Issn 1110 -6352

THE EGYPTIAN JOURNAL OF FERTILITY AND STERILITY

Volume 26 Number 3 September 2022

EFSS

The Egyptian Journal Of Fertility And Sterility

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

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Acknowledgments

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

References

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List all authors when six or less. When seven or more, list only first six and addetal. Toppozada MK, Gaafar AA, Shaala SA. In - vivo inhibition of the human non pregnant uterus by prostaglan din E2. Prostaglandins, 1974; 8: 401 - 406.

2- Books:

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

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

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Contents :

Letter from the Editor:

Dear colleagues,

Warm greetings

We welcome your comments as well as the scientific activity to be incorporated in the upcoming issues. We are pleased to invite you to the 28th Egyptian Fertility and Sterility conference, 1, 2 December 2022. Venue: Marriott hotel Zamalek Cairo. New treatments and developments in women reproductive health. Very important subjects are included in this issue. Carbetocin is superior than oxytocin combined with misoprostol in the prevention of postpartum hemorrhage in patients with severe pre-eclampsia rece. When considering conservative surgery in patients with borderline ovarian tumors, special care should be given to patients with elevated CA-125, advanced FIGO stage, and microinvasion. Vaginal cleaning with povidone iodine prior to cesarean section can prevent post-operative febrile morbidity. Combined letrazole plus CC and letrazole alone seem to be two effective approaches, with letrazole plus CC showed better ovulation results and hence better pregnancy rate outcome. Simple trans-vaginal aspiration of ovarian chocolate cyst can improve ovarian response and increase clinical pregnancy rate better than conservative management. Vitamin D deficiency is widespread between women with endometriosis. Vitamin D supplementation for 12 w improved vitamin D status and endometriosis-related pain scores. The Robson Classification System had good true negative, but high false positive predictive values for CS. Adjustment according to BMI within Robson groups significantly reduced the need for CS and may improve the decision for augmentation, instrumental and operative delivery.

Best regards.

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Carbetocin versus oxytocin combined with misoprostol for prevention of postpartum hemorrhage in patients with severe pre-eclampsia: A randomized control trial

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Abstract

Background: Oxytocin is a uterotonic medication that promotes increased uterine tone and contractions, and is commonly administered immediately following delivery of the infant's shoulder as part of AMTSL. An alternative to oxytocin is misoprostol (Cytotec), an inexpensive medication that does not require injection and is more effective than placebo in preventing postpartum hemorrhage. Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single dose injection in the route of intravenous or intramuscular.

Aim of work: To compare the effectiveness of carbetocin alone versus oxytocin combined with misoprostol in prevention of postpartum hemorrhage in patients with severe pre-eclampsia.

Patients and methods: The study comprised 124 women with severe pre-eclampsia who underwent elective caesarean section, during the period from first of April 2020 to the end Marsh 2021.

Results: There was no statistically significant difference found between two groups regarding need for additional uterotonic, need for blood transfusion, need for instrumental currtage, oliguria and length of hospital stay, and there was statistically significant difference found between two groups regarding Hb difference, and there was highly statistically significant difference found between two groups regarding post partum Hb level. There was no statistically significant difference found between two groups regarding palpitation, fever, nausea, vomiting, hot sensation, fascial flushing and malaise, and there was statistically significant difference found between two groups regarding headache.

Conclusion: Carbetocin is superior than oxytocin combined with misoprostol in the prevention of postpartum hemorrhage in patients with severe pre-eclampsia recived magnesium sulfate to prevention of eclamptic fits.

Keywords: Carbetocin, Oxytocin, Misoprostol, Postpartum hemorrhage, Pre-eclampsia.

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Introduction

Postpartum hemorrhage (PPH) is a significant problem and a major cause of maternal mortality and morbidity, resulting in up to 28% of maternal deaths [1].

It can result from uterine atony, retained placental tissue including that from abnormal placentation, maternal genital tract trauma and coagulopathies [2]. Uterine atony is the major cause of postpartum hemorrhage (PPH), accounting for up to 80% of PPH cases [3].

Risk factors for PPH may be Suspected or proven placental abruption Known placenta Previa, multiple pregnancy, pre-eclampsia/ gestational hypertension, previous PPH, obesity, Anemia, delivery by elective caesarean section, induction of labour, retained placental tissues, prolonged labour and big baby [4].

Women with pre-eclampsia have a 1.53 fold increased risk for postpartum hemorrhage. Clinicians should be aware of this and use this knowledge in the management of pre-eclampsia and the third stage of labour [5]. Magnesium sulfate was used in 10% of the deliveries; however, preeclampsia is highly correlated with use of magnesium sulfate, magnesium sulfate in the setting of pre eclampsia may impair uterine contractility, resulting in uterine atony and hemorrhage. Because of its tocolytic effect [6].

Several uterotonics agents are used to prevent PPH because of uterine atony, including oxytocin, ergot alkaloid and prostaglandin [7].

Misoprostol is a prostaglandin E1 analogue with strong uterotonic properties and has been suggested as an alternative to inject able uterotonic agents for preventing PPH, It is cheap, heat stable, and can be administered through multiple routes [8].

Misoprostol has been widely recommended for the prevention of post-partum hemorrhage when other methods are not available. The most common regimen reported for the treatment of post-partum hemorrhage is rectally [9].

Carbetocin, a long-acting oxytocin analogue that bind to oxytocin receptors with higher affinity, its contractile effect of uterus are apparent within two minutes. A 100-μg dose of carbetocin has been recommended for preventing PPH in high risk patients. An advantage of carbetocin over others uterotonics is that, owing to its long half-life, it is administrated as a single intravenous dose [10].

The aim of this study was to compare the effectiveness of Carbetocin alone versus oxytocin combined with misoprostol in prevention of postpartum hemorrhage in patients with severe pre-eclampsia.

Patients and methods

In our case, acupuncture was effective in This a randomized control study comprised 124 women with severe pre-eclampsia who underwent elective caesarean section, was conducted at Department of Obstetrics and Gynecology, Aswan University hospital, during the period from first of April 2020 to the end Marsh 2021.

This study was divided into two equal groups: Group I: patient received 100 mcg of Carbetocin (Pabal) intravenous over one minute immediately after delivery of the baby, and Group II: patient received 10 IU oxytocin (Syntocinone) iv drip and 400 mcg of misoprostol rectally after anesthesia.

Randomization:

Randomization was done using computer-generated random table. Allocation concealment was ascertained using the serially numbered closed envelopes. After assessing the eligibility and obtaining the required consent, allocation of the patients was done by telephone of the primary center in Aswan University who had the serially closed envelops. Once allocation has been obtained, it could not be changed.

Inclusion criteria: Pregnant women which diagnosed with severe pre-eclampsia, singleton pregnancy, and termination of pregnancy by Cesarean section after 28 weeks of gestation.

Exclusion criteria: (High risk patients of post-partum hemorrhage). Suspected or proven placental abruption, known placenta Previa or acreata, multiple pregnancies, obesity (BMI > 35), anemia (< 9 g/dl), retained placental tissues, big baby (> 4 kg), presence of coagulopathy, polyhydramnios, presence of Uterine fibroids, medical diseases as; cardiac, liver, renal or endocrine diseases, general anesthesia, and longitudinal uterine incision.

All patients were subjected to:

- Detailed history taking.
- General examination.
- Abdominal examination.
- Investigation was done to confirm presence of sever pre-eclampsia.

The blood pressure was measured in a sitting position with an oscillometric device on the arm. We recorded the first blood pressure measurement in Medical Records before recruitment. After parturition, we recorded the blood pressure taken in the maternity ward after leaving the postpartum ward and contact with the participants (telephone, e-mail) was maintained.

The amount of blood loss was calculated according to number of soaked pads or dressing used after delivery for the 1st 24 hours. Where each soaked dressing = 50 cc. Intra-operative blood loss. Operative blood loss was calculated from the amount of blood in the suction bottle after delivery of placenta and the number of towels used and to which degree they were socked. Blood from the uterine incision, soaked towels and blood in suction bottle before placental delivery not added to the blood measurements.

N.B.: Soaked towel = 150 cc. Semi-soaked towel = 75 cc. The amount of blood loss was calculated according to number of soaked pads or dressing used after delivery for the 1st 24 hours. Where each soaked dressing = 50 cc.

Post-partum hemorrhage was considered:

- Minor PPH: if estimated blood loss is up to 1000 ml.
- Major PPH: if any estimated blood loss is over 1000 ml.

Clinical observation of patients was continued for the first 24 hours (every 10 minutes in first hour and then every hour for remaining 23 hours) for reporting and management of any degree of postpartum hemorrhage. The need for additional uterotonics agents (methyl-ergometrine, misoprostol) was recorded in both groups. The duration of the operation and blood transfusion, maternal pulse rate and fetal body weight was also recorded.

Follow up:

Intrapartum: Uterine tone. Further need for haemostatic measures will be also assessed. The occurrence of uterine atony requiring the use of additional uterotonics is considered the primary outcome of this study. The uterine tone was assessed by using a hand resting on the fundus and palpating the anterior wall of the uterus every two hours after the delivery.

Postpartum up to 24 hour: Uterine tone. Amount of vaginal bleeding. Hemoglobin level and hematocrit value, and the need for blood transfusion.

Ethical consent:

An approval of the study was obtained from Aswan University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 26. The qualitative data were presented as number

and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P value < 0.05 was considered significant.

Results

Table (1): Personal data of patients of both groups.

		Mean /N		SD/%	Median
		Carbetocin	Oxytocin plus misoprostol		
Age		29.3	29.3	5.82	29(25-34)
BMI		27.2	27.2	4.8	27(24-33)
Residence	Rural	26 (21 %)	25(20%)	6.8	
	Urban	36(29%)	37(30%)	7.2	

As regards the mean age of the participants in both groups was 29.23 years and the median was (25 – 34) years , The mean BMI of cases were 27.23 years median (24 – 33) (Table 1).

Table (2): Comparison regarding symptoms of severity of per-eclampsia in both groups.

		Carbetocin	Oxytocin plus misoprostol	P-Value	Sig.
		No.= 62	No.= 62		
Visual symptoms	No	52 (83.9%)	57 (91.9%)	0.169	NS
	Yes	10 (16.1%)	5 (8.1%)		
Epigastric pain	No	54 (87.1%)	53 (85.5%)	0.794	NS
	Yes	8 (12.9%)	9 (14.5%)		

There was non-statistically significant difference found between two groups regarding symptoms of severe PET (Visual symptoms and Epigastric pain) (Table 2).

Table (3): The incidence of PPH, Major PPH and Uterine atony in both groups after intervention.

		Carbetocin		Oxytocin plus misoprostol		P-value	Sig.
		No.	%	No.	%		
Uterine atony	No	55	88.7%	43	69.4%	0.008	S
	Yes	7	11.3%	19	30.6%		
PPH	No	56	90.3%	45	72.6%	0.011	S
	Yes	6	9.7%	17	27.4%		
Major PPH	No	62	100.0%	60	96.8%	0.154	NS
	Yes	0	0.0%	2	3.2%		

As regards the incidence of major PPH , this table shown that, there was no statistically significant difference found between two groups regarding Major PPH, and there was statistically significant difference found between two groups regarding PPH and Uterine atony (Table 3).

Table (4): Postpartum follow up for amount of blood loss in both groups.

		Carbetocin	Oxytocin plus misoprostol	P-value	Sig.
		No.= 62	No.= 62		
Amount of Bleeding	Mean ± SD	623.39 ± 267.15	792.74 ± 393.27	0.006	HS
	Range	300 – 1400	400 – 1900		
Need for additional utertonics	No	62 (100.0%)	60 (96.8%)	0.154	NS
	Yes	0 (0.0%)	2 (3.2%)		
Need for blood transfusion	No	62 (100.0%)	59 (95.2%)	0.080	NS
	Yes	0 (0.0%)	3 (4.8%)		
Oliguria	No	62 (100.0%)	61 (98.4%)	0.315	NS
	Yes	0 (0.0%)	1 (1.6%)		

As regards to the post-partum follow up, this table showed that, there was highly statistically significant difference found between two groups regarding amount of bleeding , and non-statistically significant difference found between two groups regarding. However, the need for additional uterotonic, and the need for blood transfusion showed that there was non-statistically significant difference found between two groups regarding oliguria (Table 4).

Table (5): Comparison regarding blood pressure and heart rate and blood haemoglobin level before and after delivery.

		Carbetocin	Oxytocin plus misoprostol	P-value	Sig.
		No.= 62	No.= 62		
Systolic bl. pressure	Mean ± SD	160.32 ± 7.51	159.03 ± 6.26	0.301	NS
	Range	150 – 180	150 – 170		
Diastolic bl. pressure	Mean ± SD	109.44 ± 7.02	108.23 ± 6.66	0.327	NS
	Range	100 – 120	100 – 120		
Systolic after delivery	Mean ± SD	127.90 ± 13.69	124.03 ± 11.66	0.093	NS
	Range	100 – 160	90 – 140		
Diastolic after delivery	Mean ± SD	83.29 ± 11.69	80.55 ± 16.35	0.285	NS
	Range	60 – 110	60 – 140		
Heart rate after delivery	Mean ± SD	88.85 ± 9.71	91.74 ± 12.18	0.147	NS
	Range	73 – 110	72 – 120		
Initial Hb level.	Mean ± SD	12.20 ± 0.70	12.30 ± 0.77	0.463	NS
	Range	10.6 – 13.7	9.5 – 13.9		
Postpartum Hb level	Mean ± SD	10.34 ± 0.61	9.95 ± 0.78	0.002	HS
	Range	8.8 – 11.3	8 – 11		
Hb difference	Mean ± SD	1.95 ± 0.83	2.35 ± 0.99	0.014	S
	Range	0.3 – 4.6	0.6 – 4.5		

There was non-statistically significant difference found between two groups regarding Systolic bl pressure and Diastolic bl pressure (before and after termination of pregnancy) and shows that there was non-statistically significant difference found between two groups regarding heart rate. There was non-statistically significant difference found between two groups

regarding initial Hb. level. However, it shows that, there was highly statistically significant difference found between two groups regarding post-partum Hb level. Also, it shows that, there was statistically significant difference found between two groups regarding HGb level difference pre and post-delivery (Table 5).

Table (6): Postpartum hospital stay and ICU admission in both groups.

		Carbetocin	Oxytocin plus misoprostol	Sig.
		No.= 62	No.= 62	
Length of hospital stay	Mean ± SD	3.21 ± 0.45	3.27 ± 0.45	NS
	Range	2 – 4	3 – 4	
Need to ICU due to sever PET	No	54 (87.1%)	57 (91.9%)	NS
	Yes	8 (12.9%)	5 (8.1%)	NS
Need to ICU due to other cause	No	59 (95.1%)	60 (96.7%)	NS
	Yes	3 (4.9%)	2 (3.3%)	NS

This table shows that, there was non-statistically significant difference found between two groups regarding length of hospital stay and Need to ICU admission (Table 6).

