasis, uncontrolled diabetes mellitus, hemi/paraplegia, disseminated sclerosis, history of spinal cord injury, history of bladder injury or vesicovaginal fistula (whether present or repaired) as well as those on anticholinergics. Pregnant patients or women within 6 months of delivery, were also excluded. Patients' identities were coded by the 1ry investigator to ensure data confidentiality and to facilitate access.

All case files were reviewed to collect the following data:

- Demographic data (age, gravidity, parity, mode of delivery, presence of any complication of delivery, menopausal status, pelvic or vaginal surgery, weight, height, BMI).
- Symptoms of frequency, urgency, urge incontinence, stress incontinence and nocturia
- Pelvic organ prolapse quantification (POP-Q).

- Data of filling cystometry (reported according to the standard definitions of Drake et al., 2018 (8) with a report on the following parameters:
    a. Sensation at first urge to void in cm3
    b. Maximum bladder capacity in cm3
    c. The presence of DO is detected by the presence of spontaneous or provoked involuntary detrusor muscle contractions during the bladder filling phase
    d. Urodynamic leakage
    e. Cough test

Statistical analysis:

We calculated the needed sample size to detect the area under the receiver operating characteristic (AUROC) curve of 0.65, and we set the null hypothesis for the AUROC curve at 0.5. We took into consideration that the rate of DO in our records was approximately 25%; thus, we set the ratio between negative cases (patients with stable detrusor pressure curve) and positive cases (patients with detrusor overactivity) at 3:1. Thus, the minimum number of patients that were needed was 156 patients (with at least 39 positive cases) to have a study power of 80% and an alpha error of 0.05. Taking the average number of patients in our unit to be 120 patients per year we looked into the files of the previous 3 years assuming incomplete files and excluded patients to be at most 50% of the cases especially in the last year where the practice has been affected by the COVID-19 pandemic.

Statistical analysis was performed using SPSS 15 (Chicago, IL) and MedClac software. Categorical data were presented as frequency (%); continuous data were checked for normal distribution by inspection of histogram distribution. Normally distributed continuous data were presented as mean±SD, and abnormally distributed data were presented as median (interquartile range). Patients were classified into patients with DO and patients without DO. The Chi-square test was used to compare frequencies between the two groups. Unpaired t-test and Mann-Whitney test were used to compare the means for continuous data as appropriate. Multivariable logistic regression was used. Variables with a P value of less than 0.2 in univariate analysis were included in multivariate analysis. Variables with a P-value of < 0.05 in multivariate analysis were considered statistically significant. The variables which were independently associated with DO were used to create a score to confirm the diagnosis of OAB evaluate its severity. Receiver operating characteristic curves were constructed and the area under the curve (AUC) was determined for the new score to detect DO.

RESULTS

We found 210 women eligible for the study. 151 women (72%) had no DO (control group) and 59 (28%) had DO (study group) by the performed filling cystometry. Both groups shared similar demographics and baseline characteristics as shown in (Table 1).

The univariate analysis showed that women with DO had a higher incidence of nocturia (92% vs 62%, p <0.001), urgency (86% vs 66%, p=0.002), frequency (76% vs 51%, p=0.001) compared to the control group while all other clinical findings were comparable between the two groups of patients. (Table 2). That's why we have chosen those three variables (nocturia, urgency, frequency) to create the score. The multivariate regression model revealed that nocturia had the highest odds ratio (OR 4.81) as a predictor of DO followed by urgency (OR 2.86) and frequency (OR 1.46). (Table 3).

We developed a novel score (Detrusor Overactivity Score, DOS) based on the relative weight of each predictor in the multivariate analysis. Each symptom was given a weight as follow; nocturia = 3, urgency = 2, frequency = 1. The total score (DOS score) was cal-

culated by adding the weight of each symptom. The ability of the DOS for detecting DO was evaluated using the receiver operating characteristic curve analysis. The AUC (95% confidence interval) was 0.693 (0.626-0.754) (figure 1). The sensitivity, specificity, PPV, and NPV was 83%, 52%, 40% and 90% respectively at a cut-value of 4. The maximum score was 6 while the minimum was 1. The predictive values at different cut-off values are presented in (Table 4).

DISCUSSION

OAB syndrome is a widely prevalent and increasing condition affecting nearly 10.7 % of the worldwide population. Numbers are expected to increase from 19-31% over 10 years in different regions of the world affecting mainly developing Africa followed by Asia and Latin America(9). One cannot overlook the gap between the presence of complaints/symptoms and seeking/receiving treatments for them. Assessment of such a condition depends mainly on clinical evaluation. However, sometimes UDS are indicated in OAB cases whenever there is an uncertain diagnosis, failure or unsatisfactory response to empirical initial medical treatment or with previous lower urinary tract surgery (e.g. anti-incontinence surgery). As UDS is considered to some extent an invasive and expensive investigation, a method for selecting patients who are a candidate for such investigation is essential. We conducted this research to develop an easy scoring system to help the general practitioners confirm the diagnosis of OAB syndrome and select patients who will get benefit from undergoing urodynamic evaluation.

Our study included 210 women with the mean age at presentation 45.6 +/- 10 years denoting how this condition affects middle-aged and old age women where symptoms increase with age as previously noted by other authors (10)(11). We assessed parity, obesity and menopausal status and other risk factors for developing UI and OAB, as did other researchers from other countries (12)(13). Additionally, uterovaginal prolapse, as well as anterior and posterior compartment prolapse, are risks for developing UI, with and without DO, which was also observed by several authors (12)(14).

An important question arises; do we need UDS to accurately diagnose OAB syndrome before starting treatment? Colleagues from the UK and Germany have summarized the evidence for the utility of urodynamics in evaluating several lower urinary tract conditions one of which was OAB. They concluded that UDS should be used for diagnoses whenever in doubt and they are probably not necessary before initiating medical treatments for OAB (15). This was contrary to what has been reported earlier in 2003, by a more or less similar group who stated that UDS are mandatory for the diagnosis of OAB (3).

In our study, we tried to fill the gap and shorten the distance between the two opinions. The gap between these two opinions arises from the fact that depending only on the patients' words to reach a diagnosis may be sometimes misleading or confusing. It seems as if patients and medical practitioners speak different languages and may even have different disease concepts (15).

As ''typical SUI'' exists there are patients with ''typical OAB syndrome''. However, those groups, expressing ''typical symptoms and signs,'' represent only at best 20% each of the total population of women with symptoms of lower urinary tract dysfunction (LUTD) (17).

In such a situation, physicians are obliged to use objective methods to build up a solid diagnosis. In the case of OAB symptoms, UDS is the objective method of choice.

Additionally, one of the main causes of controversy regarding UDS assessment of OAB patients is that it has been reported that UDS fail to detect detrusor overactivity in 62-74%

in women with frequency and/or urgency symptoms and in 53- 62% of the women with urge urinary incontinence (UUI)(18). This means that over 60% of patients were exposed to an invasive investigation without any added benefit. This brings to our minds the term coined by Blaivas et al in 1996 that "The bladder is an unreliable witness" (19) and that sometimes there is poor agreement between urodynamic testing and clinical evaluation, especially when diagnosing OAB(20).

So, we believe there is a need for a simple method for selecting patients who will benefit from undergoing evaluation by UDS. This need was also realized by the International Consultation on Incontinence Research Society (ICI-RS) in 2014. They concluded that the treatment of UUI and OAB should depend on a diagnostic process with the least possible invasiveness yet with good reliability. They also concluded that there is a challenge to improve the diagnostic process for all patients with any symptom or sign of LUTD and to learn to select the patients who benefit from complete UDS(17).

In our study, the detrusor overactivity score (DOS) being based on the results of UDS offers a reasonable method of selecting patients who would benefit from UDS by using the cut off value of 4. At this cut off value, DO can be detected by 84 % sensitivity. Patients with OAB symptoms with DOS ≥ 4 are expected to have abnormalities detected by UDS while patients with a score less than 4 would probably have a UDS free of any abnormalities. Thus, it would be better for them not to undergo this invasive investigation.

To select the items included in this score, we statistically checked the relation between DO as detected by cystometry and many variables such as different urinary symptoms, stages of prolapse in addition to the demographic data. We reported that DO has a statistically significant association with nocturia (92%), urgency (86%) and frequency (76%).

We partially agree with colleagues from the Netherlands who conducted a cross-sectional study on 95 patients to report the association between OAB symptoms and results of objective parameters as filling cystometry and a self-reporting questionnaire addressing the four main symptoms of OAB (urgency, frequency, nocturia and urge incontinence). They concluded that the latter three could suggest DO with the frequency being the best symptom associated with DO detected by UDS (4). We believe that our different results could be attributed to our larger sample size and different methods used.

Numerous authors have evaluated specific symptoms for OAB with the development of several tools/questionnaires to aid in the diagnosis (21). The bladder control self-assessment questionnaire (sensitivity 85% and specificity 63%), the OAB awareness tool (V8 and V3- short form), the OAB symptom score and urinary symptom profile have been able to determine patients with OAB with great accuracy including assessing the severity of cases (22). However, these tools were designed neither as diagnostic tools nor as selecting methods for UDS and were only intended for awareness.

One of our main strengths is performing this study on a large number of patients over three years. Also, DOS is based on detrusor overactivity proven by UDS with the novel aim of selecting patients for UDS. Yet, there is no work without limitations. Our score needs further validation on other sets of patients in other centers. Additionally, we need to assess the usage of this score as a tool for the assessment of improvement after treatment.

Finally, we conclude that DOS can be offered as a reasonable method for selecting women with OAB symptoms to perform UDS whenever further objective evaluation is needed.

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

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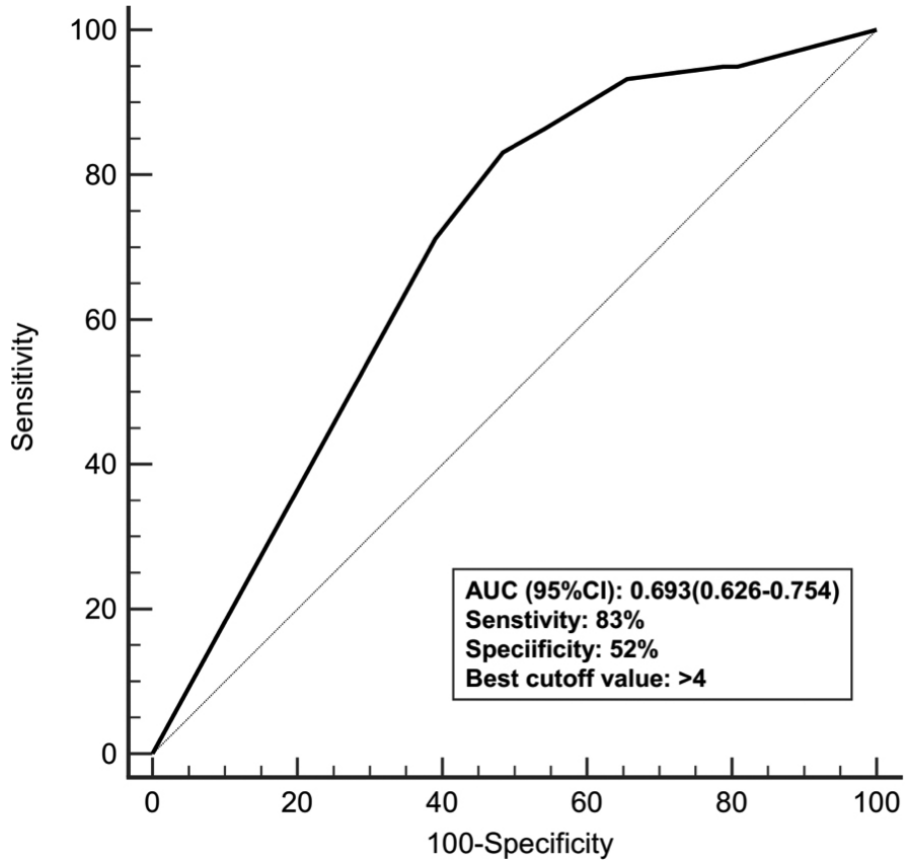

Figure 1 : Receiver operating characteristic curve for the ability of the DOS to detect detrusor overactivity. AUC: Area under curve, CI: confidence interval, DOS: detrusor overactivity score.

Table 1: demographic data and baseline characteristics. Data are presented as mean±-standard deviation, median(quartiles), and frequency (%).

	No detrusor overactivity (n=151)	Detrusor overactivity (n=59)	P value
Age	44±9	45.6±10	0.26
Gravidity	5(3-6)	5(3-6)	0.81
Parity	4(3-5)	4(3-5)	0.24
Obesity	105(70%)	44(75%)	0.50
Menopause	43(29%)	23(39%)	0.20
Previous vaginal deliveries			0.16
None	3(2%)	3(5%)	
One	8(5%)	1(2%)	
Two	19(13%)	16(27%)	
Three or more	121(80%)	39(66%)	
Previous cesarean deliveries			0.32
None	119(79%)	44(75%)	
One	27(18%)	10(17%)	
Two or more	5(3%)	5(8%)	
Previous pelvic surgeries	25(17%)	10(17%)	1.00

Table 2: clinical symptoms and risk factors for detrusor overactivity. Data are presented as frequency (%).

	No detrusor overactivity (n=151)	Detrusor overactivity (n=59)	P value
Frequency	77(51%)	45(76%)	**0.001**
Urgency	99(66%)	51(86%)	**0.002**
Urge incontinence	100(66%)	46(78%)	0.13
Nocturia	93(62%)	54(92%)	**<0.001**
Stage of anterior vaginal prolapse			0.75
0	28(19%)		
1	42(28%)		
2	56(37%)		
3	15(10%)		
4	10(6%)		
Stage of posterior vaginal prolapse			0.96
0	16(11%)		
1	19(12%)		
2	98(65%)		
3	18(12%)		

Table 3: Multivariate analysis for risk factors of detrusor overactivity.

	Odds ratio	95% confidence interval	P value
Frequency	1.46	0.64-3.34	0.37
Urgency	2.86	0.84-9.7	0.09
Urge incontinence	0.51	0.17-1.52	0.23
Nocturia	4.81	1.61-14.33	0.005

Table 4: Sensitivity, specificity, and predictive values for the DOS at different cut-off values.

Cut-off value	Sensitivity	Specificity	PPV	NPV
DOS>1	95%	21%	32%	92%
DOS>2	93%	34%	36%	93%
DOS>3	86%	46%	38%	90%
DOS>4	83%	52%	40%	90%
DOS>5	71%	61%	42%	84%
DOS>6	0%	100%	100%	72%

DOS: detrusor overactivity score, NPV: negative predictive value, PPV: positive predictive value.

Laparoscopic bilateral uterine artery ligation in the treatment of patients with adenomyosis uteri undergoing ICSI

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Abstract

Background: Adenomyosis is frequently detected in women of reproductive age. Although uterine artery ligation has minimal efficacy on its own, it can give appropriate therapeutic control when combined with other methods..

Patients and methods: This prospective pilot study involved 20 patients who had uterine adenomyosis confirmed by ultrasonography or MRI, complained of infertility, and were scheduled for ICSI. Laparoscopic ligation of both uterine arteries using hemoclips and bilateral electrocoagulation of uterine ovarian vessels was done. Intracytoplasmic sperm injection (ICSI) done six months postoperatively and recording the outcome. Moreover, recording the uterine size, the menstrual symptoms and the adenomyosis volume prior to ICSI.

Results: Generally, the all symptoms of the patients under the study were improved significantly postoperatively during follow up period after 3 months and 6 months respectively ($p < 0.05$). The uterine volume at preoperative period ranged from 160-240 cm3 with mean value (205.6±38.5) and in postoperative period ranged from 120-182 cm3 with mean value (142.6±21.3). There was a significant statistical decrease between preoperative and postoperative uterine volumes ($P<0.05$). There was no statistically significant difference between preoperative and postoperative sonographic scoring of the patients. There was no significant difference between preoperative and postoperative MRI degree of adenomyosis but there was an improve in the grade of external adenomyosis.

The outcome of ICSI 6 months postoperatively was recorded in the patients under the study, as regards the primary infertility cases it was found that 6 cases from 14 cases (42.8%) were succeded and became pregnant, while in the secondary infertility group 3 cases from 6 cases (50.0%) were succeded and became pregnant.

Conclusion: Bilateral uterine arteries ligation significantly cause reduction in the uterine volume and improve the adenomyosis symptoms and the reproductive outcome.

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These parameters showed in PCOS patients on the level of TAC; all parameters have no significant effect except for age.

Keywords: Adenomyosis, Intracytoplasmic sperm injection, Uterine artery ligation.

Introduction

Adenomyosis is a common benign gynecological disorder marked by the presence of stroma embedded within the myometrium and ectopic endometrial glands.[1] It affects the archimetra or inner myometrium and is caused by basal endometrial infiltration of the myometrium, which causes smooth muscle hypertrophy and hyperplasia.[2,3] In the past, adenomyosis was detected after histopathological examination of specimens following hysterectomies.[3] In premenopausal women who had hysterectomies for a variety of reasons, multiple studies reported a rate of more than 30% of adenomyosis in hysterectomy specimens.[4,5] However, the incidence of adenomyosis according to female's age , particularly in young women is still unclear.[5] The following criteria are used in the histologic diagnosis of adenomyosis: the existence of penetrating glands at least in one low-power field from the endo-myometrial junction or 2.5 mm below the basal layer of endometrium or deeper than 25% of total myometrial thickness. Also, myometrial smooth muscle proliferation around endometrial islands is noticed in histological diagnosis of adenomyosis. [21,29]

One third of cases with adenomyosis are asymptomatic, the other two third suffer from dysmenorrhea, menorrhagia, pelvic pain, uterine enlargement and chronic pelvic pain. [7] Adenomyosis may have a deleterious effect on female fertility, according to current research. Adenomyosis, can have an effect on uterine peristalsis, sperm transportation within the uterine cavity, and embryo implantation, ultimately results in reduced fertility. [8] Adenomyosis become related to decreased fertility and poorer results of in vitro fertilization (IVF).[7,8] Before recommending surgical or medicinal treatments, adenomyosis screening may enable subgroup identification and personalised therapy planning. However, there is currently no reliable diagnostic criteria, making adenomyosis difficult to be diagnosed, but in the hands of an experienced examiner, many diagnostic techniques such as clinical examination, transvaginal ultrasonography (TVUS), MRI, and hysteroscopic guided biopsy offer a high sensitivity and specificity.[9,19]

Magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVUS) are thought to be the two primary radiologic methods for adenomyosis diagnosis. To evaluate the severity and degree of uterine adenomyosis, a novel sonographic scoring system is created.[9,10] The score system is a technique for categorising the illness into three types: adenomyoma, focal and diffuse adenomyosis of the external myometrium, and junctional zone (JZ). For each type of adenomyotic lesion and for JZ changes, a score ranging from 1 to 4 was assigned to the extent and myometrial involvement. The resultant numerical score was divided into three categories: mild (1–7), moderate (8–13), and severe (14-20).[11,12,13]

MRI has a diagnostic accuracy of 85%, adding value in the confirmation of the diagnosis, defining the nature and degree of the disease, and detecting further uterine abnormalities. [5] T2-weighted sequences of MRI are essential for detecting adenomyosis, since they highlight the uterine zonal architecture.(14) Thickening of the junctional zone is the most frequent indicator of adenomyosis, with a thickness more than 12 mm being highly indicative of the diagnosis.[13,14]

Some publications claim that a junctional zone thickness between 8 and 12 mm can be used to diagnose adenomyosis, but additional criteria are needed. That is a discrepancy of more than 5 mm between the junctional zone's maximum and minimum thickness in both anterior and posterior parts of the uterus.[15]

Adenomyosis has been controlled by GnRH agonist or levonorgestrel intrauterine hormonal treatments, surgical resection of adenomyomas, uterine artery embolization, or magnetic resonance-guided targeted ultrasound, several retrospective research and case reviews have found an improvement in fertility. Although uterine artery ligation has minimal efficacy when used alone to treat adenomyosis, it can give appropriate therapeutic control when combined with other methods.[16]

Patients and Methods

The study was conducted as twenty patients with adenomyosis uteri diagnosed by ultrasound/ MRI and complaining of infertility and scheduled for ICSI process. Laparoscopic uterine artery ligation was done for all the studied patients with follow up of all patients after 3, 6 months respectively as regards the uterine volume, symptoms of the patients, and scoring of adenomyosis by ultrasound and MRI. ICSI was done to all patients, 6 months postoperatively and recording the outcome was done.