Table (7): Comparison regarding common side effects of both groups.

		Carbetocin		Oxytocin plus misoprostol		Test value*	P-Value	Sig.
		No.	%	No.	%			
Headache	No	58	93.5%	62	100.0%	4.133	0.042	S
	Yes	4	6.5%	0	0.0%			
Palpitation	No	62	100.0%	60	96.8%	2.033	0.154	NS
	Yes	0	0.0%	2	3.2%			
Fever	No	62	100.0%	60	96.8%	2.033	0.154	NS
	Yes	0	0.0%	2	3.2%			
Nausea	No	60	96.8%	62	100.0%	2.033	0.154	NS
	Yes	2	3.2%	0	0.0%			
Vomiting	No	60	96.8%	62	100.0%	2.033	0.154	NS
	Yes	2	3.2%	0	0.0%			
Hot sensation	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			
Fascial flushing	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			
Malaise	No	61	98.4%	62	100.0%	1.008	0.315	NS
	Yes	1	1.6%	0	0.0%			

There was non-statistically significant difference found between two groups regarding palpitation, fever, nausea, vomiting, hot sensation, fascial flushing and malaise, and there was statistically significant difference found between two groups regarding headache (Table 7).

Discussion

As the primary outcome of our study was the amount of postpartum bleeding and the occurrence of PPH, there was highly statistically significant difference found between two groups regarding the occurrence of PPH as carbetocin group have less incidence with (P value 0.011) and there was statistically significant difference found between two groups regarding the occurrence of postpartum uterine atony (P value 0.008). on the other hand, there was none statistically significant difference found between them regarding the occurrence of major PPH.

In agreement of our study, Ali et al. [11] showed that the incidence of postpartum hemorrhage was less in carbetocin group as they found in 6% (3 cases), 14 % (7 cases) and 12% (6 cases) in Carbetocin, Oxytocin and Misoprostol groups respectively. Also, they found that, the difference was moderately statistically significant, as regard to severity of postpartum hemorrhage as the incidence of major PPH was 0 (0%), 2 (4%) and 3 (6%) in Carbetocin, Oxytocin and Misoprostol respectively and the difference was highly statistically significant (P <0.0001) so , they concluded that, carbetocin was superior to oxytocin and misoprostol in prevention of atonic PPH in high-risk patients underwent elective caesarean section delivery and they recommend the use of carbetocin for all cases undergoing elective caesarean section and carry a risk factor for postpartum hemorrhage.

In Ali et al. [11], study, all the uterotonics were used separate but in our study, we use the combination between the oxytocin and misoprostol and still the carbetocin group have less incidence of PPH even if with the use of magnesium sulfate (tocolytic as a preventive measurement of convulsions in sever preeclampsia.

In our study findings were in agreement to what was reported by Dansereau et al.[12].

In accordance with our study, Larciprete et al. (13), reported that, a single injection of Carbetocin appears to be more effective than a continuous infusion of oxytocin to prevent the PPH, with a similar hemodynamic profile and minor antidiuretic effect

In the same way Attilakos et al. [14] study reported that, when carbetocin 100 μg and oxytocin 5 IU intravenously were compared for the prevention of PPH following cesarean section, there were significantly more women who needed additional oxytocics in the oxytocin group, while there were no significant differences in the estimated blood loss, uterine tone at the end of the operation, number of women with major PPH, number of women requiring blood transfusions, and the mean Hb fall after the operation.

Several studies discussed the efficacy of Carbetocin in prevention of postpartum hemorrhage during vaginal and cesarean deliveries. Boucher et al. [15] found that, a single dose of 100 μg of Carbetocin given with intravenous drip has been proved to be as effective as a 16-hour infusion of Oxytocin in prevention of intraoperative and postoperative blood loss after caesarean section.

Matching with our result, Chen et al. [16], they found in comparison the effect of Carbetocin prophylaxis in vaginal and CS that, a significant decrease in blood loss was noted with the prophylactic use of Carbetocin in cesarean deliveries.

Another study by Borruto et al. [1] were found that a single dose of Carbetocin had the same efficacy compared to two-hour Oxytocin infusion in prevention of intraoperative blood loss after removal of placental

An interesting result obtained in our study was finding that, there was none statistically significant difference found between two groups regarding need for additional uterotonic, need for blood transfusion, need for instrumental curettage, oliguria and length of hospital stay.

In the same way Ali et al. (11) study reported that, the needed for additional uterotonic agents and or for further surgical hemostatic measures were statistically significant lesser in Carbetocin group compared to the other two groups (oxytocin and misoprostol). These findings were in accordance with Borruto et al. (1) and Larciprete et al. [13].

Similarly, Fekih et al. [17] reported that a combination of misoprostol 200 μg with oxytocin has been demonstrated to reduce blood loss and the need for additional uterotonics.

But there was statistically significant difference found between two groups regarding Hb difference before and after the delivery which was less in carbetocin group with (P value 0.014).

Also, there was highly statistically significant difference found between two groups regarding postpartum serum Hb level which was higher in carbetocin group with (P value 0.002)

In disagreement with our results, El Sharkwy [18] reported that, in comparison of the combination of sublingual misoprostol and oxytocin infusion with intravenous carbetocin in the prevention of PPH during cesarean delivery in high-risk patients, they concluded that, both groups as effective as in reducing the need for additional uterotonic. These results in high-risk patient not in patients received tocolytic drugs before and after delivery as magnesium sulfate.

Also, El Sharkwy [18] concluded that in low-income countries, addition of a relatively tolerable small dose of sublingual misoprostol before CS managed by intravenous oxytocin can be a suitable substitute for the costly use of carbetocin in prevention of PPH in patients with risk factors. But in Egypt, the misoprostol not available in pharmacies and more expensive than carbetocin.

Conclusion

Carbetocin is superior than oxytocin combined with misoprostol in the prevention of postpartum hemorrhage in patients with severe pre-eclampsia recived magnesium sulfate to prevention of eclamptic fits.

Recommendation

We recommend the use of carbetocin as uterotonic to prevent the PPH in high risk patient especially sever pre -eclampsia received magnesium sulfate.

Acknowledgement

The authors are grateful for the patients without whom this study would not have been done.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

Discussion

As the primary outcome of our study was the amount of postp

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Evaluation of Prognostic Factors for Survival in Women with Borderline Ovarian Tumors

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Abstract

Objective: To evaluate the clinico- pathological features and modalities of treatment that affect recurrence and survival in patients with borderline ovarian tumors.

Methods: Data of 92 patients diagnosed with borderline ovarian tumors (BOTs) during the period from 2005 to 2017 in the National Cancer Institute (NCI) and Menoufia University Hospital, Egypt, were retrospectively analyzed.

Results: Median follow-up period was 76 months (range, 12-157 months). Histopathology was serous in 63%, mucinous in 28.3%, and endometrioid in 3.3%. Sixty five patients (70.7%) had Stage IA disease, 17 patients had Stage IB disease (18.5%), and 10 patients had advanced disease. Forty nine patients (53.3%) underwent fertility sparing surgery and 43 patients (46.7%) underwent radical surgery. The total recurrence rate was 18.5% (17/92); three patients (17.6%) among those who underwent radical surgery and fourteen patients (82.4%) among those who received fertility sparing surgery. Twelve of the recurrences (70.6%) were borderline while 5 were invasive (29.4%). Multivariate analysis showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival. Risk factors for recurrence in the fertility sparing surgery group were stage, microinvasion and elevated preoperative serum CA125.

Conclusion: When considering conservative surgery in patients with borderline ovarian tumors, special care should be given to patients with elevated CA-125, advanced FIGO stage, and microinvasion.

Keywords: Borderline ovarian tumors, Prognostic factors, Survival.

Introduction

Borderline ovarian tumors were first described by Taylor in 1929 when he noted a group of "" ovarian tumors that were associated with a favorable prognosis [1].They were first recognized as a separate pathologic and clinical entity by the International Federation of Gynecology and Obstetrics (FIGO) in 1971 and was followed by World Health Organization acceptance in 1973 [2].

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They represent a specific group of epithelial ovarian neoplasms that are histologically distinguished from ovarian carcinomas by the absence of stromal invasion. These neoplasms are also referred to as tumors of low malignant potential (LMP), which reflects their indolent natural history [3].

BOTs comprise approximately 15 % of all epithelial ovarian tumors; the mean age of occurrence is approximately 10 years younger than that of women with frankly malignant ovarian cancer, a fact that emphasizes the importance of fertility-sparing surgery in patients who want to preserve their childbearing potential [4, 5].

Surgery is the main treatment modality for BOTs, but considerable debates exist on the extent of surgery. Some surgeons do not perform the complete staging because the survival is high regardless of stage [5]. Borderline Ovarian Tumors are associated with a significantly more favorable prognosis than epithelial ovarian cancer, the 5-year overall survival rate for early stage I BOT is approximately 98%; and the 5-year overall survival of advanced disease is between 86% and 92% [6].Follow up should be long term because recurrences may develop after more than 15 years. In conservatively treated women, close follow up is crucial, with special attention to the remaining ovary [7].

In the current study, we evaluated the clinico- pathological features and modalities of treatment that may affect the recurrence rate and survival in such patients.

Patients Methods

The present study was approved by the local ethical committee of the National Cancer Institute (NCI) and Menoufia University Hospital, Egypt, where the study was conducted. The files of 92 patients who were diagnosed and treated for borderline ovarian tumor were retrospectively reviewed between March 2005 and February 2017. From the hospital records, data related to the patients' age, menopausal state, parity and pre-operative CA-125 (Cancer Antigen-125) were collected. Furthermore, type of surgical technique, histopathologic type, mean tumor diameter, presence and characteristics of tumor implants, results of the peritoneal washings, lymph node status, stage at the diagnosis, and accompanying pathologies if any, were reviewed. Additionally, chemotherapy requirements after surgery, postoperative follow-up periods, and data related with the disease recurrence and conditions necessitating recurrent operations were evaluated.

Pathological staging was done according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) 2014. Comprehensive surgical staging with peritoneal sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, appendectomy and omentectomy were performed in patients who were postmenopausal, completed their family or had additional disease that required extensive surgery. Fertility sparing surgery retaining the uterus and the adnexa at one or both sides were performed in patients who were premenopausal and wish to preserve their fertility. Types of fertility preserving surgery performed were: unilateral salpingo-oophorectomy (USO), unilateral salpingo-oophorectomy plus contralateral ovarian cystectomy, unilateral ovarian cystectomy and bilateral ovarian cystectomy. All patients were operated on using open surgery.

Chemotherapy was recommended for all BOT patients with lymph node metastasis, or invasive implants, or with stage III/IV. Follow- up of patients was performed once every 3 months in the first 2 years and every 6 months in the next 3 years and yearly thereafter. At the time of follow-up, patients received routine gynecological examination, test for tumor markers and ultrasound.

If tumor markers and/or ultrasound were abnormal, then patients would be examined by CT. Recurrence was defined as the same tumor cell type detected after an apparent complete surgical resection. Disease free survival (DFS) was defined as the time from the date of surgery to the date of recurrence or to the last date of follow-up. Patients with incomplete data were excluded.

Statistical analysis: The collected data, were tabulated and analyzed by IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range. Qualitative data were expressed as frequency and percentage. Univariate analysis was done to assess association between individual variables with disease free survival and recurrence. The survival curves and rates were calculated using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. A p-value < 0.05 was considered significant.

Results

A total of 92 BOT cases were identified. Patients and disease-related characteristics are shown in Table I. The mean age at primary diagnosis was 42.7 years (range=15-71 years); 66.3% (n=61) of women were premenopausal and 33.7% (n=31) were postmenopausal. Serum CA125 was elevated in 47 patients (51.1%). The tumor was larger than 11 cm in 49 patients (53.3%) and malignant ascites was present in 7 patients (7.6%).

Histopathology revealed serous BOT in 61 (66.3%) patients which was considered the most frequent pathologic type, 23 patients had mucinous BOT (25%), endometrioid in 3 patients (3.3%), mixed in 4 patients (4.3%), and only one patient had Brenner tumor (1.1%).

In sixty five patients the disease was stage IA (70.7%) and the remaining 27 patients were: stage 1 B (18.5%, n=17), stage 1C (4.3%, n=4), stage II (2.2%, n= 2), stage III (4.3%, n=4). Forty patients had micropapillary disease (43.5%) and two patients had microinvasion (2.2%). Implants were found in 6 (6.5%) patients of whom 1 patient had invasive implants. They were localized at the omentum, tubes, peritoneum, parametria, Douglas pouch, uterus, cervix, lymph nodes, sigmoid, rectum and appendix.

Details of the surgical procedures and adjuvant chemotherapy are given in Table 2. Forty nine patients (53.3%) underwent fertility sparing surgery, of whom 19 patients underwent unilateral ovarian cystectomy, 5 patients underwent bilateral ovarian cystectomy, 25 underwent unilateral salpingo-oopherectomy.43 patients (46.7%) underwent radical surgery including total abdominal hysterectomy and bilateral salpingo-oophorectomy. Eighty three patients (90.2%) had their primary surgery without grossly detected residual disease or cyst rupture. Tumor rupture occurred during surgery in 5 patients (5.4%). Pelvic and para-aortic lymph nodes were sampled in ten patients, none of which showed tumor invasion. Postoperative adjuvant chemotherapy was given in two patients who had peritoneal implants using regimen of paclitaxel and carboplatin 3-6 cycles.