Preoperative evaluation of all the studied patients included the basic demographic clinical data of the studied patients group, symptoms including menstrual symptoms, infertility, deep dyspareunia, and pelvic pain. Moreover, preoperative recording of uterine volume by 3-D ultrasound, sonographic scoring of adenomyosis, and MRI findings of the studied patients group. The operative data of the studied patients group were recorded including the technique of bilateral uterine artery ligation, any additional laparoscopic intervention for any associated pelvic pathology, and any operative complications reported.

Postoperative evaluation of the all studied group were done after 3 months and 6 months respectively as regards symptoms of the patients, uterine volume, sonographic scoring, and MRI scoring of adenomyosis. Six months postoperatively, ICSI was done to all patients under the study and the outcomes were recorded. Prior to performance of ICSI ,all the patients who had surgery were subjected to three dimensional Doppler study of endometrial flow index (FI) and vascularization flow index (VFI) which are markers of endometrial receptivity and blood flow. Fortunetly, the former markers were not altered by the surgical procedure and the recorded values permit ICSI process

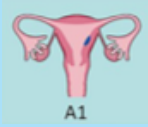
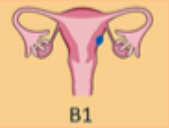
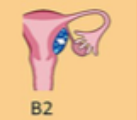
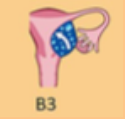
The preoperative assessment and postoperative follow up by ultrasound and MRI were

	Score (1)	Score (2)	Score (3)	Score (4)
Diffuse adenomyosis of the outer myometrium	1 myometrial wall involvement with myometrial wall thickness ≤20mm.	*2 myometrial wall involvement with wall thickness ≤20mm. *1 myometrial wall involvement with wall thickness <20≤30.	*1myometrial wall thickness <30mm. *2 myometrial wall involvement with wall thickness <20≤30.	* 2myometrial wall involvement with wall thickness <30mm. * All the uterus involvement with globally enlarged uterus.
Diffuse adenomyosis of the inner myometrium or junctional zone (JZ)	*Maximum JZ thickness <6≤8 mm in length. *Diffuse infiltration of the JZ ≤20mm in length.	* Maximum JZ thickness <8mm *Diffuse infiltration of the JZ <20mm in length or ≤50% of the uterus.	* Diffuse infiltration of the JZ <50%≤80% of uterus.	* 80% to total infiltration of the JZ.

Focal adenomyosis of the outer myometrium	*1focal intramyometrial lesion ≤10mm.	* ≥2focal intramyometrial lesion ≤10mm. *1focal intramyometrial lesions <10≤20mm.	* ≥2focal intramyometrial lesions <10≤20mm. * 1focal intramyometrial lesion <20mm.	* ≥2 focal intramyometrial lesion <20mm. * ≥3 focal intramyometrial lesions.
Focal adenomyosis of the inner myometrium or (JZ)	*1focal lesion of the JZ by hyperechoic tissue or cystic areas ≤10mm.	* ≥2 focal lesions of the JZ ≤10mm. * 1 focal lesion of the JZ <10≤20mm.	* ≥2 focal focal lesions of the JZ <10≤20mm. * 1 focal lesion of the JZ <20mm.	* ≥2focal lesions of the JZ <20mm. * ≥3focal lesions of the JZ.
Adenomyoma	*1 adenomyoma with largest diameter ≤20mm	* 2 adenomyomas with largest diameter ≤20mm * 1 adenomyoma with largest diameter <20≤30mm.	* 2 adenomyomas with largest diameter <20≤30mm . * 1 adenomyoma with largest diameter <30≤40mm.	* ≥3 adenomyomas. *1adenomyoma with largest diameter <40mm.

OAB syndrome is a widely prevalent and infollowed according to new sonographic scoring and MRI based classification that shown underneath in Table 1 and Table 2 respectively.

Table1: New Sonographic Classification of Adenomyosis (Journal of Minimally invasive Gynecology)[17]

	Size		
	1 (<1/3)	2 (<2/3)	3 (>1/3)
Affected area	Focal		Diffuse
A (Internal adenomyosis) Thickness of JZ > 12mm			
	Focal		Diffuse
B (External adenomyosis) Thickness of JZ < 8mm			

The presence of concomitant pathologies		Localization	
C0	none	D1	Anterior
C1	peritoneal endometriosis	D2	Posterior
C2	ovarian endometriosis	D3	left lateral
C3	deep infiltrating endometriosis	D4	Right lateral
C4	uterine fibroids	D5	Fundus
C5	others		

Table2: Magnetic resonance imaging□based classification of adenomyosis (Journal of Obstetrics and Gynecology Research)[18]

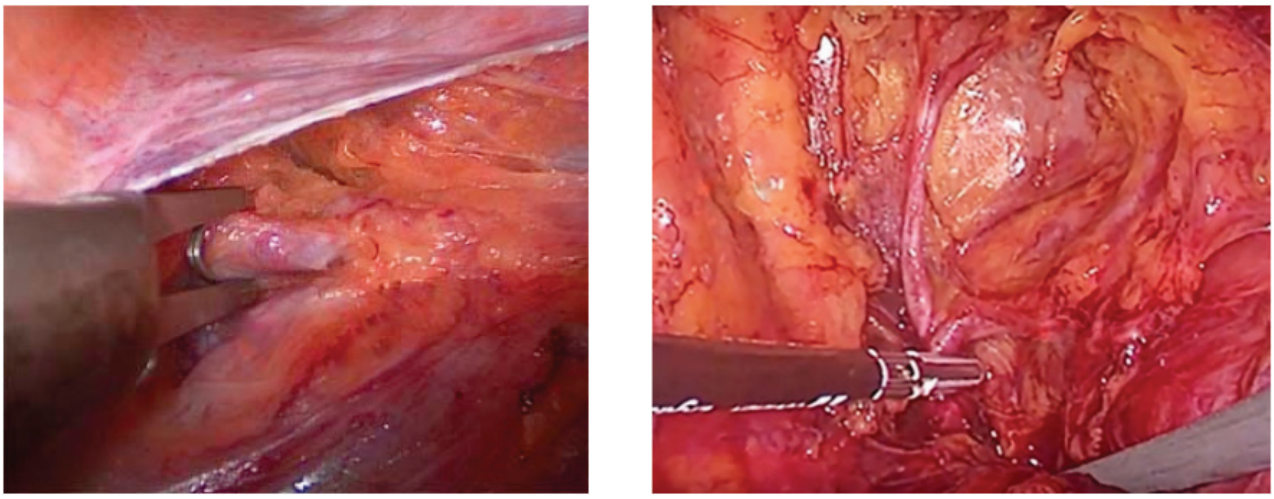


Figure (1)

Different operative methods of bilateral uterine artery ligation

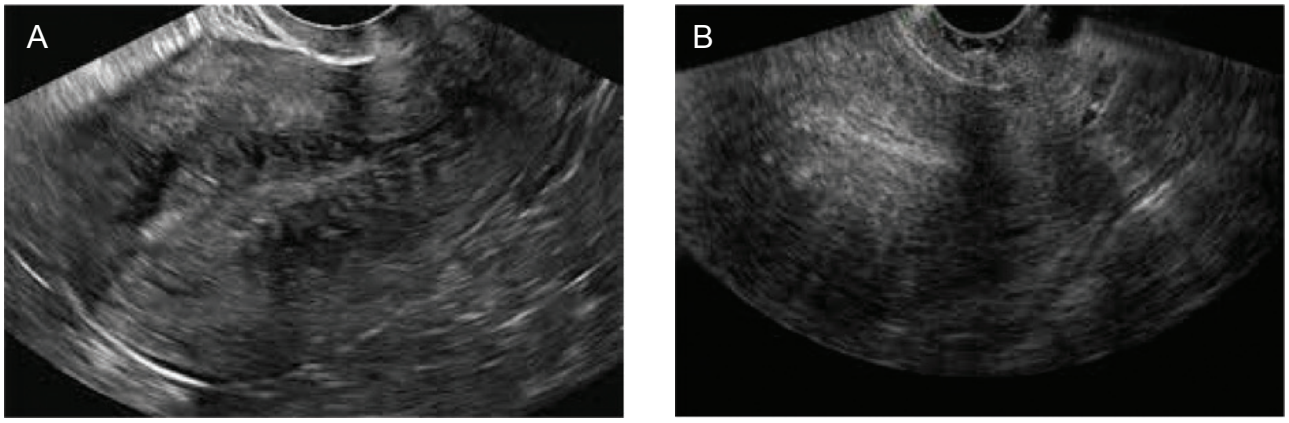


Figure (2)

(A) Preoperative ultrasound shows diffuse adenomyosis of inner myometrium score (4).
(B) Postoperative ultrasound follow up after 6months shows diffuse adenomyosis of inner myometrium score (2).

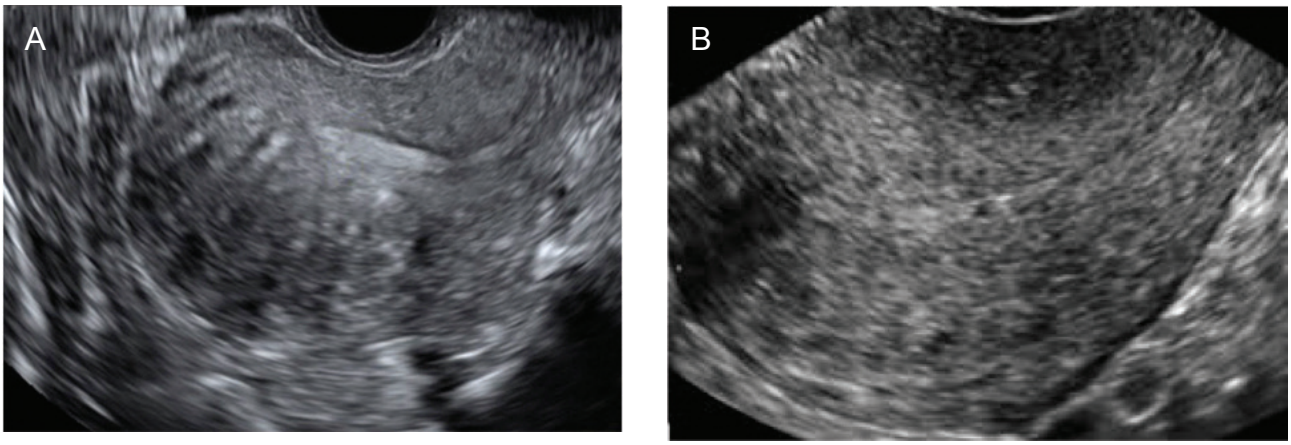


Figure (3)

(A) Preoperative ultrasound shows diffuse adenomyosis of outer myometrium score (4).
(B) Postoperative ultrasound follow up after 6months shows diffuse adenomyosis of outer myometrium score (2).

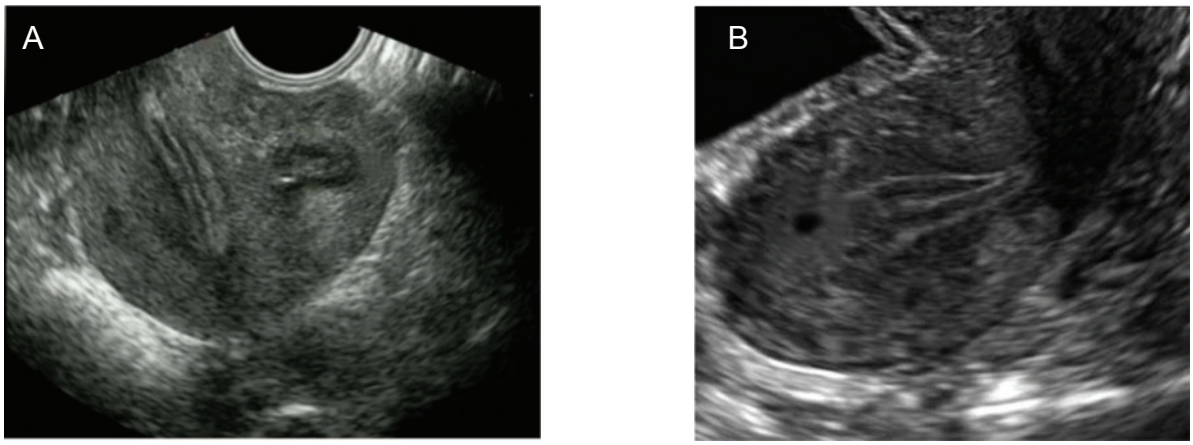


Figure (4)

(A) Preoperative ultrasound shows adenoma score (3).
(B) Postoperative follow up ultrasound after 6 months shows adenoma score (1) with marked reduction of the uterine volume.

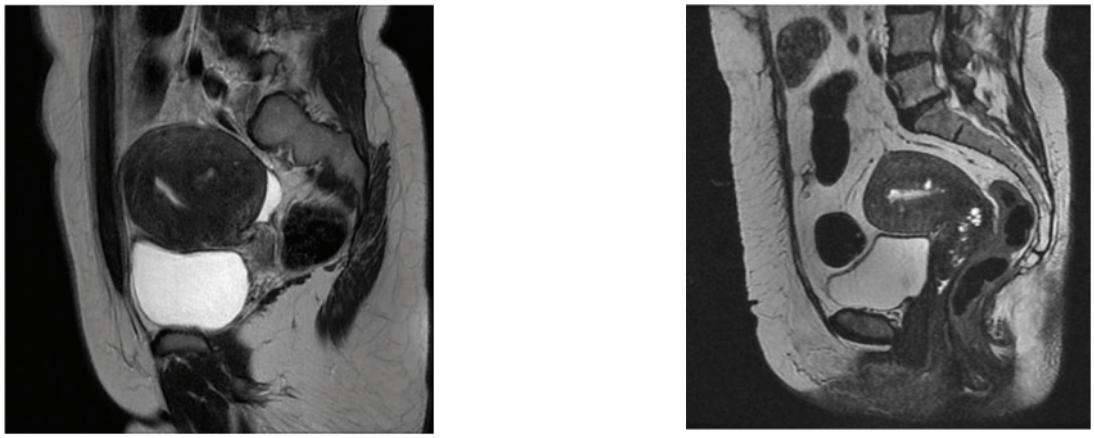


Figure (5)

(A) Preoperative MRI shows internal adenomyosis.
(B) Postoperative follow up MRI after 6 months shows reduction in size of adenomyosis and the uterine volume

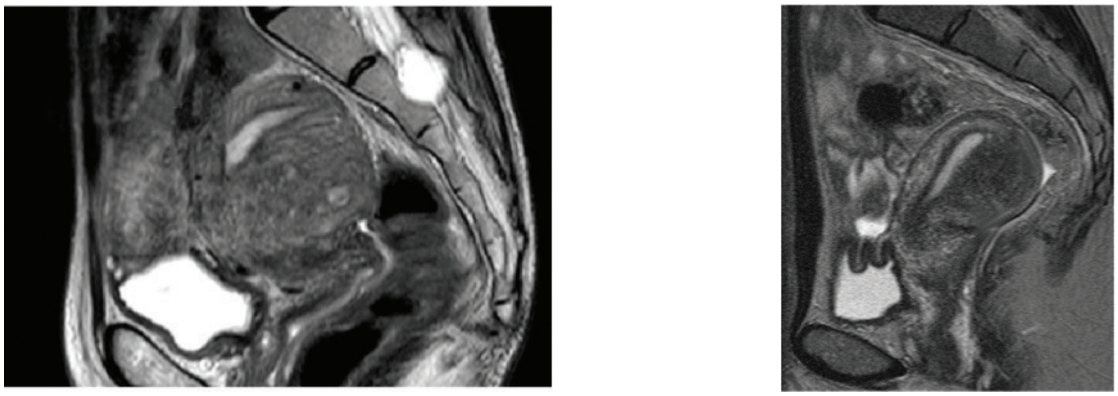


Figure (6)

(A) Preoperative MRI shows external adenomyosis.
(B) Postoperative follow up MRI after 6 months shows reduction in size of adenomyosis and the uterine volume

The data was obtained and entered into the computer. Software called Statistical Package for Social Sciences (SPSS/version 24) was used for the statistical analysis.

The statistical test used as follow:

Arthematic mean, standard deviation, and for normally distributed data, comparison between two independent populations were done using independent t-test. While the Chai square

	Number	Percent
Age		
29-34 years	11	55.0
35-40 years	9	45.0
Range	29-40	
Mean ±S.D.	34.8±7.98	
Body mass index (BMI)		
25.5-29.5 (kg/m^2)	17	85.0
29.5-32.0 (kg/m^2)	3	15.0
Range	26.0-32.0	
Mean ±S.D.	28.2±4.58	
Symptoms:		
A. Menstrual symptoms		
Dysmenorrhea	18	90.0
Heavy menstrual bleeding (HMB)	16	80.0
Intermenstrual bleeding (IMB)	11	55.0
B. Infertility		
Primary	14	70.0
Secondary	6	30.0
C. Deep dyspareunia	18	90.0
D. Pelvic pain	12	60.0

test was applied for categorised parameters. The significant level was 0.05.

Results

160-199 Cm3	9	45.0
200-240 Cm3	11	55.0
Range	160-240	
Mean ±S.D.	205.6±38.5	

Our studied cases included 20 patients aged between (29-40) years with the mean age (34.8±7.98). The body mass index (BMI) of the studied patients ranged between (26.0 - 32.0) kg /m2 with the mean BMI (28.2±4.58). Preoperative evaluation of the patient's symptoms revealed that, 18 patients (90%) complained of dysmenorrhea, 16 patients (80%) with (HMB), and 11 patients (55%) with (IMB). The Primary infertility was recorded in 14 patients (70%) while secondary infertility was recorded in 6 patients (30%). The deep dyspareunia was shown in 18 patients (90%) while pelvic pain was shown in 12 patients (60%). The basic demographic and clinical data of the studied patients group is shown in Table (3):

The uterine volume of the studied patients as being detected by 3-D ultrasound prior to surgery was ranged between 160-240 cm3 with a mean of (205.6±38.5). Preoperative uterine volume by 3-D ultrasound is shown in Table (4).

The preoperative sonographic scoring of adenomyosis of the studied patients group is shown in **Table (5):**

	Number	Percent
Diffuse adenomyosis		
Outer myometrium (score 3)	5	20.0
Inner myometrium (score 4)	5	20.0
Focal adenomyosis		
Outer myometrium (score 4)	6	30.0
Inner myometrium (score 2)	2	10.0
Adenoma	2	10.0

The preoperative MRI findings of the studied patients group is shown in **Table (6):**

I. Size of adenomyosis by MRI		
A. Internal adenomyosis		
A1	0	0.0
A2	7	35.0
A3	0	0.0
B. External adenomyosis		
B1	3	15.0
B2	7	35.0
B3	3	15.0
II. Location of adenomyosis by MRI		
D1	6	30.0
D2	5	25.0
D3	4	20.0
D4	3	15.0
D5	2	
III. Associated pathology by MRI		
C0	8	40.0
C1	7	35.0
C2	3	15.0
C3	1	5.0
C4	1	5.0

The operative data of the studied patients group is shown in **Table (7):**

	Number	**Percent**
I. Technique of bilateral uterine artery ligation		
Haemoclips	6	30.0
Electrocoagulation	12	60.0
Suturing	2	10.0
II. Additional laparoscopic intervention		
None	7	35.0
Electrocoagulation of endometriotic peritoneal implants	8	40.0
Ovarian cystectomy	4	20.0
Uterosacral resection	1	5.0

III. Operative complications		
Anesthesia complications	1	5.0
Slipped ligature	2	10.0
Injury of inferior epigastric vessels	1	5.0
Wound infection	3	15.0

Table (8), shows the symptoms preoperatively and at different period of follow up at 3 and 6 months postoperatively respectively. The dysmenorrhea was found in 90% of the patients preoperatively and decreased significantly after 3 months to be found in 50% of the patients only, finally after 6 months only 5 cases (25.0%) had dysmenorrhea ($p < 0.05$). Heavy menstrual bleeding was found in 80.0% of the cases preoperatively, and decreased significantly after 3 and 6 months to be 30.0% and 20.0%, respectively, of the cases only. The intermenstrual bleeding was found in 55.0% of the patients preoperatively that had been decreased significantly to be only 15.0% after 3 months and declined to 10.0% of the patients after 6 months.

The deep dyspareunia was found in 90% of the patients preoperatively and decreased significantly after 3 and 6 months to be found in 50.0% and 30.0% of the patients respectively. Finally, the pelvic pain was found preoperatively in 60.0% of the patients and decreased significantly to found in 40.0% of the patients after 3 months and in 30.0% of the patients after 6 months follow up.