Table 1: The main patient and disease characteristics

Studied variables	No.	%
Age / years		
- ≤40	51	55.4
- >40	41	44.6
Mean ±SD	42.7±15.8	
Range	15 – 71	
Parity		
- Nullipara	22	23.9
- Multipara	70	76.1
Menopausal status		
- Premenopausal	61	66.3
- Postmenopausal	31	33.7
Ultrasound finding		
- Solid	53	57.9
- Cystic	20	21.7
- Multi-loculated	19	20.7
Ascites		
- Positive	7	7.60
- Negative	7	7.60
- Not available	78	84.8
CA 125		
- ≤ 35	45	48.9
- >35	47	51.1
Mean ±SD	134.1±236.4	
Median	44.5	
Range	4.70 – 1589	
Site		
- Right	40	43.5
- Left	32	34.8
- Bilateral	20	21.7
Size		
- ≤ 11	43	46.7
- > 11	49	53.3
Mean ±SD	13.5±6.17	
Range	4 – 30	
Histological subtypes		
- Serous	58	63.0
- Mucinous	23	28.3
- Endometrioid	3	3.30
- Brenner	1	1.10
- Mixed	4	4.30
Micropapillary		
- Yes	40	43.5
- No	22	23.9
- Not applicable	30	32.6

Microinvasion - Yes - No	 2 90	 2.20 97.8
Implants - Yes - No	 6 86	 6.5 93.5
Type of implant - Invasive - Non invasive	 1 5	 16.7 83.8

Table 2: Details of the surgical procedures and adjuvant chemotherapy

Studied variables	Studied group	
	No.	**%**
Type of surgery: **Fertility sparing** - Unilateral ovarian cystectomy - Bilateral ovarian cystectomy - Unilateral salpingo-oophorectomy **Radical surgery**	 **49** 19 5 25 **43**	 **53.3%** 38.8% 10.2% 51.0% **76.7%**
Lymphadenectomy - Yes - No	 10 82	 10.9% 89.1%
Residuals, cyst rupture - Yes - No - Unknown	 5 83 4	 5.40% 90.2% 4.30%
Adjuvant chemotherapy Yes No	 2 90	 2.2% 97.8%

Follow up and outcome

Details of the recurrence and survival are given in Table 3.The median follow-up period for the whole group was 76 months (range, 12-157 months). Recurrence of the disease was observed in 17 patients (18.5%) during follow up period, while 75 patients (81.5%) were disease free at the last follow up. The Mean time to recurrence (disease free survival) among patients was 104.4 months. Out of 17 patients who were recurred, 6 cases recurred in the same ovary, 7 cases recurred in the opposite ovary, one case recurred in both ovaries and 3 cases recurred in the peritoneum or LNs. Twelve of the recurrences (70.6%) were borderline whereas 5 were invasive (29.4%).Thirteen patients (76.5%) underwent surgery for recurrence, 1 (5.9%) received systemic chemotherapy, 2 (11.7%) treated by both surgery and chemotherapy and 1 (5.9%) received Hyperthermic Intraperitoneal Chemotherapy (HIPEC) plus surgery. Follow-up of those 17 patients revealed that they were all alive at the last contact. By the end of the study only one case died; she had stage III disease.

Table 3: Details of Recurrence and survival among patients treated for Borderline Ovarian Tumors:

Studied variables	Studied group	
	No.	%
Recurrence		
- Yes	17	18.5
- No	75	81.5
Site of relapse	N=17	
- Ipsilateral ovary	6	35.3
- Contralateral ovary	7	41.2
- Both ovaries	1	5.9
- Peritoneal or nodal	3	17.6
Type of relapse	N=17	
Borderline	12	70.6
Invasive	5	29.4
Treatment of relapse	N=17	
- Surgery	13	76.5
- Systemic Chemotherapy	1	5.90
- Surgery and chemotherapy	2	11.7
- HIPEC	1	5.90
Survival		
Died	1	1.10
Survived	91	98.9

Factors affecting recurrence and disease free survival

With Kaplan-Meier analysis, the mean disease free survival (DFS) was significantly higher in patients older than 40 years (75.6 months) (range, 69.8 – 81.5) than younger patients (69.7 months) (range, 59.7 – 79.5). Stages IA and IB had significantly higher disease free survival than other stages 79.7months (range, 73.2 – 86.1) versus 55.0 months (range, 29.6 – 80.4). Patients with microinvasion had significantly shorter disease free survival 10.5 months (range, 9.52 – 11.5) versus 77.6 months (Table 4).

Table 4: Disease free survival of BOTs and its relation to different prognostic factors

Prognostic factors		Disease free survival	SE	Log rank	P value
		Mean (95% CI)			
Age / years	≤ 40 > 40	69.7 (59.7 – 79.5) 75.6 (69.8 – 81.5)	5.04 2.97	4.68	**0.031***
Menopause	Pre Post	97.8 (80.0 -115.6) 76.2 (69.7 – 82.6)	9.10 3.31	3.00	0.083
Parity	Nullipara Multipara	63.2 (46.7 – 79.8) 80.0 (73.2 – 86.9)	8.46 3.50	3.27	0.070
Laterality	Unilateral Bilateral	76.5 (65.4– 87.7) 65.9 (57.8– 73.9)	5.68 4.09	0.770	0.680

Tumor size	≤ 11 > 11	71.7 (61.3 – 82.1) 73.0 (66.3– 79.7)	5.31 3.40	2.36	0.124
CA125	≤ 35 >35	82.6 (74.9 – 90.4) 68.7 (59.3 – 78.2)	3.94 4.83	2.73	0.098
Stage	IA&IB Other stages	79.7(73.2 – 86.1) 55.0 (29.6 – 80.4)	3.29 12.9	6.47	**0.011***
Histology	Serous Mucinous Others	74.0(65.5 – 82.5) 72.6 (62.7 – 82.5) 67.1(52.7 – 81.5)	4.34 5.03 7.36	0.794	0.672
Lymphadenectomy	Yes No	70.1 (46.2 – 94.1) 77.6 (70.8 – 84.5)	12.2 3.48	0.743	0.389
Microinvasion	Yes No	10.5 (9.52 – 11.5) 77.6 (70.9 – 84.1)	0.50 3.35	30.1	**0.001***
Micropapillary	Yes No Not applicable	73.2(62.3 – 83.4) 79.4 (67.9 – 90.8) 71.7(62.4 – 81.8)	5.22 5.85 4.74	0.618	0.734
Surgical ttt	Fertility sparing Radical	68.5(58.2 – 78.8) 75.8 (70.2 – 81.4)	5.26 2.86	5.65	**0.017***
Adjuvant chemotherapy	Yes No	11.0 (9.61 – 12.4) 76.1 (70.1 – 83.4)	0.70 3.41	5.22	**0.022***

***Significant**

Radical surgery had significantly higher DFS than fertility sparing surgery [75.8 months (range, 70.2 – 81.4)] versus 68.5 months (range, 58.2 – 78.8). Patients who received adjuvant chemotherapy had shorter DFS [11.0 months (range, 9.61 – 12.4)] versus 76.1 months (range, 70. 1 – 83.4).

Multivariate analysis showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival (Table 5).

Table 5: Multivariate Cox regression analysis for detection of the independent risk factors for worse disease free survival among BOTs patients:

Variable	WALD	Hazard ratio	P value
Age	1.02	0.792	0.311
Stage	3.47	1.27	0.062
Surgical ttt	6.57	3.13	**0.010***
Adjuvant chemotherapy	3.66	2.05	0.056
Micro invasion	0.135	0.607	0.714

***significant**

Univariate analysis of prognostic factors for disease free survival among fertility sparing surgery group suggested that FIGO stage, presence of microinvasion and elevated preoperative serum CA125 more than 35 IU/ml were significant risk factors for worse DFS (Table 6). The

mean disease free survival in patients treated with fertility sparing surgery was significantly higher in patients with preoperative serum CA125 less than 35IU/ml than those with preoperative serum CA125 more than 35 IU/ml; (80.1 months, range, 69.3 – 90.9) versus 53.1 months (range, 36.6 – 69.4) . Stages IA and IB had significantly longer disease free survival than other stages (73.1 months, range,62.8 – 83.4) versus 36.7 months(range,3.55 – 69.9). Patients with microinvasion had significantly shorter disease free survival 10.5 months (range, 9.52 – 11.5) versus 69.7 months (range, 59.5 – 80.0).

Table (6): Factors affecting disease free survival among fertility sparing surgery group (univariate analysis)

Fertility sparing group		Disease-free survival	SE	Log rank	P value
		Mean (95%CI)			
Age	≤ 45 years > 45 years	67.7 (56.6 – 78.7) 60.8 (39.4 – 82.2)	5.62 10.9	0.124	0.725
Parity	Nullipara Multipara	58.4 (39.1 – 77.8) 73.1 (60.9 – 85.3)	9.87 6.23	1.43	0.231
Laterality	Unilateral Bilateral ≤	70.1 (53.9 – 86.4) 57.6 (37.6 – 77.5)	8.29 10.1	0.492	0.782
Tumor size	≤11 cm > 11 cm	67.7 (61.3 – 81.2) 63.5 (49.8 – 77.2)	6.87 6.98	0.322	0.570
CA-125	≤ 35 IU /ml > 35 IU / ml	80.1 (69.3 – 90.9) 53.1 (36.6 – 69.4)	5.49 8.32	5.81	0.016*
FIGO stage	IA & IB Other stages	73.1 (62.8 – 83.4) 36.7 (3.55 – 69.9)	5.25 16.9	6.89	0.009*
Histopathologic subtypes	Serous Mucinous Others	64.2 (50.8 – 77.5) 72.0 (59.3 – 84.6) 51.0 (28.9 – 73.1)	6.82 6.45 11.2	1.57	0.456
Lymphadenectomy	Yes No	64.3 (15.2 – 113.3) 69.6 (58.8 – 80.4)	25.0 5.15	0.603	0.438
Microinvasion	Yes No	10.0 (10 – 10) 69.7 (59.5 – 80.0)	0.00 5.23	14.6	0.001*
Micropapillary	Yes No Not applicable	57.8 (40.2 – 75.3) 77.2 (60.9 – 93.6) 69.1 (56.1 – 82.1)	8.34 9.34 6.63	2.49	0.287
Type of fertility sparing surgery	-unilateral ovarian cystectomy -Bilateral ovarian cystectomy - Unilateral salpingo-oophorectomy	66.7 (50.1 – 83.4) 57.6 (37.6 – 77.5) 65.5 (51.1 – 80.2)	8.50 10.1 7.43	1.96	0.907

*Significant

However, multivariate analysis showed that microinvasion is the only independent risk factor affecting DFS among fertility sparing surgery group (table 7). In addition, there was no statistically significant difference regarding the overall survival in relation to type of surgery (table 8).

Table (7): Multivariate Cox regression analysis for detection of the independent risk factors affecting DFS among fertility sparing surgery group.

Variable	WALD	Hazard ratio	P value
FIGO stage	1.85	0.915	0.173
CA 125	0.648	0.612	0.421
Microinvasion	4.96	2.82	0.026 *

Table (8): The overall survival in relation to type of surgery

Fertility sparing group		Disease-free survival Mean (95%CI)	SE	Log rank	P value
Type of surgery	Fertility sparing Radical	90.5 (87.8 – 93.2) 79.3 (76.0 – 82.5)	1.38 1.65	0.07	0.788

Discussion

Borderline ovarian tumors are known to have usually an indolent nature with uncertain behaviors. Due to their atypical properties they are classified as a separate entity in the subject of ovarian malignancies. However, there are some features of BOTs that need special consideration such as peritoneal implants invasive or non-invasive, micropapillary architecture in serous BOT or presence of micro-invasion [8]. Furthermore, there are still debates related to type of surgical management, staging and adjuvant therapy.

This study has retrospectively analyzed the oncological outcomes of 92 borderline ovarian tumor patients with different clinico-pathological factors and different types of surgeries. It is expected that this study can help young patients with borderline ovarian tumor to select an optimal treatment. Borderline ovarian tumors are common in young women of childbearing age in which fertility-sparing surgery has been preferred. While the oncologic outcomes of BOTs patients after fertility-sparing surgery become a heated topic of discussion, there is no international guideline on this issue to help clinicians select treatment and follow-up plans. The results of the present study contain two important messages. The first one concerns the oncological result of BOTs. The second important point concerns the risk factors for recurrence after fertility-sparing surgery.

Regarding our data in terms of survival and relapse in relation to FIGO stage, we found that stages IA and IB had significantly higher disease free survival than other stages [79.7 months (73.2 – 86.1)] versus 55.0 months (29.6 – 80.4) which is in line with results of Du Bois et al and Trillsch et al who found that FIGO stage and sub-classification of extra-ovarian disease into invasive and noninvasive implants appear to be the major predictor not only for recurrence but also for survival [9,26]. Seong et al stated that the 5-year survival for stage I borderline ovarian tumor patients was approximately 95% to 97%, while the 5-year survival for stage II-III patients was only 65% to 87% [10].

In our study, microinvasion was found in 2.2% of patients and there was significant association between microinvasion and recurrence. Also, patients with microinvasion had significantly lower disease free survival [10.5 months (9.52 – 11.5)] versus 77.6 months (70.9 – 84.1). Consistent with these findings, Buttin et al found that recurrence rates were significantly higher in women with microinvasion compared to the rate of recurrence in women without microinvasion (23% versus 3.5%) [11].This is against Hogg et al who reported that microinvasion does not increase the chances of recurrence or affect the survival [12]. This difference may be due to the relatively small number of patients

with microinvasion in our study which is recognized as a considerable limitation to apply the finding of our series regarding the negative impact of microinvasion on the prognosis of borderline ovarian tumor.

Our results showed no difference in the disease free survival between different histopathologic subtypes which is similar to the findings of Loizzi et al [13]. On the contrary, Karlsen et al found a negative correlation between the serous histology and the risk of tumor relapse [14]. Chen et al demonstrated a longer recurrence interval in patients with serous borderline ovarian tumors who underwent fertility sparing surgery than those with mucinous tumors (35.9 versus 18.5 months, $P < 0.001$) [15]. Others observed that mucinous subtype-mostly in association with invasive implants has been associated with a worse prognosis in comparison to serous BOTs [16].

Unfortunately, the impact of micropapillary pattern on serous borderline ovarian tumor patients remains a source of controversy at present. Micropapillary architecture that was seen in 42% of our patients, was not a significant risk factor for recurrence or worse disease free survival in our study. Matching with these results, Du Bois et al found that the micropapillary growth pattern was not evidently associated with poor prognosis of borderline ovarian tumor patients [17]. Although many authors described it as risk factor for relapse or death from the disease, Chen Xi et al analyzed 178 borderline ovarian tumors patients and showed that micropapillary pattern was significantly associated with better DFS (P=0.0008) [18]. Conversely, Smith et al and Shih et al have shown that micropapillary histology is more associated with advanced stages, invasive implants, higher recurrence rates and lower survival [19, 20]. In comparing the typical borderline pattern with the micropapillary pattern in seven published studies, Lu and Bell found that both the relapse rate and death due to tumor were significantly increased in the micropapillary type (32% versus 15% and 15% versus 8%, respectively). Since these micropapillary types more often have invasive implants, it is difficult to discern the isolated impact of the micropapillary feature on survival [21].

In the current study, peritoneal implants were seen in 6.5% of the study population, and this was not significantly associated with recurrence or worse disease free survival. Several other studies have shown that borderline ovarian tumors with invasive implants are associated with an increased risk of recurrence and often a more aggressive clinical course [22]. In a review published in 2002 by Seidman and Kurman involving 245 studies and 4,129 patients, the survival rate for patients with invasive implants was 66% after a mean follow-up period of 7.4 years, compared to 95% for patients with noninvasive implants [23].