Generally, the all symptoms of the patients under the study were improved significantly postoperatively during follow up period after 3 months and 6 months respectively. ($p < 0.05$).

Table (8): Comparison between pre and post operative data at different period of follow up.

Symptoms	Preoperative		3 months post-operative		6 months post-operative		P value
	No.	%	No.	%	No.	%	
A. Menstrual symptoms							
Dysmenorrhea	18	90.0	10	50.0	5	25.0	0.003*
Heavy menstrual bleeding (HMB)	16	80.0	6	30.0	4	20.0	0.001*
Intermenstrual bleeding (IMB)	11	55.0	3	15.0	2	10.0	0.013*
B. Deep dyspareunia	18	90.0	10	50.0	6	30.0	0.004*
C. Pelvic pain	12	60.0	8	40.0	6	30.0	0.017*

The uterine volume at preoperative period ranged from 160-240 cm3 with mean value (205.6±38.5) and in postoperative period ranged from 120-182 cm3 with mean value (142.6±21.3). There was a significant statistical decrease between preoperative and postoperative uterine volumes ($P < 0.05$).

The diffuse adenomyosis score 3 and 4 was found in 25% in both scores with non-significant decrease to be 10% postoperatively. The focal adenomyosis score 4 and 2 was found in 30.0% and 10.0% preoperatively with non-significant decrease to be 15.0% and 5.0% postoperatively. The adenoma was found in 2 patients preoperatively and was found in only one patient postoperatively. Also, there was no significant difference between pre and postoperative sonographic scoring of the patients.

Regarding MRI findings, the size of adenomyosis by MRI showed internal adenomyosis as type A2 in 7 cases (35.0%) preoperatively that changed to type A1 in 3 cases (15.0%) while the other 4 cases still type A2.

The preoperative external adenomyosis grade B1 was found in 15.0% of the patients, 35.0% of cases were B2 while 15.0% of cases were B3. Postoperatively, grade B1 was detected in 30.0% of cases and grade B2 was detected in 30.0% of cases while only 5.0% were grade B3. There was no significant difference but there was an improve in the grade of external adenomyosis.

Table (9): Comparison between pre and post operative uterine volume, sonographic scoring and MRI findings.

	Pre operative		Post operative		P value
	No.	%	No.	%	
Uterine volume Cm^3					
Range	160-240		120-182		0.002*
Mean ±S.D.	205.6±38.5		142.6±21.3		
Sonographic Scoring:					
1-Diffuse adenomyosis:					
Outer myometrium (score 3)	5	25.0	2	10.0	0.36
Inner myometrium (score 4)	5	25.0	2	10.0	0.36
2-Focal adenomyosis:					
Outer myometrium (score 4)	6	30.0	3	15.0	0.25
Inner myometrium (score 2)	2	10.0	1	5.0	0.40
3-Adenoma	2	10.0	1	5.0	0.40
MRI findings:					
Internal adenomyosis :					
A1	0	0.0	3	15.0	0.11
A2	7	35.0	4	20.0	
A3	0	0.0	0	0.0	
External adenomyosis :					
B1	3	15.0	6	30.0	0.34
B2	7	35.0	6	30.0	
B3	3	15.0	1	5.0	

Table (10) shows the outcome of ICSI 6 months postoperatively in both types of infertility recorded in the patients under the study, as regards the primary infertility cases it was found that 6 cases from 14 cases (42.8%) were succeded and became pregnant, while in the secondary infertility group 3 cases from 6 cases (50.0%) were succeded and became pregnant.

Table (10): Outcome of ICSI 6 months post operative.

	Preoperative		6 months post operative			
			Succeed		Failed	
	No.	%	No.	%	No.	%
Primary infertility	14	70.0	6	42.8	8	57.2
Secondary infertility	6	30.0	3	50.0	3	50.0

Discussion

As a result of the lack of standardized diagnostic criteria, adenomyosis continues to remain difficult to recognize, evaluate, and study, particularly in patients who want to keep their uterus (Loring et al., 2021).[13]

Adenomyosis and fertility problems have been linked on numerous occasions, owing to the anatomical and pathological symptoms that are caused by adenomyosis on the female genital tract (Squillace et al., 2021).[24]

Regarding the preoperative symptoms of adenomyosis recorded in the current study, dysmenorrhea was reported in (90%) of the studied cases; heavy menstrual bleeding (HMB) in (80%); intermenstrual bleeding in (50%); primary infertility in (70%); deep dyspareunia in (90%) and pelvic pain in (60%) of the studied cases.

In agreement with our results, the most main signs of adenomyosis in women are pain, HMB, infertility, and miscarriage (Vannuccini et al., 2017).[30] Myometrial hypercontractility, as proposed by enhanced expression of oxytocin receptors (OTRs) and elevated contractile amplitude of uterine smooth muscle cells (uSMCs) in adenomyotic uterus, can clarify dysmenorrhea and dyspareunia (Nie et al., 2010).(20) The altered membrane depolarization of uSMCs caused by potassium channel disorder contributes to abnormal uterine contractility in adenomyosis (Brainard et al., 2007).[4]

Endometrium as well as myometrium have shown overexpression of endothelial nitric oxide (NO) synthase in women with adenomyosis-related HMB, confirming the importance of NO in controlling the amount of menstrual bleeding (Oh et al., 2013).[21] Infertility and poor implantation consequences are very common in patients with adenomyosis, owing to changed uterine surroundings, dysfunctional uterine contractility, inflammatory responses, and irregular eutopic endometrial activity (Benagiano et al., 2014).[2]

In agreement with our results, Liu et al. (2014)(12) discovered that dysmenorrhea was the most consistently reported sign by 81.7% of patients, either alone or in conjunction with other complaints. In Yildirir et al., (2022)(35); chronic pelvic pain (27.1%) and menometrorhagia (22.2%) were the most main symptoms, and leiomyomas (29.4%) and abnormal uterine bleeding (AUB) (14%) were the commonest indicators for hysterectomy.

The mean uterine volume in the studied cases was (205.6±38.5). Also, in Miyagawa et al., (2021)[14] study, the median uterine volume estimated from the long, short, and transverse uterine diameters were 217 (71-1400) cm^3.

Preoperative sonographic scoring of adenomyosis in the studied cases; diffuse adenomyosis in (40%), focal adenomyosis in (40%), and adenoma in (10%) of the studied cases. In comparison with previous researches; preoperative (MR) images from 45 patients with pathologically proven adenomyosis in the study of Byun et al., (1999)[5] revealed diffuse adenomyosis in 30 cases (66.7%) and focal adenomyosis in 15 cases (33.3%). In Salem et al., (2019)(15) study (75%) were diffuse form and (25%) were focal form.

The thickening of the junctional zone is the most common feature for the assessment of adenomyosis, with a thickness greater than 12 mm being strong predictors of the diagnosis (Larsen et al., 2011).[9]

Preoperative MRI findings of the studied patients showed that (35%) had internal adenomyosis (A2), (35%) had external adenomyosis (B2). Regarding the MRI results in Tadjerouni et al., (2021)(27) study, 109 women (44.0%) only had external adenomyosis, while 78 (31.5%) only had internal adenomyosis. Our results regarding the associated pathology by MRI showed that (40%) had (C0) and (35%) had (C1). In MRI findings of Salem et al., (2019)(15) study uterine fibroids were found in 11/24 cases (45.83%) and ovarian endometriosis in 2/24 cases (8.3%).

Regarding the operative complications in the current study, wound infection was reported in (15%) of cases, Slipped ligature in (10%) of cases, anaesthesia complications in (5%) of cases and injury of inferior epigastric vessels in (5%) of cases.

Laparoscopic surgery is linked to reduced complications, less postoperative pain, adhesions, and a faster recovery than laparotomy. However, laparoscopy has limitations such as inaccurate evaluation of the extent of adenomyosis and a limited motion range accessible to rebuild a myometrial defect without appropriate eradication of dead space. Laparoscopic surgery may be an option for treating small and localized adenomyosis, whilst open surgery is required for diffuse adenomyotic lesions across the uterus (Shim et al., 2019).[22]

Laparoscopy is a viable route that should be used on a regular basis to treat the condition, with a lower risk of conversions and intra-operative side effects (Smith et al., 2018). [23]

Our results showed statistical significant decrease in dysmenorrhea at 3 months and 6 months postoperative. Also, there was statistical significant decrease regarding heavy menstrual bleeding and intermenstrual bleeding at different period of follow up respectively ($P < 0.05$).

The beneficial effects of laparoscopic uterine artery ligation in adenomyosis was discussed previously in the study of Wang et al., (2002) (32), they explored the laparoscopic uterine artery ligation impacts in 20 women with symptomatic adenomyosis. Thirteen of the sixteen patients had bleeding control, and five had eumenorrhea or hypomenorrhea. Twelve of the sixteen patients had their dysmenorrhea under control, and six were analgesic-free. Nevertheless, nine women reported non-menstrual pain following surgery, with three requiring hysterectomy. Only 15% of patients were satisfied, and 45% were dissatisfied. The poor satisfaction rate suggested non effective treatment of symptomatic adenomyosis by laparoscopic uterine artery ligation.

There was statistical significant decrease between pre and postoperative uterine volume ($P < 0.05$). There was statistical significant decrease in postoperative period than preoperative period for diffuse, focal adenomyosis and adenoma. There was statistical significant difference between pre and postoperative uterine volume regarding internal and external adenomysosis by MRI ($P < 0.05$).

Similarly, the volume of the uterus was continuously reduced at 3, 6, 12, and 36 months postoperatively, and had shrunk by 58.3% compared to the preoperative volume at 36 months. At 36 months, only 1.7% of patients had undergone a hysterectomy. Furthermore, when compared to preoperative scores, patients' health-related quality of life scores were significantly higher ($p<0.01$) (Takeuchi et al., 2014) .[28]

In Verit et al., (2019)(31) study, they discovered that the uterine artery blood deliver became now no longer compromised after bilateral uterine artery ligation (UAL). The end result is specially essential for younger ladies who're watching for destiny pregnancies, due to the fact it's miles well known that uterine blood glide is critical for selling a receptive endometrium, embryo implantation, trophoblast invasion, and a prosperous pregnancy.

Chang et al., (2009)[6] suggested that bilateral UAL during laparoscopic myomectomy did now no longer lower uterine artery PI and RI values at three months after surgery. Uterine artery ligation is related to minimal side effects and is being preferred due to restoration of fertility even after surgery (Shaikh et al., 2021).[16]

The current study results showed that primary infertility that succeeded after 6 months postoperative was (42.8%) while secondary infertility was (50%).

The impact of adenomyosis treatment on pregnancy outcomes was discussed in previous researches. Sudhakar et al., (2022) (26) evaluated the impact of adenomyosis on pregnancy outcome in ICSI/FET cycles.

They found marked enhancement in clinical pregnancy rate after GnRH agonist pretreatment, conservative surgery, or combination therapy. Younes and Tulandi, (2017) [36] came to the conclusion that adenomyosis was linked to lower fertility and poorer pregnancy outcomes in IVF. These consequences improved after adenomyosis treatment.

The outcomes of conservative surgery, which included laparoscopy or laparotomy, had been derived from research findings in women with adenomyosis. Laparoscopic cytoreductive surgery was considered to be appropriate for women with localized adenomyosis who have ended in failure standard medical interventions and assisted reproductive technology. One spontaneous pregnancy occurred 21 months after surgery, according to Wang et al., (2006)[33] study.

In subfertile women with adenomyosis, conservative surgery or combination therapeutic interventions had significant benefits not only for alleviating symptoms but also for continuing to increase the pregnancy rate in comparison to GnRH by itself (Al Jama et al., 2011).[1] When adenomyotic women who having undergone conservative surgery with or without GnRH-a were particularly in comparison to those that obtained GnRH-a alone for 6 months, the accumulated 3 years clinical total fertility rate and final successful delivery incidence were greater (Wang et al., 2009).(34) Two studies revealed a number of births (Takeuchi et al., 2006[28]; Tadjerouni et al., 1995)[27] and one revealed a pregnancy rate (Strizhakov and Davydov, 1995). [25]

The present study results revealed that laparoscopic bilateral uterine arteries ligation significantly reduced uterine adenomyosis-related symptoms, volume and achieved reasonable fertility outcomes.

The number of participants who participated in this study was small to draw definitive conclusions about our findings. Despite these limitations, we believe this study is a unique kind.

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Total antioxidant capacity and oxidative stress in Polycystic ovary syndrome, a case-control study

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrinological syndrome among reproductive-age women. Oxidative stress (OS) elaborates on PCOS pathological process. OS is a state where oxidative powers exceed the antioxidant systems, serum's ability to reduce the free radical's formation and protect the cell from oxidative stress. TAC protects the cell from the harmful effects of radicals. Examples are superoxide and radical hydroxyl ions. Any change in the level of plasma's antioxidants or oxidative stress can disturb TAC.

Aim of the study: This study evaluated serum Total Antioxidant Capacity (TAC) levels in PCOS patients compared to the healthy control group.

Methods: The women with PCOS were considered cases and TAC levels compared to healthy women. All were recruited from outpatient clinics in the Duhok governorate in Iraqi Kurdistan between November 2021 and February 2022. One hundred twenty women (60 PCOS patients and 60 healthy subjects). PCOS was diagnosed according to the Rotterdam criteria (2003). All patients underwent clinical assessment.

Results: The PCOS patients and controls were similar in age and BMI. The PCOS showed highly significant differences in the clinical parameter as hirsutisms. Patients with PCOS are likely to have a morphology of>12 follicles per ovary (95.0%) in contrast to <12 follicles per ovary (93.33% in the controls (P<0.0001). The PCOS patients had substantially higher volumes of the right and left ovary than the controls (P=0.0008). A similar pattern was found for the morphology of the left ovary. This study showed highly significant differences in the mean concentration of testosterone in PCOS patients, which was significantly higher (0.31) compared to its attention in the controls (0.19; P<0.0001). PCOS patients had a substantially lower level of TAC (2.24) compared to the controls (2.51; P<0.0001).

These parameters showed in PCOS patients on the level of TAC; all parameters have no significant effect except for age.

Conclusions: This study revealed that the serum TAC levels

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are significantly lower in PCOS patients than in control patients.

Keywords: Total antioxidant capacity, Polycystic ovary syndrome, oxidative stress

Introduction

Polycystic ovarian syndrome (PCOS) is the most typical endocrine disorder that causes reproductive complaints. This syndrome is characterized by the presence of two or more criteria, which are both clinical and biochemical. It includes excessive androgen, chronic anovulation (CA) or oligo-ovulation, and polycystic ovaries morphology (PCOM) [1-6].

PCOS is associated with a metabolic disorder [7], a heterogeneous disease with individualized predisposition detected by genetic and environmental causes between 9% and 18% in reproduction ages. About 80% of women have anovulatory infertility [8]. PCOS has been mainly related to low-grade chronic inflammation and oxidative stress (OS) [9, 10].

OS is identified as a situation where oxidative powers exceed the antioxidant systems leading to imbalance. The Reactive Oxygen Species (ROS) rise in response to oxidative stress [11]. The main actions of ROS in the cell functions are activating redox-sensitive transcription factors; it is an essential issue in human reproductive medicine [12].I t elaborates on the pathological processes that go with insulin resistance (IR), hyperandrogenism, and obesity [13]Metabolic syndromes accelerate the OS progression in patients with PCOS and minuscule the antioxidative capacity [14]. OS is closely related to PCOS pathogenesis as it suggests OS in PCOS patients is more severe than in non-PCOS patients [15]. The molecules in the cells that avert these OS reactions are named antioxidants, organized by a complex antioxidant system.[16].

Total Antioxidant Capacity (TAC) is the ability of serum to reduce the free radical's formation and protect the cell construction from the harmful effects of radicals. It is one of the antioxidant fortifications present in the body. Any modification in the plasma level of antioxidants or oxidative stress can disrupt TAC [17]. TAC may be used in the Workup of PCOS as a test of diagnosis and progress [18]. TAC measures the total antioxidants in the patient serum [17]. Also, TAC in Follicular fluid (FF) creates a microenvironment for the emerging oocyte and has a straight effect on the quality of the oocyte; it would increase during the growth of follicles because of the TAC developmental capability [19]. Insufficient antioxidants in FF may oppose these roles [20].

Regarding female infertility, particularly PCOS, evidence has shown decreased antioxidant status in the insulin resistance of PCOS patients [21]. Some studies are conducted to identify the correlation between PCOS and oxidative stress using other microelements rather than TAC [1, 17, 18, 22-26]. One only depended on biochemical criteria [22]. However, results would be more reliable when reassessed by more than one parameter. TAC may be used in the Workup of PCOS as a test of diagnosis and progress [18]

Patients and methods

In this case-control study, the women with PCOS were considered the cases, and levels of TAC were compared to healthy women. One hundred twenty women (60 PCOS patients and 60 healthy subjects). PCOS was diagnosed according to the Rotterdam criteria (2003).

The cases and controls were recruited from the outpatient clinics in Sumel and Sennuny, Duhok governorate in Iraqi Kurdistan, between November 2021 and February 2022. The patients who attended the outpatient clinics were clinically screened for the eligibility criteria. The data were collected from the patients and controls following approval by the Duhok General Health Directorate and

ethical committee of Duhok University and the ministry of health of Kurdistan. The letter of consent was obtained from the patients before inclusion in the study. The procedure study procedure explained the patients before inclusion in the study.

The patients included in this study were 18 and 38 years old. The patients were screened endovaginally by ultrasound. A blood sample was taken from each patient. The diagnosis of PCOS was made according to the Rotterdam European Society of Human Reproduction, ion and Embryology (ESHRE) revised consensus criteria 2003 [2-5]. Chronic anovulation (CA), hyperandrogenism, clinical (including signs such as hirsutism) or biological increase level of testosterone, and polycystic ovaries visible on ultrasound as the presence of at least one of ovaries with >10 cm3 or comprise at least 12 follicles between 2 to 9 mm in diameter.

Clinical examination

Regarding the three criteria, CA (chronic anovulation) is defined as fewer than eight menstrual cycles per year or more than 35 days between cycles. Hyperandrogenism is characterized by clinical features (acne, hirsutism, and androgenic alopecia) or raised testosterone levels. Ultrasound features are classified as extra than 12 antral follicles (measuring 2–9mm in diameter) or an ovarian volume more significant than 10 cm3 in either ovary.

Physical examination

All women underwent measurement for weight and body mass index (BMI). Systemic examination and assessment of the hair according to the Ferriman-Gallwey score were done [27].

Exclusion Criteria

They are hypo and hyperthyroidism, congenital adrenal hyperplasia, androgen tumors, hyperprolactinemia, chronic medical diseases such as insulin-dependent diabetes mellitus, hypertension, heart and blood vessels disease, and uterine cancer.

Measurements

All patients underwent assessment for main risk factors such as age, previous pregnancy, parity, marital status, education, irregular cycle, alcohol consumption, family history of PCOS, family history of diabetes, infertility problem, and mother's history of menstrual abnormality [28].

Transvaginal ultrasound

All have a transvaginal ultrasound, DW C60 made by DAWEI medical brand from China with a CE-supported certificate. The frequency othe f vaginal probe was between 7.5-10 MHz to identify PCOS, which means the presence of at least one of the ovaries with >10 cm3 or containing at least 12 follicles 2 to 9 mm in diameter.

Blood Samples

Hormonal tests, testosterone, and TAC testosterone were measured from plasma by an automated instrument. Plasma total antioxidant capacity (TAC) was assessed using the Enzyme-Linked Immunosorbent Assay (Human Total antioxidant status (TAOS) ELISA Kit

And Human Total antioxidant capacity-AOC ELISA Kit) [29, 30]. Serum sample serum was selected and frozen until the complete number was ordered. The testosterone test was performed by Cobas e411 (ROCH diagnostics), an automated instrument, principle, ELICIA.

Statistical Analysis

The general information of the patients and cases were presented in mean and standard

deviation or number and percentage. The homogeneity of the PCOS and control groups in terms of age and BMI was examined in an independent t-test and Pearson Chi-squared test. The transvaginal ultrasound (U/S) comparisons between patients with PCOS and controls were analyzed in an independent t-test and Pearson Chi-squared test. Comparisons of Testosterone and TAC test results between patients with PCOS and controls were examined in an independent t-test. The role of general characteristics, Testosterone, and transvaginal ultrasound outcomes on the level of TAC in PCOS patients was examined in standard least squares with affect leverage. The normality of the data was checked by drawing a histogram, and the outliers were checked by drawing the box plots of two study groups. The extreme outliers were not included in the mean and Standard Deviation (SD) measurement of the outcomes and other information in this study. A p-value of less than 0.05 determined the significant level of difference. The statistical calculations were performed in JMP Pro 14.3.0 tool.