Our study showed that the recurrence rate in patients underwent fertility sparing surgery was notably higher than that of patients received radical surgery (28.6% versus 7%, $P = 0.008$*). Trillsch et al. reported a recurrence rate of 10-20% in patients underwent fertility sparing surgery, which was markedly higher than that in those received radical surgeries (5%) [9].Multivariate analysis of our cases showed that fertility-sparing surgery was the only independent risk factor for worse disease free survival among patients of borderline ovarian tumor. Duration of disease-free survival were significantly shorter in cases managed by fertility sparing surgery than radical surgery [68.5 months (58.2 – 78.8)] versus 75.8 months (70.2 – 81.4). However, other studies reported that fertility sparing surgery is not regarded as a prognostic factor for recurrence [13].

In our series, a univariate analysis was performed to identify risk factors for worse disease free survival and subsequent recurrence in patients who underwent fertility sparing surgery (no=49). FIGO stage, elevated CA 125 > 35 IU/ml and presence of

microinvasion were significant risk factors. However, multivariate analysis confirmed only microinvasion as an independent risk factor for recurrent disease. Conversely, in the large series of Morice et al (2012), the risk of recurrence after conservative surgery was not related to microinvasion [8].

Fertility-preserving surgery can be performed in different types with different impacts on oncologic and pregnancy outcomes of BOT patients. In comparison to salpingo-oophorectomy, cystectomy retains more normal ovarian tissue and increases pregnancy success rate. On the other hand, cystectomy carries a significantly higher risk of recurrence [9]. In terms of different forms of fertility sparing surgery, our results showed that disease-free survival did not differ significantly between unilateral ovarian cystectomy compared to salpingo-oophorectomy (66.7months (50.1 – 83.4) versus 65.5 months (51.1 – 80.2).

Whether conservative surgery is appropriate for borderline ovarian tumors is an important matter to be resolved. In our study, the recurrence rate after conservative surgery was high (28.6%, nearly one-third of patients), but fortunately the great majority of the recurrent tumors were borderline lesions with no impact on outcome nor survival and only two patients had invasive recurrence. Moreover, the two patients were successfully treated with second round radical surgery and were alive and disease free by the end of the study. Likewise, a recent review of literature concerning the risk of recurrent invasive BOT among1500-1800 conservative surgical procedures, only 10 cases were reported [8]. Similarly, Zanetta et al reported a recurrence rate of 17% (28/164) in 164 patients treated with fertility sparing surgery for stage I borderline ovarian tumor, with 23 patients had borderline recurrence and 5 patients had invasive disease. Our results, therefore, do not challenge the use of conservative surgery as the standard of care in young patients with BOTs. Nevertheless, they indicate that the risk of an invasive recurrence exists and, hence, the risk of death. A careful and prolonged follow-up is, therefore, mandatory and patients should be informed of this rare risk.

Concomitantly, the overall survival in our study was statistically non-significant when compared between patients who underwent fertility sparing surgery and those who received radical surgery. The only one patient who died had FIGO stage III with invasive implants. Analogous to these findings, Donnez et al reported that although recurrence was more common in cases treated by conservative surgery (3 out of 16, 18.7%) than by radical surgery (0 out of 59, 0%), subsequent treatment resulted in no tumor-related deaths [25].

The present study is retrospective with a relatively small number of patients that represents a major limitation to apply the findings reported here. Additionally, the reproductive outcomes of BOT patients after fertility sparing surgery were not available. Moreover, Only 2 borderline ovarian tumor cases had microinvasion which is recognized as another considerable limitation. Consequently, studies including a large cohort size and a long-term follow-up period are needed to evaluate the correlation between microinvasion and prognosis of borderline ovarian tumors after fertility sparing surgery.

Conclusion

In conclusion, although recurrence was detected in 17 out of 92 cases with borderline ovarian tumor, no tumor-related deaths were found, and patients had a favorable long-term prognosis. Recurrences are amenable to treatment with completion surgery.

Fertility-sparing surgery is an acceptable and appropriate option for patients with BOTs who wish to preserve fertility. The higher risk of local relapse is not associated with decreased overall survival. When

considering conservative surgery in patients with borderline ovarian tumor, special care should be given to elevated CA-125, advanced FIGO stage or microinvasion. To reinforce the present study results, we expect that a large scaled prospective clinical study involving many institutions will be performed to obtain more evidence.

Author contributions

NIE, MEE, and MZS contributed to study design. NIE, MZS, ASH, NMH, and AA performed data collection; all authors contributed to analyses, interpretation of data, manuscript preparation and revising it critically.

Acknowledgement

None

Conflict of interest

None

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Correlation of Urinary Protein Creatinine Ratio Versus Urinary Tract Infection in Assessment of Severity of Pre-Eclampsia

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Abstract

Background: Preeclampsia is a pregnancy specific syndrome that can affect every system in the body. Preeclampsia can be categorized into severe" and "non-severe." According to the blood pressure measurement and presence of proteinuria. Urinary tract infections are the most common medical complication of pregnancy with an estimated incidence of approximately 20%. UTIs in pregnancy have been associated with increased risks of chorioamnionitis and endometritis. About the fetus, it has been shown that UTI is associated with fetal growth restriction, stillbirth, preterm labor, and delivery, increased perinatal mortality, mental retardation, and developmental delay.

Methods: This was a prospective cross-sectional study conducted on 50 patients whom were diagnosed with preeclampsia and were admitted to El Shatby university hospital. Based on Urinary tract infection, two groups were enrolled; Group A (25 cases) included preeclamptic patients without urinary tract infection and Group B (25 cases) included preeclamptic patients with urinary tract infection.

Results: Urine culture and Bacterial identification were performed in preeclamptic patients with UTI (group B=25). E. coli was responsible for 68 % of the cases, Klebsiella was found in 12 % of the cases, Pseudomonas was found in 12 % of the cases, Methicillin-resistant Staphylococcus aureus (MRSA) was found in 4 % of the cases and Methicillin-resistant coagulase-negative staphylococci (MR-CONS) was found in 4 % of the cases. Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A ($r = 0.064$, $P = 0.763$) while there was positive significant correlation between them in group B ($r = 0.501$, $P = 0.011$) and the total sample ($r = 0.734$, $P < 0.001$)

Conclusion: Protein creatinine ratio positively correlates with the severity of preeclampsia. Urinary tract infection

(UTI) during gestation is associated with increased severity of preeclampsia. Escherichia coli was found to be the most prevalent organism isolated in preeclamptic patients with UTI.

Keywords: Preeclampsia, Proteinuria, Urinary tract infections, urinary protein creatinine ratio, asymptomatic bacteriuria, pyelonephritis.

Introduction

Preeclampsia is a pregnancy specific syndrome that can affect every organ system in the body. It is diagnosed by high blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic and proteinuria.[1]

Proteinuria is one of the diagnostic criteria of the preeclampsia syndrome and it reflects the endothelial leakage. Proteinuria is described by 24-hour urinary excretion exceeding 300 mg; a urine protein: creatinine ratio ≥ 0.3; or persistent 30 mg/dL (1+ dipstick) protein in random urine samples. [2] Overt proteinuria may not present in some preeclamptic pregnant women so another diagnostic criteria were added like thrombocytopenia, renal or liver dysfunction, cerebral symptoms, or pulmonary edema. [3,4]

Preeclampsia can be categorized into "severe" and "non-severe." According to the blood pressure measurement, presence of proteinuria, symptoms like headache, visual disturbances, upper abdominal pain or epigastric pain, signs like decreased urine output, seizures, elevated serum creatinine level, elevated liver transaminases, thrombocytopenia, pulmonary oedema and fetal growth restriction. [5]

It affects Young females more than older females, but the older women are at high risk for chronic hypertension with superimposed preeclampsia. It affects nulliparous women more than multiparous women. There are several other risk factors associated with preeclampsia. These include obesity, multifetal gestation, maternal age, hyperhomocysteinemia, and metabolic syndrome. [6-8] Preeclampsia is more common in the first pregnancy and the risk of having preeclampsia in next pregnancy is much lower. [9]

The exact cause is unknown abut there are many mechanisms are described to explain preeclampsia; Abnormal trophoblastic invasion of maternal spiral vessels, production of blocking antibodies to different placental antigenic sites, Maternal maladaptation to inflammatory changes of normal pregnancy, Genetic factors including inherited predisposing genes and epigenetic influences, Endothelial dysfunction and vasospasm because of imbalance of prostaglandins production and increased sensitivity to angiotensin II. [10]

Normally renal blood flow and glomerular filtration rate are increased during pregnancy but with preeclampsia renal perfusion and glomerular filtration are reduced due to increased renal afferent arteriolar resistance. [11,12]

There are also morphological changes characterized by glomerular endotheliosis blocking the filtration barrier. Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals, that is, 1 mg/mL, and sometimes even higher. [13] Abnormal values usually begin to normalize 10 days or later after delivery. [14] In most preeclamptic women, urine sodium concentration is elevated. Urine osmolality, urine: plasma creatinine ratio, and fractional excretion of sodium also indicate that a prerenal mechanism is involved. Also, Plasma uric acid concentration is elevated in preeclampsia because the elevation exceeds the reduction in glomerular filtration rate, enhanced tubular reabsorption and increased placental urate production in response to increased oxidative stress. [15]

Oliguria is a sign of severity in preeclampsia, but intensive intravenous fluid therapy is not indicated as a treatment unless decreased

urine output is due to hemorrhage or fluid loss. Proteinuria is one of the diagnostic criteria of preeclampsia syndrome. Proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. [16] For a 24-hour quantitative specimen, the threshold value used is > 300 mg/24 hr. Determination of urinary protein: creatinine ratio may replace the 24-hour quantification. [17-19]

Urinary tract infections are the most common medical complication of pregnancy with an estimated incidence of approximately 20%. [20] Urinary tract infection ranges from asymptomatic bacteriuria to severe pyelonephritis. There are different classifications for UTI, and these can be divided into lower UTI which is infection involving the urethra and bladder, or upper UTI, mainly involving the kidneys. [21]

The most significant factor predisposing women to UTI in pregnancy is asymptomatic bacteriuria and due to the high rate and potential seriousness of pyelonephritis, it is recommended that all pregnant women be screened for ASB at the first prenatal visit. Asymptomatic bacteriuria is seen more frequently in parous women and women of low socioeconomic status. [22]

The increased susceptibility in pregnancy is due to several physiological changes that make asymptomatic bacteriuria progress to symptomatic UTI. These include changes in bladder volume, decreased bladder tone and ureteric dilatation secondary to an increased level of progesterone. This will lead to urinary stasis and chronic residual urine with subsequent UTI. Uropathogens responsible for UTI in pregnancy are like those in non-pregnant women, with E. coli responsible for over 80 percent of the cases. [23]

UTIs in pregnancy have been associated with increased risks of chorioamnionitis and endometritis. About the fetus, it has been shown that UTI is associated with fetal growth restriction, stillbirth, preterm labor, and delivery, increased perinatal mortality, mental retardation, and developmental delay. [24] Christensen et al hypothesized that UTI played a role in preeclampsia by serving to enhance maternal systemic inflammatory response. UTI can potentially lead to activation of systemic inflammatory response and endothelial injury; this in turn can lead to placental hypoxia and uteroplacental atherosis, and eventual development of preeclampsia. [25]

The aim of this study was to correlate between urinary protein creatinine ratio and urinary tract infection in assessment of severity of preeclampsia.

Methods

This was a prospective cross-sectional study conducted on 50 patients whom were diagnosed with preeclampsia and were admitted to El Shatby university hospital during the period of case recruitment, from March 2020 to January 2021. Sample size was calculated using AUC (Area under the ROC Curve) power Analysis in Medcalc program that achieve 80% power with a significance level 0.05 by the Department of Community Medicine and Biostatistics at Alexandria University. The study was approved by the ethical committee of Faculty of Medicine, Alexandria University.

Based on Urinary tract infection, two groups were enrolled; Group A (25 cases) included preeclamptic patients without urinary tract infection and Group B (25 cases) included preeclamptic patients with urinary tract infection. Inclusion criteria were: Pregnant female in the third trimester, Hypertension plus proteinuria (Proteinuria >300 mg/24 hours or Protein: creatinine ratio ≥ 0.3 or Dipstick > 1+ persistent proteinuria), and Pregnant pre-eclamptic females with signs and symptoms of urinary tract infection. Exclusion criteria were: Known chronic kidney disease patients, Known nephrotic syndrome patients or Known Lupus nephritis patients.

Informed consent was obtained from each woman involved in the study. All cases were subjected to: Complete history taking (Age, obstetrical history in terms of gravidity, parity , previous abortion, mode of delivery and gestational age in weeks), Complete general examination, Regular two-hourly blood pressure monitoring, Ultrasonographic examination for assessment of fetal wellbeing (mean gestational age, estimated fetal weight, amniotic fluid index and doppler indices using Mindray DC 30 machine), Full laboratory investigations including complete blood picture, coagulation profile, liver functions tests, kidney functions tests and proteinuria via Urinary protein: Creatinine ratio.

A clean catch midstream urine sample was collected for each case and immediately delivered to the microbiology lab of Alexandria main university hospital. A wet film was performed to detect pyuria and bacteriuria and urine culture was done. Bacterial identification using the standard microbiological techniques and antimicrobial susceptibility using disk diffusion method were done. The two groups were compared as regard to the severity symptoms and signs of PET [26]:

Abnormality	Non severe	Severe
1.Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
2.Systolic BP	< 160 mm Hg	≥ 160 mm Hg
3.Proteinuria	None to positive	None to positive
4.Headache	Absent	Present
5.Visual disturbances	Absent	Present
6.Oliguria	Absent	Present
7.Convulsion (eclampsia)	Absent	Present
8.Upper abdominal pain	Absent	Present
9.Serum creatinine	Normal	Elevated
10.Thrombocytopenia (< 100,000/μL)	Absent	Present
11.Serum transaminase elevation	Minimal	Marked
12.Fetal-growth restriction	Absent	Obvious
13.Pulmonary edema	Absent	Present

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) (27, 28) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Results

This study was carried out at Shatby university hospital for 10 months on 50 patients who were pregnant at third trimester with confirmed preeclampsia. The patients were categorized into 2 groups according to the presence of Urinary tract infection: **Group (A):** 25 preeclamptic patients without urinary tract infection, and **Group (B):** 25 preeclamptic patients with urinary tract infection. There were no statistically significant differences between the two groups as regard age, Obstetrical History (Gravidity, Parity, Previous Abortions, mode of delivery and patients' gestational age in weeks)

I) Blood pressure and urinary parameters

Systolic blood pressure in group (A) ranged between 150 – 180 while in group (B) ranged between 160 – 180. Diastolic blood pressure In group (A) ranged between 100 – 120 while in group (B) ranged between 100 – 130. There were statistically significant differences between groups as regards Systolic blood pressure only (P=0.019). **Table 1**

In addition to the blood pressure criteria, a protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher is required to diagnose preeclampsia. In group (A) it ranged between 0.34 – 5.7 while in group (B) ranged between 3.7 – 16.6. Group (B) was found to have elevated protein creatinine ratio in a statistically significant difference (P<0.001). **Table 1**

Table (1): Comparison between the two studied groups according to blood pressure and Protein creatinine ratio

Blood pressure	Group A (n=25)	Group B (n=25)	p
Systolic			
Min. – Max.	150.0 – 180.0	160.0 – 180.0	0.019*
Mean ± SD.	163.6 ± 9.95	170.0 ± 8.66	
Median (IQR)	160.0(160.0 – 170.0)	170.0(160.0 – 180.0)	
Diastolic			
Min. – Max.	100.0 – 120.0	100.0 – 130.0	0.259
Mean ± SD.	108.0 ± 6.45	110.4 ± 7.35	
Median (IQR)	110.0(100.0 – 110.0)	110.0(110.0 – 110.0)	
Protein creatinine ratio			
Min. – Max.	0.34 – 5.70	3.70 – 16.60	<0.001*
Median (IQR)	2.30(1.7 – 3.1)	7.88(6.0 – 9.4)	

Urine culture and Bacterial identification were performed in preeclamptic patients with UTI (group B=25). E. coli was responsible for 68 % of the cases, Klebsiella was found in 12 % of the cases, Pseudomonas was found in 12 % of the cases, Methicillin-resistant Staphylococcus aureus (MRSA) was found in 4 % of the cases and Methicillin-resistant coagulase-negative staphylococci (MR-CONS) was found in 4 % of the cases.

Preeclamptic patients with UTI caused by E–coli showed highest sensitivity to imipenem and meropenem (100%) followed by piperacillin tazobactam and gentamycin (88.2%) then ampicillin sulbactam (82.4%) then nitrofurantoin, ciprofloxacin and cefotaxime (76.5%), while 41.2% of cases were resistant to amoxicillin clavulanate. As for Klebsiella strains, (33.3%) were sensitive to imipenem, meropenem, ampicillin-sulbactam, cefotaxime and ceftriaxone while all strains were resistant to amoxicillin clavulanate, piperacillin tazobactam and aminoglycosides. Pseudomonas strains showed highest sensitivity to imipenem, aminoglycosides and quinolones (100%). Both strains of MRSA and MR-CONS were sensitive to linezolid and vancomycin.

II) Signs of severity of preeclampsia

Signs of severity were assessed in all patients in both groups A and B. Cases in group A showed from 2 to 8 sign of severity while in group B showed from 6 to 12 sign of severity. There were statistically significant differences between the 2 groups where P <0. 001.Also in Group A only 6 cases (24%) had more than 5 signs of severity but in Group B the 25 cases (100%) had more than 5 signs of severity. There were statistically significant differences between the 2 groups where P <0.001which indicates that signs of severity present more with preeclamptic patients with UTI. **Table 2**

Table (2): Comparison between the two studied groups according to signs of severity

	Group A (n=25)		Group B (n=25)		P
	No.	%	No.	%	
indicators of severity					
>5	6	24.0	25	100.0	<0.001*
≤5	19	76.0	0	0.0	
Total no. of indicators of severity					
Min. – Max.	2.0 – 8.0		6.0 – 12.0		<0.001*
Mean ± SD.	4.76 ± 1.59		8.64 ± 1.85		
Median (IQR)	5.0 (4.0–5.0)		8.0 (7.0–10.0)		

Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A (r = 0.064, P = 0.763) while there was positive significant correlation between them in group B (r = 0.501, P = 0.011) and the total sample (r = 0.734, P <0.001) which means that protein creatinine ratio increases with increase signs of severity. Table 3

Table (3): Correlation between total no. of indicators of severity with protein creatinine ratio and in each group and total sample

Protein creatinine ratio	Total No. of indicators of severity	
	R	**P**
Group A (n=25)	0.064	0.763
Group B (n=25)	0.501*	0.011*
Total (n=50)	0.734*	<0.001*

Discussion

Preeclampsia is a major cause of maternal morbidity, although its precise etiology remains elusive. A variety of risk factors have been associated with increased probability of preeclampsia like nulliparity and maternal age above 35 years. [29] Several studies suggest that urinary tract infection (UTI) during gestation is associated with elevated risk for preeclampsia, while others have failed to prove such an association.[30]

This study correlated protein creatinine ratio and urinary tract infection to the severity of preeclampsia. Features of severity of preeclampsia have been compared between two groups. It was found that all the cases (100%) in group B had more than 5 signs of severity but in Group A only 6 cases (24%) had more than 5 signs of severity. There were statistically significant differences between the 2 groups which indicates that signs of severity present more with preeclamptic patients with UTI. In 2008 in Soroka University Medical Center, Anatte Karmon and Eyal Sheiner performed a retrospective study on pregnant women between years 1988 and 2006 who were exposed to at least one UTI episode during gestation were 1.3 times more likely to have mild preeclampsia and 1.8 times more likely to have severe preeclampsia as compared to unexposed women. [30] Such results coincide with Izadi et al data who concluded that UTI is a risk factor for developing severe preeclampsia. [31]

In our study, Escherichia coli species was the most prevalent organism isolated in 68% of cases followed by Klebsiella in 12% and pseudomonas in 12 %. Also, Preeclamptic

patients with UTI in group B showed highest sensitivity to imipenem (84 %) followed by meropenem (80 %) then ciprofloxacin and gentamycin (72 %). Kaduma J et al conducted a 1:2 matched case-control study on pregnant women with preeclampsia (cases) and without preeclampsia (control). Pregnant women with preeclampsia had 7.7 odds of having significant bacteriuria than those without preeclampsia [OR=7.7, 95% CI (4.11-14.49); p-value <0.001]. Escherichia coli (45.5%), and Klebsiella spp. (23.6%) predominated, and resistance to gentamicin, ceftriaxone, and piperacillin-tazobactam ranged from 9.0% to 29.0% in these dominant species. [32]

Proteinuria has been assessed in all the cases of both groups using protein creatinine ratio. Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A (r = 0.064, P = 0.763) while there was positive significant correlation between them in group B (r = 0.501, P = 0.011) and the total sample (r = 0.734, P <0.001) which means that protein creatinine ratio increases with increase signs of severity.

A meta-analysis was performed by Yan et al aimed to examine the relationship between UTI during pregnancy and preeclampsia. It was found that the ratio of UTI to non-UTI in Preeclampsia is 1.31 times than that of non-Preeclampsia which indicates that UTI during pregnancy may be a risk factor for development of Preeclampsia.[33]

It is hypothesized that UTI played a role in preeclampsia by serving to enhance maternal systemic inflammatory response. One mechanism by which UTI could hypothetically cause preeclampsia might be related to arterial damage triggered by infection, resulting in relative uteroplacental ischemia.[34,35]

In a study by LaMarca et al, inflammatory responses in preeclamptic pregnancies were found to be excessive as compared to that in normal pregnancies. UTI which is one of the most common maternal infections, can potentially lead to activation of systemic inflammatory response and endothelial injury; this in turn can lead to placental hypoxia and uteroplacental atherosis, and eventual development of Preeclampsia.[36]

Conclusion

In addition to revealing a statistically significant increased values in preeclamptic patients with UTI, Protein creatinine ratio positively correlates with the severity of preeclampsia. Urinary tract infection (UTI) during gestation is associated with increased severity of preeclampsia. Escherichia coli was found to be the most prevalent organism isolated in preeclamptic patients with UTI.

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Combined letrozole with clomiphene citrate versus letrozole only in induction of ovulation in polycystic ovary syndrome patients (A Randomized controlled trial)

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Abstract

Objective: to compare adding clomiphene citrate to letrozole in comparison with letrozole only Patients and method : A total of 64 infertile woman with PCOS were assessed in this randomized controlled trial in Department of Obstetrics and Gynecology at Imbaba General hospital and Banha university hospital .

Results: The serum pregnancy test was positive in only (6,3%) group A who receive letrazole alone while shows (12.5%) in group B who took combined therapy with no significance in P value(0.39) so group B shows higher pregnancy rates, The six weeks pulsations shows higher percentages in group B (9.4%) in compare to Group A (3.1%) with P value of (0.3) , There is good significance in the number of follicles (with P value 0.006) with appearance of one follicle in group B was higher than group A (68.8% in group B versus 37.5% in group A) ,Also the appearance of 2 mature follicles happen only in group B (6.3%). the follicular size appeared significance with P value (<0.001) as group B ranges (20.21+_1.47) versus group A (17.17+-0.94), Endometrial thickness also show significance with P value (<0.001) with ranges (10.06+_1.6) in group B which has better ranges than group A (8.13+_1.79).

Conclusion: combined letrazole plus CC and letrazole alone seem to be two effective approaches, with letrazole plus CC showed better ovulation results and hence better pregnancy rate outcome.

Keywords: PCOS, clomiphene citrate, letrozole, Insulin resistance.

Introduction

Over the last decade, abnormal placentation (accreta, iInfertility is a worldwide problem (1). Female and male factors is about forty percent each. The commonest cause for women is ovulatory failure (twenty five percent), then tubal blockage (twenty percent) (2).Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder, affecting about 6–10% women of reproductive age

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worldwide. infertility in PCOS mostly due to insulin resistance and hyperandrogenemia at the center stage in the pathogenesis, PCOS is responsible for 80% of an ovulatory infertility in women.(3) the existence of low-grade inflammation (LGI) and the contribution of oxidative stress (OS) to be included in PCOS disorder.(4) The pathogenesis of PCOS can be observed by the biomarkers such as nitric oxide (NO), Malonaldehyde (MDA), and the anti-oxidative biomarkers, primarily the total antioxidant capacity (TAC), glutathione peroxidase (GPx), superoxide dismutase (SOD), and glutathione stimulating hormone (GSH).(5)

The basic method of managing PCOS is depend on modifications of lifestyle which consist of an appropriate and healthy diet with regular exercises, weight loss for obese patients, and behavioral changes as quitting smoking and drinking alcohol.(6)

One of the main component of PCOS treatment in women with obesity is weight loss. (7)

CC has considered the standard drug for ovulation induction in PCOS patients (8) Letrozole has been proposed for the treatment of CC resistant PCOS patients.(9) To compare between clomiphene citrate and letrazole, the half-life of Letrozole is about 45 hours which is less than Clomiphene citrate, so the Letrozol give a good situation for ovulation in compare with Clomiphene citrate.(10)

Patients and methods

A total of 64 infertile woman with PCOS were assessed in this prospective study in Department of Obstetrics and Gynecology at Imbaba General Hospital.

1.Inclusion criteria:

Age 18-35 with PCOs &infertility , infertility diagnosis known as couple can't achieve pregnancy after twelve months of regular timed unprotected intercourse in women aged less than 35 or after six months in women aged more than 35, PCOS based on the Rotterdam ESHERE/ASRM-Sponsored consensus with having of at least two of the three criteria (Teede et al.,2018).:(Oligo-ovulation and or anovulation which known as presence of secondary amenorrhea or less than eight menstrual periods per year, clinical Hyperandrogenism. And Poly cystic ovarian morphology with follicular number per ovary equal or more than 20 (follicle measure 2-9mm) and /or ovarian volume >10mml on either ovary.) And Normal concentration of sperm of fifteen million/mL with normal motility of more than forty percent.

2.Exclusion criteria :

Present using hormonal contraception-pregnancy-known other infertility causes-Hyperprolactinemia-Thyroid disease, uncontrolled medical diseases or diseases not recommended with pregnancy as hypertension, diabetes mellitus type 1 or type 2- endometrial cancer or hyperplasia-Allergy to letrozole or CC-any contraindications to letrozole or CC and finally Clinical suspicion of any other reasons similar to PCOS necessitate extra evaluation

Procedure:

History: Age, Menstrual history: age of menarche, menstrual disorders (oligomenorrhea), duration of amenorrhea , History of Infertility: history of previous pregnancy, duration of infertility.

General examination: As BMI, blood pressure, acne, no neck masses (thyroid), no galactorhea, abdominal obesity, excess hair distribution (hirsutism) (clinical signs of hyperanderogenism)

Local examination: Normal external female genitalia, no clitromegaly, no vaginal or cervical lesions, bimanual examination.

Ultrasound examination: (transvaginal ultrasound)

To confirm PCOS diagnosis criteria based on Rotterdam ESHRE/ASRM Criteria (follicular number per ovary equal or more

than 20 (follicle measure 2-9mm) and /or ovarian volume >10mml on either ovary) and to exclude any ovarian masses

Basal hormonal assays:

It will be performed on day two of menstrual cycle in women with oligomenorrhea and at any time in woman with amenorrhea including the measurement of: Luteinizing hormone (LH)-Follicular-stimulating hormone (FSH) - and Estradiol (E2).

In group A (nu=32)

Letrazole will be started from the third day to the seventh day of the cycle with a dose of 2.5 mg daily

In group B (nu=32)

Letrazole and clomiphene citrate will be started from the third day to the seventh day of the cycle with a dose of 2.5 mg letrazole daily and 50 mg clomiphene citrate daily

Primary outcome:

- The Size and the number of developing follicles on cycle day twelve -fourteen by ultrasound.
- Endometrium thickness on cycle day twelve to fourteen by ultrasound
- Ovulation in day twenty one of the cycle by measuring Mid-luteal progesterone level >3ng/dl

Secondary outcome:

- Pregnancy rate chemical (by serum pregnancy test) and clinical (sac by ultrasound at 6 week gestation).

Statistical Analysis:

Data were coded and entered using the statistical package SPSS version 22.data will be expressed as frequency and percentage. Chi2 test and Fisher Exact tests used when comparing the incidence of studied parameters. Numerical data will be summarized as mean and standard deviation and compared using independent t test. P value less than or equal 0.05 is considered significant (Chan., 2003).