Results

The study found that the PCOS patients and controls were similar in age (26.34 vs. 27.91 yrs., P=0.0739) and BMI (26.55 vs. 26.60 kg/m2; P=0.9532). The majority of the patients and controls were obese (45.0% vs. 38.33%), followed by average weight (33.33% vs. 38.33%; P=0.9034), respectively (Table 1).

The study showed that the PCOS patients had moderate (85.0%) and severe (15.0%) hirsutism in contrast with minimal (45.0%) and mild hirsutism (55.0%; P<0.0001). In terms of the morphology of the right ovary, the study showed that PCOS patients were more likely to have >12 follicles per ovary (95.0%), while the controls were more likely to have <12 follicles per ovary (93.33%; P<0.0001). A similar pattern was found for the morphology of the left ovary. In addition, the study showed that PCOS patients were more likely to have an irregular menstrual cycle (68.33%) compared to a regular menstrual cycle (58.33%; P=0.0033), see Table 2, Figs 1-2).

The study showed that the mean concentration of testosterone was significantly higher in PCOS patients (0.31) compared to its concentration in the controls (0.19; P<0.0001). But, the PCOS patients had a substantially lower level of TAC (2.24) compared to the controls (2.51; P<0.0001), see Table 3 and Fig 3.

In terms of the role of general characteristics and biomedical measurements on the level of TAC in PCOS patients, the study showed that TAC is highly associated with increasing age. The study showed that the level of TAC significantly decreased with age older than 26.0 years. Other medical and clinical factors were not shown to associate with the level of TAC in PCOS patients (Table 4 and Fig 4).

DISCUSSION

This case-control study showed that the PCOS patients had a significantly lower TAC level than matched control women. The literature has stated that oxidative stress (in contrast to TAC) is higher in PCOS patients [14, 15, 21, 31-33]. TAC is the facility of serum to overpower the oxidative stress to retain the cell structure healthy from the adverse effects of oxidative materials. TAC was lower in PCOS patients in our study, in agreement with other studies, as all documented a decrease in TAC level. Patient with PCOS. TAC could be used to prevent the growth or development of insulin resistance and oxidative stress by routine assessments. Also it may be working as an indicator in early diagnosis of PCS .[17, 22, 26].

Regarding the general characteristics, the mean age was 26.34 and 27.91 for both PCOS and the control group. BMI with a mean value of 26.55 for the study group and 26.60for

the control group. No significant difference among both groups was noticed for age and BMI. This could be one of the strong points of this study. So, the general characteristics were found to have no significant difference between both groups. Some studies documented that age negative correlates with TAC[34]. Some studies also reported that weight had decreased the TAC level [6, 35]. Neither age nor weight affected the TAC in this study, as the differences in these characteristics were insignificant between both groups.

The menstrual cycle assessment was considered one essential parameter of PCOS confirmation diagnosis. The confirmatory biochemical testosterone was found to be agreed with TAC which is found to be highly significant between PCOS and the control group. It was found that the mean value of testosterone level is higher in the study group, 0.31, than in control 0.11. Such an outcome level of testosterone means a correct choice for our study group of patients.

On physical examination between both groups of patients, hirsutism was assessed according to the Ferriman-Gallwey score [27]. Patients with moderate and severe hirsutism were mainly distributed among the PCOS group, with a highly significant outcome.

The role of general characteristics on the level of TAC. It is found that the level of TAC is decreased with increasing age [36]. Fortunately, the mean value of age in both control and PCOS were close, which doesn't affect our study's results. BMI in the profiler showed that as weight increased, the TAC level decreased, which agreed with a number of studies because these studies also reported that TAC level decreases with increased BMI and age [34, 36], but in underweight patients, that showed a decrease in TAC. A systematic review by Solmi also proved that the underweight has high oxidative stress [37]. Risi argued in a narrative review that obesity and underweight are two sides of one coin [38].

Other parameters include ovarian morphology and volume of both right and left ovaries, testosterone hormone level, menstrual cycle, and degree of hirsutism; all were found to be no significant change at the level of TAC in PCOS patients. Instead, the morphology assessment by endovaginally ultrasound and testosterone test profiler showed a negative correlation but not to a significant level.

Limitations

In this study, we only used total testosterone as a biochemical test far better if we used more than one test. We only used two-dimensional ultrasound to assess the ovarian volume and follicular number per ovary. Three-dimensional (3-D) ultrasound may be more promising regarding image quality, storage, data, and image interpretation. It may provide more understanding pathophysiology of PCOS severity assessment, regardless of the accuracy [39, 40].

Conclusions and Recommendations

This study showed that serum TAC levels are significantly lower in PCOS patients than in non-affected individuals. A prospective case-control and randomized control study are advisable to know about the fluctuation of the level of TAC with the change of weight and age and the severity of PCOS. Also, to know if the administration of antioxidants will affect the level of TAC. It is essential to consider TAC in routine monitoring of PCOS patients as a regular assessment if the above-recommended points are considered. Systematic review and metanalysis may be suggestable in this area of research.

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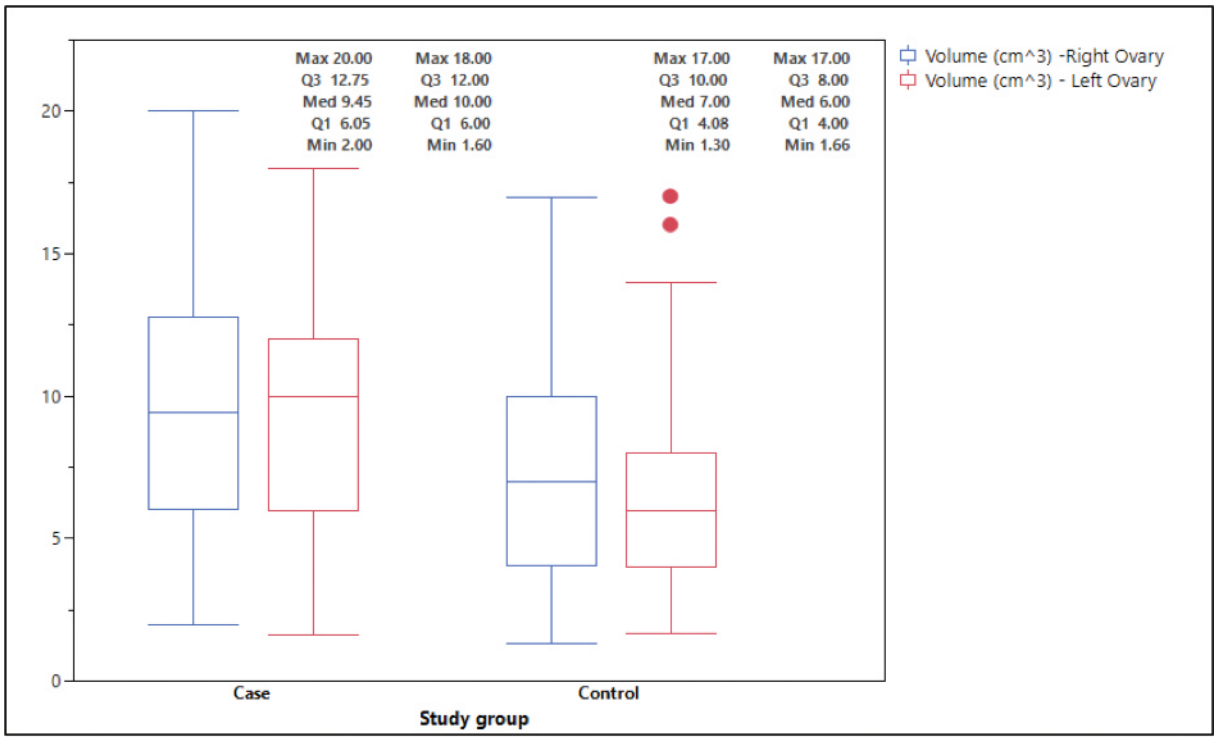

Figure 1: Comparisons of ovarian volume between patients with PCOS and controls

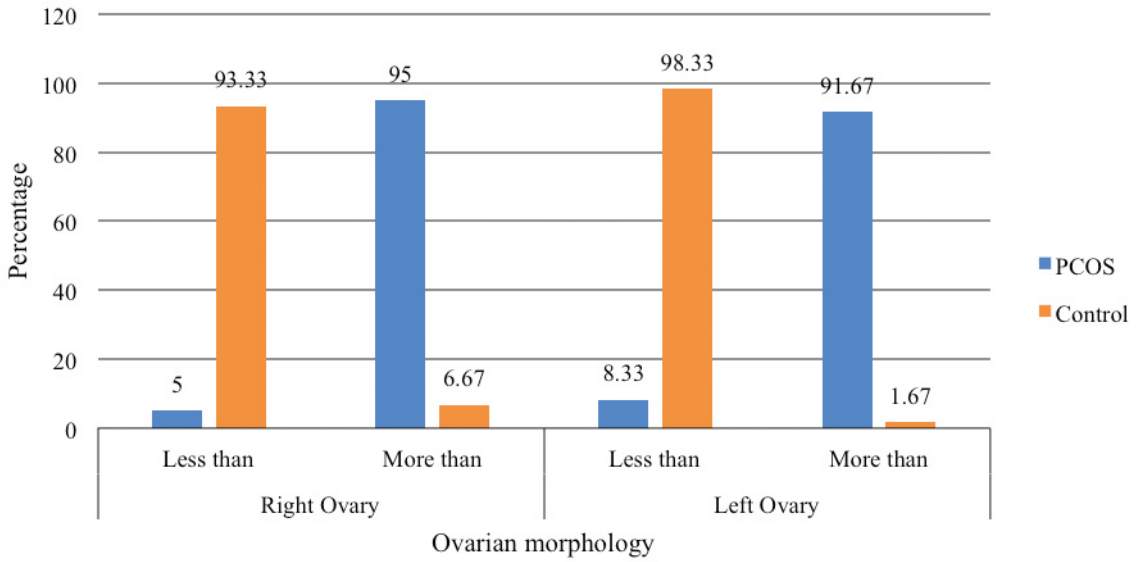

Figure 2: Comparisons of ovarian morphology between patients with PCOS and controls