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Table (1): age, BMI, Type of infertility and Marriage years of studied groups

	Group A	**Group B**	**P value**
Age	25.03±2.8	24.81±3.64	0.7

	Group A	**Group B**	**P value**
BMI	28.91±2.33	28.42±2.3	0.4

infertility		group A	Group B	P value
1ry	Count	24	31	0.013
	%	75.00%	96.90%	
2ry	Count	8	1	
	%	25.00%	3.10%	

	Group A	**Group B**	**P value**
marriage yrs.	1.7±0.98	1.28±0.37	0.14

Table (2): FSH, LH, and E2 D2 of studied groups

	Group A	**Group B**	**P value**
FSH D2	8.03±2.34	8.01±2.07	0.96

	Group A	Group B	P value
LH D2	10.6±3.13	10.39±3.2	0.79

	Group A	Group B	P value
E2 D2	61.53±16.05	72.22±20.96	0.025

Table (3): Results of studied groups

		Group A	Group B	P value
0	Count	20	8	0.006
	%	62.50%	25.00%	
1	Count	12	22	
	%	37.50%	68.80%	
2	Count	0	2	
	%	0.00%	6.30%	

	Group A N=12	Group B N=24	P value
Follicle size at day 12-14	17.17±0.94	20.21±1.47	<0.001

	Group A	Group B	P value
Endometrium Thickness at day 12-14	8.13±1.79	10.06±1.61	<0.001

	Group A	Group B	P value
Progesterone D21 after induction	19.77±3.28	20.62±4.84	0.4

Serum pregnancy test		Group A	Group B	P value
Negative	Count	30	28	0.39
	%	93.80%	87.50%	
Positive	Count	2	4	
	%	6.30%	12.50%	

Clinical pregnancy		Group A	Group B	P value
Negative	Count	31	29	0.3
	%	96.90%	90.60%	
Positive	Count	1	3	
	%	3.10%	9.40%	

Discussion

From these considerations and controversies, we had studied combined letrazole- CC and letrazole alone in Infertile Women with PCOS. Throughout the study, no changes in food intake or physical activity were performed. According to our protocol, the patients were given instruction to follow their habitual diet and physical activity to avoid any effect of these co-intervention confounders that might have bias effect on the study results.

This randomized controlled study included 64 young infertile women with PCOS to compare the hormonal-metabolic profile FSH,LH,E2, and outcomes between women receiving combined letrazole and cc versus letrazole alone in induction of ovulation

There were no significant differences between the two groups in terms of age- BMI-marriage years before starting the treatment.

The serum pregnancy test was positive in only (6,3%) group A who receive letrazole alone while shows (12.5%) in group B who took combined therapy with no significance in P value(0.39) so group B shows higher pregnancy rates which is similar in a study by (11) documented that Letrozole was found to be associated with a higher probability of clinical pregnancy compared to CC .And also similar in (11)as its study showed the clinical pregnancy and ongoing pregnancy rates of the Letrazole group were significantly higher than in the CC group.

The six weeks pulsations shows higher percentages in group B (9.4%) in compare to Group A (3.1%) with P value of (0.3) which is similar in a study done by (13) showed highly significant number of pregnancies as evidenced by positive pregnancy test results and intrauterine gestational sacs in letrozole group versus gonadotropin group with also statistically significant in pregnancy rate per cycle.

The level of progesterone has no significance (P value =0.4) with ranges (19.77+_ 3.28) in group A and ranges (20.62 +-4.84) in group B. also (14) shows the same results.

There is good significance in the number of follicles (with P value 0.006) as the results shows the appearance of one follicle in group B was higher than group A (68.8% in group B versus 37.5% in group A) ,Also the appearance of 2 mature follicles happen only in group B (6.3%) which is similar in(15) which showed that the ovulation rate in the combined letrazole and CC was slightly higher than the CC only with no statistically significance .and also in (16)which proved that Letrozole was reported to be significantly better for induction of ovulation in females who were resistant to the CC. but the results of (12) show different results as the successful ovulation rate was the same between the Letrozole group and CC group .

Study by (17) reported that the total number of follicles during stimulation in long time letrazole was significantly greater than short time letrozole.

Our study showed that the follicular size appeared significance with P value (<0.001) as group B ranges (20.21+_1.47) versus group A (17.17+-0.94) which was different as in the study by (15) Which showed that the median number of women with follicle more than 14 mm and the median largest follicle size in the combined letrazole and CC versus CC group were comparable. Also in study by (19) resulted that there were significant differences between the letrozol group compared to the letrozol plus electro acupuncture group on the endometrial thickness and on the number of follicles on days six, eight, ten, and twelve in infertile women with PCOS.

Endometrial thickness also show significance with P value (<0.001) with ranges (10.06+_1.6) in group B which has better ranges than group A (8.13+_1.79) which is similar in (15) which measured the mean measurement of endometrial thickness was 6.85 mm in the combined letrazole and CC

group, and 7.40 mm in the CC group, and the same results in (16) which proved higher Endometrial thickness value was noted in letrozol group than to Clomiphene Citrate group.

Conclusion and Recommendations

1.The current RCT showed that combined letrazole plus CC and letrazole alone seem to be two effective approaches to the treatment of patients with PCOS. In view of the effectiveness for a higher pregnancy rate, letrazole plus CC showed better ovulation results and hence better pregnancy rate outcome. Even if, a wider trials to detect statistically significant differences between the 2 different strategies are recommended.

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Pregnancy rate after trans-vaginal aspiration of ovarian endometrioma in infertile patients

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Abstract

Objectives: study the effect of simple trans-vaginal aspiration of chocolate cyst on pregnancy rate among the infertile patients diagnosed with ovarian endometrioma less than 6 cm.

Study design: controlled clinical trial.

Subjects and methods: 100 cases recruited for the trial and divided into two groups

Group one: the intervention group 50 cases diagnosed with ovarian endometrioma undergone chocolate cyst aspiration in zinat alhayat hospital after consultation and written consent.

Group two: 50 controls comprises the nonintervention group and cyst left without aspiration

All cases and controls done AMH, antral follicle count, stromal flow resistive index and CA 125 at the first month, Cases and controls followed in a period of 3 month the first month passed without induction

Second and third months ovulation was induced in both groups with HMG meriofert 75 unit at day 3,5and 7 then follicular growth monitored and ovulation triggered by HCG, pregnancy diagnosed with quantitative HCG and followed to the clinical pregnancy rate with viable fetal pulsations at 6 weeks.

Outcome measures: CA 125 antral follicle count stromal flow resistive index, deep dyspareunia and clinical pregnancy rate.

Results: regarding antral follicle count a good count of 12 found in the intervention group in 35 out of 50 compared to 20 out of 50 in the control group with p value 0.002, regarding significant stromal flow resistive index of 0.5 there were 40 out of 50 in cases and 25 out of 50 in controls with p value of 0.001,a statically significant difference with p value of 0.001 was found retrograding deep dyspareunia ,and clinical pregnancy observed in 30 cases out of 50 compared to 15 out of 50 in controls with p value of 0.002.

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Conclusion: simple trans-vaginal aspiration of ovarian chocolate cyst can improve ovarian response and increase clinical pregnancy rate better than conservative management

Keywords: infertility, chocolate cyst, simple trans-vaginal aspiration, pregnancy rate.

Introduction

Endometriosis affects 20% to 40% of women consulting for fertility disorders. (1)

Endometriosis can affect about 30 percent of infertile females and can be subtle which skipped diagnosis by the classical tools ,cases of endometriosis in infertile patients affect ovary commonly ,it can be a surface lesion in the form of powder burn or ectopic endometrial cells can implant themselves in the ovarian cortex creating a chocolate cyst .(2,3)

Chocolate cyst is a common condition in infertile females and ovary is a primary site for endometriotic implantation due to trans-tubal regurgitation of menstrual blood containing ectopic endometrium into the substance of the ovary.

Ovarian endometrioses can affect ovulation by impairing ovulation and by affection of the oocyte quality alongside the accompanying pressure; also these effects with pressure and intense inflammation induce a variable degrees of pain.(4)

Advances in the management of endometriosis include three- dimensional volumetric analysis and also a laparoscopic and robotic interventions but still endometriosis is a major problem due to advanced age at marriage and delaying fertility.(5,6)

Endometriosis surgery especially invasive can affect ovarian reserve and antral follicle count so efforts made to find alternatives for the invasive surgery one of them is trans-vaginal aspiration.

Intra-cytoplasmic sperm injection especially with the long protocol improves also pregnancy rate in patients with endometriosis but due to the cost and the psychological burden many cases prefer delaying IVF for these reasons. (7, 8)

Conventional endometriosis laparoscopic surgery with cystectomy may decrease the ovarian reserve by the excision of the ovarian cortex. (10)

Many surgical interventions done to reduce pelvic pain in endometriosis and improve fertility rate specially the minimally invasive approach gained special concern, but laparoscopic cystectomy can affect the ovarian reserve and antral follicle count after surgery. (11)

Endometriomas can affect quality of life in effected women regarding the pelvic pain, infertility, and the ovarian reserve and consequently ovarian response, the inflammatory reaction induced by endometriosis with release of inflammatory cytokines can affect implantation and create peritoneal adhesions aiding in the infertility. (12)

Materials and methods

Study duration: from December 2020 to December 2021

Study setting: zinat alhayat hospital Benha city

Sample size: 100 cases divided into two groups each group consisted of 50 cases

Ethical approval: written consent taken from all participants

Inclusion criteria

Infertility for 2 years

Single unilateral or bilateral ovarian chocolate (endometrioma) cyst

Cyst size not exceeding 6cm

Exclusion criteria

Male factor

Extra pelvic endometriosis

Multicystic cases

Cyst size more than 6 cm

Hydrosalpinx

Tubal block

The study included 100 patients with infertility and proved to have endometriotic chocolate cyst unilateral or bilateral but single ones not exceeding 6 cm diameter cases divided into two groups

Group one (the intervention) aspiration group

Group two the control group (nonintervention)

In the intervention group cases were scheduled to trans-vaginal cyst aspiration in Zinat al-Hayat hospital after preparing with essential laboratory investigations and ultrasound evaluation to confirm presence of the chocolate cyst and exclude cases of extra ovarian endometriosis or other pelvic organ affection by endometriosis.

History

Duration of infertility

Male factor

Pelvic pain patient given a pain scale to rate pain from 1 to 10 including pelvic pain or provoked deep dtspareunia

Dyspareunia.

Complete examination

General abdominal and local examination.

Complete ultrasound evaluation

Midline structures like uterus and cervix.

Ovaries (both sides).

Sliding test.

Hydrosalpinx .

Torus uterinus.

Uterosacral ligaments.

Basal investigations (at the initial evaluation)

CBC (complete blood count)

Blood glucose

TSH (thyroid stimulating hormone)

FSH (follicle stimulating hormone)

CA125 (cancer antigen 125)

VITAMIN D3

HB AB (hepatitis B antibody and antigen)

HC AB (hepatitis c antibody)

AMH (anti-mullerian hormone).

Intervention

Cases scheduled for trans-vaginal aspiration had an overnight fast.

Intervention was performed under general anesthesia and trans-vaginal ultrasound control (mind ray dc 6). Prophylaxis with 1g Cefotaxime was given intra-operatively and all cases received betadine vaginal douches for 4 days then neutral douche received 2 days before the procedure.

Initial trans-vaginal scan done with rapid diagnostic thorough sweep to exclude contraindication then full pelvic ultrasound evaluation to scan uterus cervix, Douglas pouch ,uterosacral ligament and torus uterinus .Then full ovarian scan on both sides to localize endometrioma and assess the size .

Trans-vaginally aspiration done under ultrasound guidance; with a single lumen 17 Gx250 mm needle.

Contents sent for cytological examination to prove the pathological condition it is my routine to add penicillin gram mixed with 10 ml saline to be flushed into the cyst to lower infection rate.

Cases and controls followed monthly for three months and all cases and controls given induction of ovulation by HMG 75 u im on day 3,5 and 7 then ovulation monitored by folliculometry and the course was repeated at third month if no pregnancy obtained .

First month

no induction leaving cases for spontaneous pregnancy.

Second and third month

cases and controls given induction with HMG in the form of meriofert 75 units IM (IBSA) at day 3,5and 7a pregnancy test done if there was a missed day a urine pregnancy test done clinical pregnancy was defined as the visualization of a positive fetal heart with ultrasound at 6 weeks, pregnant cases were followed and given a perfect antenatal care.

Outcome measures

Serum CA 125

Antral follicle count (counted for each ovary)

Clinical pregnancy rate (visible pulsations at 6 w)

Dyspareunia relief

Stromal flow resistive index less than 0.5

Results

Following surgery investigations done at the first month without intervention

Regarding antral follicle count there were a statistically significant difference in the intervention group with antral follicle count of 12 per ovary in 35 out of 50 while in the control group p value =0.002 a high statistical difference and this was reflected upon the pregnancy rate.

Regarding resistive index below or equal to 0.5 there were 40 cases out of 50 in the intervention group compared to 25 out of 50 in the control group with p value 0.001 that highly signify a positive impact.

Regarding deep dyspareunia 10 out of 50 complained in the intervention group compared to 25 out of 50 in the control group with p value of 0.001 and a high statistically significant difference.

The most important was a clinical pregnancy rate which was 30 out of 50 in the intervention group compared to 15 out of 50 in the nonintervention control group with p value of 0.002 a high statically significant difference see table one .

Table one (outcome measures)

item	Group one	Group 2	P value	significance
Ovarian Stromal flow RI <0.5	40	25	0.0017	S
AMH basal	3.1	3.02	>0.05	NS
Day 3FSH	7	8	>0.05	NS
AFC 12 or more	35	20	0.0026	S
CA125 <35	38	22	0.001	S
Clinical pregnancy	30/50 (60%)	15/50 (30%)	0.002	S
Deep dyspaeunia	10/50 (20%)	25/50 (50%)	0.001	S

Discussion

Endometriosis is a major problem of pelvic pain and infertility and prevalence in infertile females may reach about 30 percent, ovarian endometrioma is a special case due to its negative effect on ovarian reserve and oocyte quality

Attempts mad through many surgical interventions to increase fertility rate and improve pelvic pain and quality of life and the most important surgical intervention is the laparoscopic cystectomy, cystectomy also may affect ovarian reserve and decrease the fertility potential

Our study was an alternative surgical dimple intervention through ovarian chocolate cyst aspiration trans-vaginally to evacuate cyst contents and decrease inflammatory reactions

Cases recruited from infertile patients attending elshrouk IVF hospital and diagnosed with subfertility and the sole cause is single ovarian endometriotic cyst not exceeding 6 cm

Cysts aspirated and sent for cytological examinations and all cases and controls followed 3 moth with ultrasound and pregnancy test if there was a missed period

The first month after intervention left free without induction and CA 125 stromal resistive index pelvic pain CA125 evaluated without induction

the second and third month following aspiration total cases and controls undergone ovarian induction with human menopausal gonadotropins 75 unit at the 3rd the 5th and the 7th days of menstruation ,folliculometry done , HCG was given when follicles reached 20 mm ,pregnancy tested with quantitative HCG and followed to the clinical pregnancy diagnosed by fetal pulsation atv6 w.