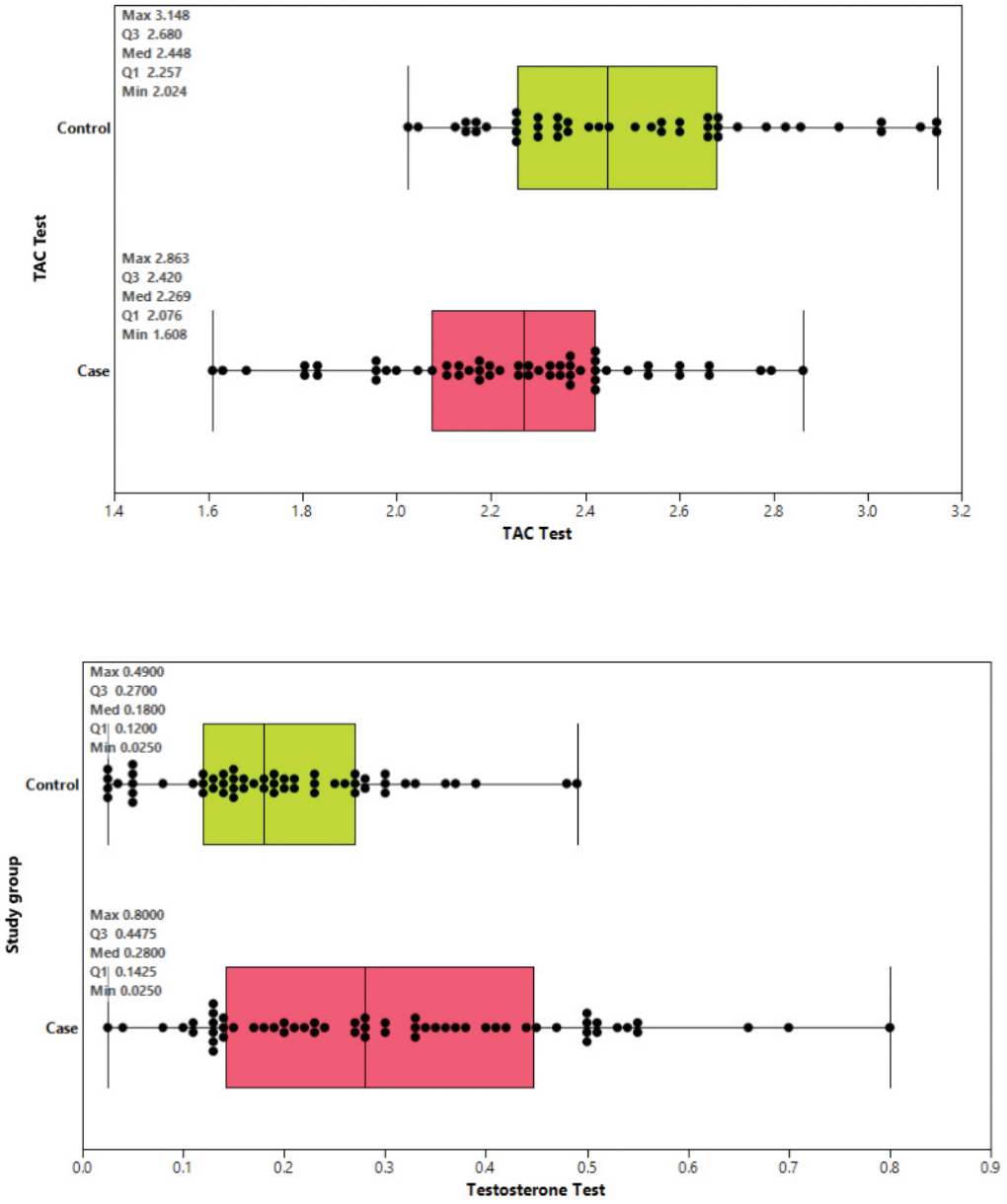

Figure 3: Comparisons of Testosterone and TAC test results between patients with PCOS and controls

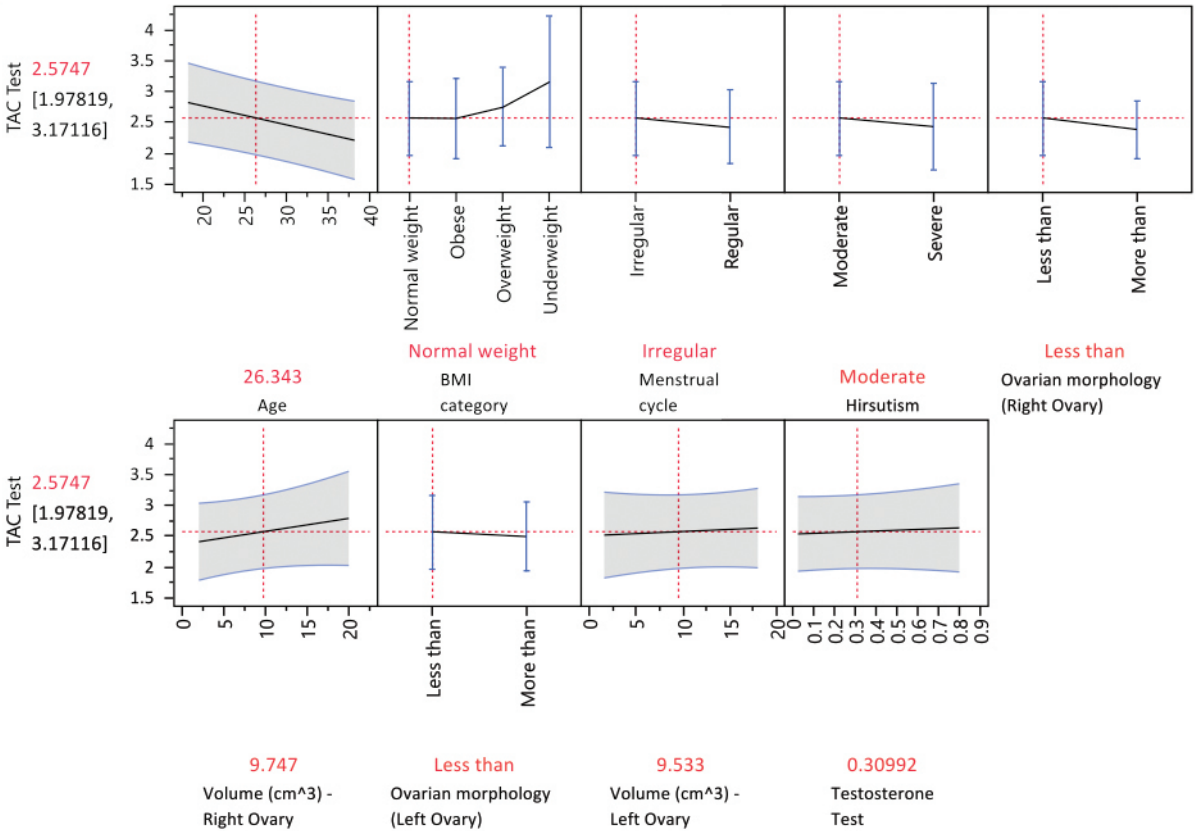

Figure 3: Profiler of the role of general characteristic, Testosterone, and endovaginally U/S outcomes on level of TAC in PCOS patients

Table 1: Comparisons of general characteristics between PCOS and control groups

Age and BMI	Study groups		p-value (two-sided
	PCOS (n=60)	Control (n=60)	
Age	26.34 (4.92	27.91 (4.61	0.0739[a]
BMI	26.55 (4.40	26.60 (4.15	
Underweight	1 (1.67	1 (1.67	0.9532[a]
Normal weight	20 (33.33	23 (38.33	
Overweight	27 (45.00	23 (38.33	0.9034[b]
Obese	12 (20.00	13 (21.67	

[a]An independent t-test and [b] Pearson Chi-squared tests were performed for statistical analyses.

Table 2: Comparisons of physical examination and Endovaginally U/S between patients with PCOS and controls

Physical examination and Endovaginal U/S outcomes	Study groups		p-value (two-sided
	PCOS (n=60)	Control (n=60)	
Hirsutism Minimal Mild Moderate Severe	 0 (0.00 0 (0.00 51 (85.00 9 (15.00	 27 (45.00 33 (55.00 0 (0.00 0 (0.00	**<0.0001[b]**
Right Ovary **Ovarian morphology** Less than 12 follicles More than 12 follicles Volume (cm^3)	 3 (5.00 57 (95.00 9.75 (4.08	 56 (93.33 4 (6.67 7.30 (3.72	**<0.0001[b]** **0.0008[a]**
Left Ovary **Ovarian morphology** Less than 12 follicles More than 12 follicles Volume (cm^3)	 5 (8.33 55 (91.67 9.53 (3.79	 59 (98.33 1 (1.67 6.76 (3.44	**<0.0001[b]** **<0.0001[a]**
Menstrual cycle Irregular Regular	 41 (68.33 19 (31.67	 25 (41.67 35 (58.33	**0.0033**
[a]An independent t-test and [b] Pearson Chi-squared tests were performed for statistical analyses.			

Table 3: Comparisons of Testosterone and TAC test results between patients with PCOS and controls

Outcomes	Study groups		p-value (two-sided
	PCOS (n=60)	Control (n=60)	
Testosterone test **Range (Min-max)**	0.31 (0.18 0.025-0.8	0.19 (0.11 0.025-0.57	**<0.0001**
TAC Test **Range (Min-Max)**	2.24 (0.29 1.61-4.10	2.51 (0.31 2.02-17.23	**<0.0001**
[a]An independent t-test was performed for statistical analyses. The red bold numbers show significant differences.			

Table 4: Role of general characteristics, Testosterone, and endovaginally U/S outcomes on level of TAC in PCOS patients

Factors (n=60)	Outcome: TAC test Presentations	P-value
Age		**0.00933**
Menstrual cycle		0.25754
Volume (cm^3) -Right Ovary		0.27451
BMI category		0.30380
Hirsutism		0.38885
Ovarian morphology (Right Ovary)		0.51705
Testosterone Test		0.70679
Volume (cm^3) - Left Ovary		0.71295
Ovarian morphology (Left Ovary)		0.71545
Standard least squares with effect leverage were performed for statistical analyses. The red bold numbers show the predictors of TAC in PCOS group.		