There was a high significant clinical pregnancy rate in the intervention group with 30 out of 50 cases compared to only 16 clinical pregnancies out of 50 with p value 0.002.

The presented work also found a high statistically significant difference regarding stromal flow resistive index belowv0.5 with good antral follicle count stromal flow resistance index was 0.5 in about 40 out ofv50 in the intervention group compared to 35 out of 50 in the control group with p value 0.001 and the deep dyspareunia found in 10 out of 50 in the intervention group compared to 25 out of 50 in the controls with p value of 0.001.

A retrospective study by Guo found that aspiration of chocolate cyst improved oocyte quality and ovarian response prior to in vitro fertilization. (12)

Lee et al found that both conservative management and ovarian aspiration with ethanol sclerotherapy had the same good results. (13)

Despite the various interventions of ovarian endometriosis still chocolate cyst remained a problem of pelvic pain and infertility

The good aspect in the presented work was the significant clinical pregnancy rate and the changes in antral follicle count and stromal flow index which were positively changed and reflected upon the main outcome which was the clinical pregnancy rate

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Vitamin D Supplemental Therapy for Women with Endometriosis may ameliorate Endometriosis-associated Pelvic Pain

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Abstract

Objectives: Evaluation of the effect of 12-wk vitamin D supplemental therapy (VDST) on serum levels of 25-hydroxy vitamin D (25OH-VD) and endometriosis-related pain scores in women with endometriosis

Patients & Methods:41 women with endometriosis were evaluated for presence and severity of dysmenorrhea, dyspareunia and non-menstrual pelvic pain and gave blood samples for estimation of serum 25OH-VD level. All women received VDST as 5000 units/day for 12 weeks and clinical pain scores and serum 25OH-VD were re-evaluated.

Results: After VDST, median value of total pain score was decreased by 25% and the frequency of patients had mild pain was increased by 1.5 folds, while the frequency of patients had severe pain was decreased by 50%. Moreover, the frequency of patients dependent on gabapentin alone or with injectable NSAID was reduced by 75% with concomitant increased frequency of patients dependent on oral NSAID by 2.2 folds. Furthermore, VDST increased serum 25OH-VD levels by 25% with concomitant decreased frequency of women had VD deficiency (VDD) by 1.3 folds. There was negative significant correlation between change of serum 25OH-VD levels and total pain score.

Conclusion: VDD is widespread between women with endometriosis. VDST for 12-wk improved VD sufficiency status and endometriosis-related pain scores.

Keywords: Endometriosis, Vitamin D, Vitamin D Supplemental Therapy, Endometriosis-associated pain

Introduction

Vitamin D (VD) is a secosteroid with a pleiotropic role in multiple physiological processes [(1)]. It is fat-soluble vitamin acting through VD receptor, which is expressed in most of non-skeletal tissues [(2)], to affect multiple biologic functions [(3)]. VD can regulate both innate and adaptive immunity through regulation of cell proliferation, differ-

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entiation and apoptosis [4] and can influence interleukin expression and antimicrobial responses [5].

Serum 25-hydroxy VD (25OH-VD) levels are variable in women and are higher in non-pregnant than in pregnant women and in non-pregnant tends to change during phases of the ovulatory cycles; being higher during luteal than follicular phases [6]. Moreover, VD is synthesized in female reproductive tissues and components required for its synthesis are expressed in the ovary, decidua, endometrium and placenta [7].

Endometriosis is multifactorial disorder, which is dependent on intrinsic and extrinsic factors, but inflammation and immune cell deregulation seems to play a pivotal role in pathogenesis of endometriosis and associated infertility [8]. The immune system abnormalities demonstrated in endometriosis may reflect either chronic inflammatory response or an autoimmune reaction to the presence of ectopic endometrial tissue [9]. Endometriosis could be considered as an autoimmune disease because it shares similarities to several autoimmune diseases with special regard to role of the human leukocyte antigen-C genotype, which is an essential regulator of the activity of natural killer cell that is associated with endometriosis progression [9].

Vitamin D deficiency (VDD) was found to be associated with several autoimmune diseases including autoimmune thyroiditis, rheumatoid arthritis, and systemic lupus erythematosus [10], which are more prevalent in adolescents and adult women [11]. Thus, the active VD metabolites are potentially effective in the treatment of several autoimmune diseases most probably through VD modulatory effect on immune system [12]. VD displays its immune regulatory effect via its intracellular receptors that are present in monocytes, macrophages, T cells, B cells, natural killer cells, and dendritic cells [13] to form a heterodimeric complex, which induces engagement of VD response element and recruitment of activators and enzymes with histone acetylation activity to induce structural changes in chromatin and regulation of targeted gene [14].

Hypothesis

This study supposes that VDD may have a possible relation to the development of endometriosis and so VD supplemental therapy (VDST) may help to minimize the severity of associated manifestations.

Objectives

Evaluation of the effect of 12-wk of vitamin D supplemental therapy (VDST) on serum levels of 25-hydroxy vitamin D (25OH-VD) and on endometriosis-related pain scores in women with endometriosis

Designn

Prospective comparative interventional study

Setting

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Patients & Methods

The present study was started since July 2018 to Jan 2021 to allow evaluation of changes at the end of the 12-w VDST for the last enrolled case. The study protocol was approved by the Local Ethical Committee and women who signed a written fully informed consent to participate in the study were included. All women who attended the Outpatient Clinic of Obstetrics and Gynecology Department, at Benha University hospital with clinical manifestations suggestive of endometriosis or with previously diagnosed endometriosis were eligible for evaluation.

Inclusion criteria

Endometriosis was clinically diagnosed according to the guidelines of the International

Classification of Disease (15) depending on the presence of dysmenorrhea, dyspareunia and non-menstrual pelvic pain (NMPP) in a woman free of other pathologies giving a similar clinical picture.

Exclusion criteria

Presence of other pathologies giving a clinical picture mimics that of endometriosis, presence of other causes of types of pain similar to that caused by endometriosis, refusal to participate the study.

Clinical evaluation

- Demographic data including age, weight and height for calculation of body mass index (BMI) as weight (kg)/ height (m^2) [16] and women were classified according to BMI using the World Health Organization ranges as underweight: BMI<18.5 kg/m^2, normal weight: BMI=18.5-24.9 kg/m^2, overweight: BMI=25-29.9 kg/m2 and obese: BMI=≥30 kg/m^2 [17] .

- History taking concerned with family history of endometriosis, autoimmune diseases, presence of diabetes mellitus, essential hypertension, kidney diseases, previous gynecological surgeries, and previous treatment for endometriosis.

- Number of living offspring, current status of fertility and if infertility was a complaint, data related to its duration, possible causes and previous management was collected.

- Diagnosis and evaluation of endometriosis-related pain

A. Types and severity evaluation

1. Dysmenorrhea was diagnosed on fulfillment of five criteria: hypogastric pain during menstruation, radiating to the lower back, lower limbs, or inguinal region with an intensity of ≥2 on the Wong–Baker scale during the last 3 months, causing inability to perform daily activity and need for analgesia (18). Severity of dysmenorrhea was evaluated and scored using the WaLID score that entails evaluating four variables each of which was scored on 4-point scale (0-3) for a total score ranged between 0 and 12. The variables of WaLID score include working ability evaluating if pain is disabling to perform usual activities (never, almost never, almost always, always), anatomical location and irradiation of pain (No, one site, 2-3 sites, ≥4 sites), pain intensity as evaluated using Wong–Baker pain range (No, hurts a little, little more-to-even more, hurts a lot-lot more) and was scored on 4-point scale (0-3) (19) during the last three months and number of days of pain (0, 1–2, 3–4, ≥5) during menstruation [20].
2. Dyspareunia, is a descriptive term for pelvic or vaginal pain associated with intercourse and was evaluated using Marinoff Dyspareunia Scale, which scored the sexual function in relation to pain on a 4-point scale as no pain with intercourse (score=0), pain with intercourse doesn't prevent the completion (score=1), requiring interruption or discontinuance (score=2) or preventing any intercourse (score=3) [21].
3. Non-menstrual pelvic pain (NMPP) was measured using a 4-point pain-effect scale ranging from 0 (no pain) to 3 (severe pain).
4. Total pelvic pain score: pain intensity of dysmenorrhea, NMPP, and dyspareunia was ranging between 0 and 3 for each item for a total pain score ranging between 0 and 9.

B. Duration of pain was defined as the length of time between onset of pain and enrolment in the study

C. Type of analgesia used was scored on 4-point scale as drug score; non-steroidal anti-inflammatory drugs; oral (score=1), or injectable (score=2), gabapentin or similar drugs (score=3) or both analgesic modalities (score=4).

- Complete gynecological examination for presence of pelvic and/or abdominal tenderness, hematuria or rectal bleeding

Transvaginal Ultrasonography (TVU)

TVU imaging was done (Hitachi EUB-5500) using examining vaginal probe (10-3 MHz), curve probe (5–1 MHz) and linear probe (12–3 MHz) according to the International Deep Endometriosis Analysis (IDEA) Consensus Group (22). The stage of endometriosis was scored according to the revised American Society for Reproductive Medicine (rASRM) score [23].

Evaluation of VD sufficiency status

Random blood samples were obtained under complete aseptic conditions from the antecubital vein in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at -20oC till estimation of fasting serum 25OH-VD levels using an ELISA kit (Cayman Chemical, Ann Arbor, MI, USA) [24]. The interassay variation for samples containing high, medium or low levels of VD were 4, 6.3, 6, respectively after samples' levels were measured 60 times each using a single set of reagents as documented by the manufacturer. Vitamin D sufficiency status was defined according to 25OH-VD concentration as follows: ≥75 nmol/L sufficient level, 50-75 nmol/L insufficient level and <50 nmol/L deficient level. Vitamin D deficiency was categorized as mild, moderate and severe if 25-OHD concentration was 25-50 nmol/L, 12.5-25 nmol/L and <12.5 nmol/L, respectively [25].

Protocol for VDST

The VDST was provided as rapid release softgel capsule of vitamin D3 once daily, 5000 units/day using Sunvite (Puritan's Pride; Nestlé Health Science S.A, USA) for 12 weeks.

Follow-up

At the 12th week of VDST, all women were evaluated for endometriosis-related pain and gave blood samples for re-estimation of serum 25OH-VD.

Study outcomes

1. The relation between the percentages of changes in serum 25OH-VD and total pelvic pain score at the end of VDST.
2. The prevalence of VDD among the studied population of endometriosis women and the change after VDST.

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers, percentages, median and interquartile ranges (IQR). The percentage of change was calculated as the value determined after VDST minus the value determined before VDST and the difference was divided by the value determined before VDST and multiplied by 100. Parametric data were compared using paired t-test and Mann-Whitney test. Non-parametric data were compared using Chi-square test. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Throughout the duration of the study, 53 women were eligible for evaluation; 12 were excluded for not fulfilling the inclusion criteria and 41 women were enrolled in the study. Baseline demographic data of enrolled women are shown in table 1.

Table (1): Baseline demographic data

Data			Findings
Age	Categories	<30 years	10 (24.4%)
		30-39 years	17 (41.5%)
		≥40 years	14 (34.1%)
	Mean (SD)		35.2 (7.6)
	Range		23-48
BMI (kg/m^2)	Categories	≤24.9	7 (17.1%)
		25-29.9	23 (56.1%)
		30-34.9	10 (24.4%)
		≥35	1 (2.4%)
	Mean (SD)		35.2 (7.6)
	Range		23-48
Family history of endometriosis	Yes		6 (14.6%)
	No		35 (85.4%)
Smoking history	Yes		4 (9.8%)
	No		37 (90.2%)
No of living offspring	0		7 (17.1%)
	1		14 (34.1%)
	2		15 (36.6%)
	3		5 (12.2%)
Duration of infertility	Categories	<5 years	17 (41.5%)
		≥5 years	24 (58.5%)
	Mean (SD)		5 (1.8)
	Range		2-10

Data are presented as numbers, percentages, mean, SD and ranges; BMI: Body mass index

The presenting clinical manifestations were variable but all patients complained of pain, and 4 patients complained of hematuria (n=1; 2.4%) or rectal bleeding (n=3; 7.3%). Clinical examination detected pelvic tenderness in 17 patients (41.5%) and abdominal tenderness in 8 patients (19.5%). One woman had pelvi-abdominal tenderness and rectal bleeding with occasional hematuria. Rectal bleeding was the main complaint of two women in association with pelvi-abdominal tenderness. WaLID dysmenorrhea scoring illustrated the impact of dysmenorrhea pain on patients' quality of life that was severe for 12 patients (29.3%), moderate in 17 patients (41.5%) and mild in only 4 patients (9.7%), while 8 patients (19.5%) documented no impact of dysmenorrhea on their quality of life (Table 2).

Table (2): WaLID dysmenorrhea score

	Walking ability	Location of pain	Intensity of pain	Days of pain	Total
No	8 (19.5%)	8 (19.5%)	8 (19.5%)	8 (19.5%)	8 (19.5%)
Mild	9 (22%)	24 (58.6%)	18 (43.9%)	12 (29.3%)	4 (9.7%)
Moderate	15 (36.6%)	8 (19.5%)	15 (36.6%)	15 (36.6%)	17 (41.5%)
Severe	9 (22%)	1 (2.4%)	0	6 (14.6%)	12 (29.3%)

Data are presented as numbers, percentages

Mean duration of pain as a complaint was 11.6±4.6 years and only one woman had pain since 20 years and 5 women had pain since less than 5 years. Pain duration was ranging between 5 and 10 years in 12 women (29.3%), between 10 and years in 14 (34.1%) and was in range of 15-20 years in 11 women (26.9%). VDST improved pain scores, regarding dysmenorrhea, dyspareunia and NMPP and total pelvic pain score. Despite the non-significant differences between patients' distribution among pain scores and the non-significant difference in median values of different pain scores; number of patients had mild total pain was increased by 1.5 folds after VDST in comparison to before VDST and number of patients had severe total pelvic pain was decreased by 50% (Table 3).

Table (3): Pain severity scores before and after VDST

Item Grade Time	Dysmenorrhea		Dyspareunia		NMPP		Total	
	Before	After	Before	After	Before	After	Before	After
No	8 (19.5%)	9 (22%)	17 (41.5%)	20 (48.8%)	11 (26.9%)	15 (36.6%)	-	-
Mild	18 (43.9%)	22 (53.6%)	8 (19.5%)	9 (22%)	4 (9.8%)	10 (24.4%)	17 (41.5%)	25 (61%)
Moderate	15 (36.6%)	10 (24.4%)	14 (34.1%)	11 (26.8%)	16 (39%)	11 (26.8%)	14 (34.1%)	11 (26.8%)
Severe	0	0	2 (4.9%)	1 (2.4%)	10 (24.3%)	5 (12.2%)	10 (24.4%)	5 (12.2%)
P value	0.492		0.802		0.123		0.169	
Median score	1 (1-2)	1 (1-1.5)	1 (0-2)	1 (0-2)	2 (0-2.5)	1 (0-2)	3 (1-6.5)	3 (1-5.5)
P value	0.379		0.407		0.072		0.18	

Data are presented as number, percentages, median and interquartile range; p value indicates the significance of difference between before and after VDST; P value <0.05 indicates significant difference; p value >0.05 indicates non-significant difference

The beneficial effect of VDST was reflected on the frequency and score of the use of analgesia, where the frequency of patients required gabapentin alone or with injectable NSAID was reduced by 75% and the number of patients used oral NSAID was increased by 2.2 folds (Table 4).

Table (4): Types and frequency of the used analgesics before and after VDST

Type of analgesia Time	Before VDST	After VDST
Oral NSAID (Score = 1)	5 (12.2%)	11 (26.8%)
Injectable NSAID (Score = 2)	24 (58.6%)	27 (65.9%)
Gabapentin (Score = 3)	4 (9.7%)	1 (2.4%)
Gabapentin + NSAID (Score = 4)	8 (19.5%)	2 (4.9%)
P value	0.049	
Median (IQR)	2 (2-3)	2 (1-2)
P value	0.021	

Data are presented as number, percentages, median and interquartile range; p value indicates the significance of difference between before and after VDST; P value <0.05 indicates significant difference; p value >0.05 indicates non-significant difference

Patients' distribution within the main VD sufficiency statuses showed significant (p=0.011) improvement after VDST with a decreased frequency of women had VDD by 1.3 folds in comparison to the detected distribution before initiation of VDST. Patients' distribution among VDD statuses was significantly (p=0.0315) improved with decreased frequency of patients had severe deficiency by 3 folds (Fig. 1). The mean levels of serum 25OH-VD estimated after 12-wk VDST was significantly (p=0.0122) higher in comparison to mean level estimated before start of VDST with median percentage of increase of 25% (IQR: 11.6-54.35). Total endometriosis-related pain score determined after 12-wk VDST was significantly (p=0.007) lower in comparison to score determined before VDST with median percentage of decrease of 25% (IQR: 0-33.3) (Table 5). Moreover, there was negative significant correlation (Rho=-0.318, p=0.043) between the percentages of change of serum VD and total pain score.

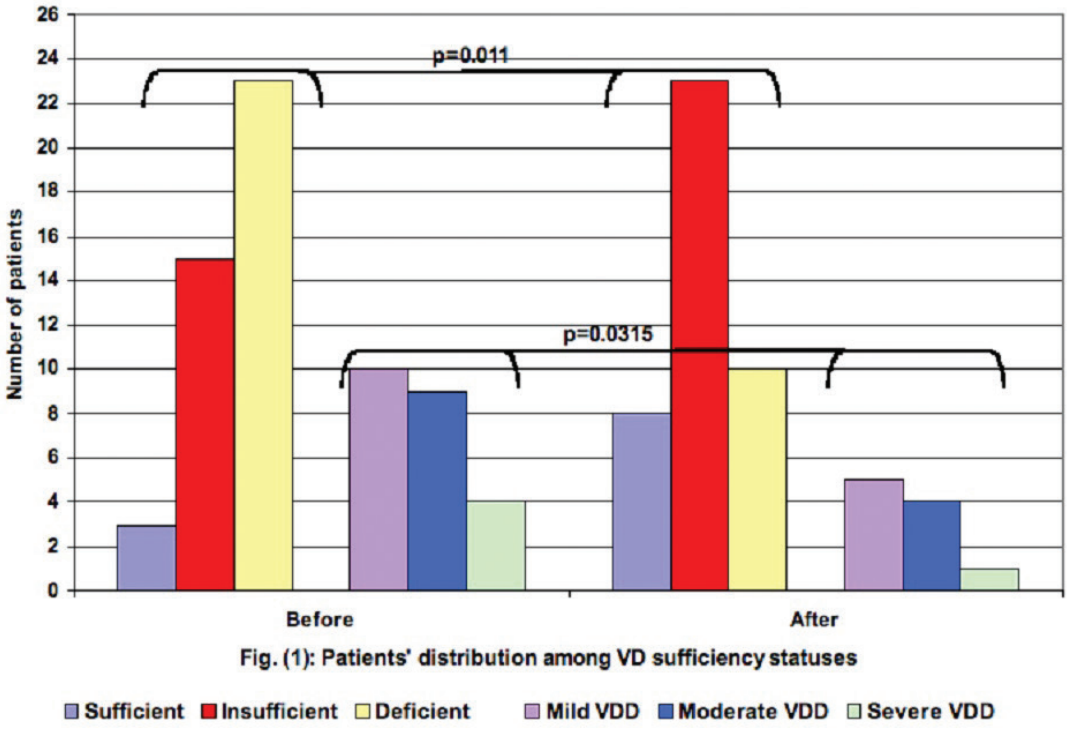

Fig. (1): Patients' distribution among VD sufficiency statuses

Table (5): Serum VD data

P value	After VDST	Before VDST	Data	Time	
0.011	8 (19.5%)	3 (7.3%)	Sufficient		Sufficiency status
	23 (56.1%)	15 (36.6%)	Insufficient		
	10 (24.4%)	23 (56.1%)	Deficiency		
0.0315	5 (12.2%)	10 (24.4%)	Mild		VDD
	4 (9.8%)	9 (22%)	Moderate		
	1 (2.4%)	4 (9.8%)	Severe		
0.0122	55.1 (18.3)	44.1 (20.2)	Mean (SD)		Serum level (nmol/L)
	11-78	9.5-77	Range		
	38.3 (38.1)		Mean (SD)	% of change	
	1.3-138.1		Range		

Data are presented as numbers, percentages, mean, standard deviation (SD), range; VDD: Vitamin D deficiency; P value indicates the significance of difference between before and after VDST; P<0.05 indicates significant difference

Discussion

All enrolled women showed varied degrees of VD deficiency (VDD), apart from three women (7.3%) who had sufficient serum VD level. This finding indicated that VDD is a widespread problem and is coincident with that recently reported in apparently healthy and diseased individuals [26, 27, 28]. VDD was detected in about 93% of the studied endometriosis women; this frequency of VDD indicated a certain relation between VDD and endometriosis. In line with these findings, Ciavattini et al. [29] found a relatively higher rate of women with ovarian endometriosis and VDD and detected a significant linear correlation between 25-OH VD serum levels and diameter of ovarian endometrioma. Qui et al. [30] detected lower VD status in women with endometriosis when compared with controls and a negative relationship between VD levels and severity of endometriosis, and concluded that VDD was a potential risk factor for endometriosis.

Delbandi et al. [31] found 25-OH VD level estimated in serum and peritoneal fluid samples of women with endometriosis were significantly lower than control group and women with serum levels <20 ng/mL had a 2.7 times higher risk of endometriosis than women with serum levels >20 ng/mL and concluded that women with VDD are at higher risk of endometriosis. The obtained results and these findings on literature review were contradictory to that obtained by Somigliano et al. [32] who reported non-significantly higher serum 25-OH VD in women with endometriosis than control and Almassinokiani et al. (33) who reported no effect for VDST. However, Somigliano et al. [32] could not explain their results and attributed the difference to the seasonal effect, which must be the same for all study participants and Almassinokiani et al. [33] used VDST after laparoscopic management of endometriosis and reported non-significant difference in pain which may be attributed to the complexitiy of the disease condition, stimulation of nociceptive cytokines by surgery and this case collection was different than that studied in the current study

Supplemental VD therapy was found to significantly improve serum levels of 25-OH VD with significant improvement of the frequencies of VD sufficiency status. Moreover, there was a positive significant correlation between the percentage of increase of serum 25-OH VD and the percentage of decrease of total pelvic pain scores.

These data illustrate two positive findings; firstly, there is a possible role of VDD for the pathogenesis of endometriosis and may be attributed to improved local and/or systemic inflammatory milieu. In support of the anti-inflammatory effect of VD, Chen et al. [34] detected a negative significant correlation between serum 25-OH VD and IL-6 concentrations in women had tubal factor infertility and considered VDD as a risk factor for this category of infertility. Secondly; the reported improved total pelvic pain score suggested a possible corrective role of VD-ST for endometriosis-associated or -induced manifestations. Similarly, Farland et al. [35] in an interesting observational cohort study, reported that residential ultraviolet (UV) level at birth, at age 15 and 30 were associated with a decreased risk of endometriosis. Clinically, Nodler et al. [36] found adolescent and adult women with endometriosis experienced significant improvement in pain score on VD-ST in comparison to worst pain in the past month. Also, Mehdizadehkashi et al. [37] reported that women with endometriosis who received VD showed significant improvement of pelvic pain scores with significant reduction of levels of total/HDL-cholesterol ratio and high-sensitivity C-reactive protein and significant increase in total antioxidant capacity.

In trial to explain the immunomodulatory effect of VD and the reported effects of VDST, Karagul et al. [38], experimentally, found VD increased P53 mRNA expression in human endometrial cancer cell line (HEC-1A) and caused paraptosis-like HEC-1A cell death. Also, Ghanavatinejad et al. [39] found pretreatment of endometrial cells stimulated by lipopolysaccharide markedly reduced LPS-induced toll-like receptor-4 protein expression with subsequent reduction of activation of nuclear factor-κB intracellular signaling pathway and inflammatory cytokine production and reduction of MyD88 gene expression which acts as an adaptor between extracellular stimuli and intracellular signaling pathways. Clinically, Pazhohan et al. [40] reported that high-dose VD to endometriosis women changed the activity of β-catenin protein, which inhibits Wnt/β-catenin signaling pathway that is responsible for cell proliferation, in blood samples and endometrial biopsies in comparison to control women with endometrium.

The used dose, 5000 U daily for 12 week, provided a cumulative dose of 420,000 U that was coincident with Janice et al. (41) who detected linear increase of serum 25-OH VD with 800 to 4,000 IU/d of vitamin D3 for 16 wk, without a ceiling effect. Also, Khawaja et al. (42) reported no difference in the effect on serum 25-OH VD on using cholecalciferol 50 000 IU/week versus 7000 IU/day for 8 weeks and concluded that timing and frequency of the dosing have no effect on the rise in serum 25(OH)D levels as long as the accumulative dose of cholecalciferol is similar.

Conclusion

VD deficiency is widespread between women with endometriosis. VDST for 12-wk improved VD sufficiency status and is associated with improved pain scores.

Limitation

The study was limited to the duration of VDST and to women with endometriosis-associated dysmenorrhea. Case collection needed to be verifies to exclude those had complicated disease to evaluate the long-term effect of VDST on prevention of disease progression and on fertility in infertile women secondary to endometriosis.

Recommendation

Wider scale study to include women with other pathologies inducing chronic pelvic pain. Evaluation of endometriosis lesions after VDST to assess if there is associated effect.

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Adjustment of Robson Classification System to Body Mass Index might improve the predictability for Operative delivery and reduce its false-positive results

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Abstract

Objectives: To determine the impact of obesity on decision-making concerning mode of delivery and to compare these data versus the reliance on the Ten-group Robson Classification System (RCS) alone.

Patients & Methods: 554 parturient free of pregnancy-associated medical diseases were evaluated clinically at time of enrolment for RCS class and at time of admission for delivery, for body mass index (BMI) grading. Mode of delivery was predetermined according to RCS class and clinical judgment taking in consideration maternal age and BMI. Parturient distribution after labor according to mode of delivery was compared to that predetermined by clinical and RCS evaluation.

Results: According to RCS class, elective CS was predicted for 204, spontaneous deliveries for 166 and 184 parturient were predicted to require induction of labor. Clinically, 163 parturient were predicted to have unaided vaginal delivery, 95 parturient will have CS and 296 parturient will require induction of labor. The probability to have CS was significantly higher on reliance on RCS grading system. Actually, 327 women had unaided and 23 had instrumental vaginal delivery and 204 required CS. The actual frequency of CS was related to nulliparity, history of previous CS, BMI and RCS grading. Statistical analyses defined nulliparity as the significant sensitive and high BMI as the significant specific predictor for CS. In comparison to parturient had ≤32 kg/m^2, the cumulative hazard to have CS was increased by 10% with BMI >32-34 kg/m^2, 45% with BMI 34-35 kg/m^2 and by 100% at BMI≥ 36.5 kg/m^2.

Conclusion: The Robson Classification System had good true negative, but high false positive predictive values for CS. Adjustment according to BMI within Robson groups significantly reduced the need for CS and may improve the decision for augmentation, instrumental and operative delivery.

Keywords: Robson Ten-group Classification System, Body mass index, Mode of delivery, cesarean section

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Introduction

Current labor practices showed acceleration in interventions for initiation, monitoring, acceleration or termination of the physiological process of pregnancy and childbirth [1]. These practices aim to reduce the rate of cesarean section (CS), attendance to emergency rooms, length of hospital stay and need for intensive care units for both the parturient and the newborn; however, these variables showed significant regional variations and need to be standardized [2].

Risk factors for getting operative delivery are multiple, but the most common include age older than 35 years especially for primigravida, obesity [3], smoking, multiple pregnancies, previous diseases and/or current pregnancy-associated diseases as diabetes, preeclampsia [4], previous CS, history of abortions, need for induction [5], and emotional factors as anxiety [6].

The World Health Organization (WHO) statement for the optimal CS rate at both population and hospital level [7], and the association between CS and maternal and neonatal mortality [8] demonstrated that if the CS rate rises up to 10–15%, the number of maternal and newborn deaths decreases, but at rate above 15% did not grantee any better rates of mortality and morbidity [9].

Robson Classification System (RCS) allocates pregnant women at the time of delivery into 10 groups, which are based on parity, onset of labor, gestational age, fetal presentation, and number of the fetuses. RCS was recommended as a global standard for assessing, monitoring, and comparing CS rates within healthcare facilities over time, and between facilities [10].

Hypothesis

RCS was based on only 5 of the variables suggestive of the possibility of getting CS. However, RCS did not take in account other important risk factors for CS as obesity that may modify the classification groups if it is considered.

Objectives

The current study aimed to determine the impact of obesity on decision making concerning mode and outcome of delivery and to compare these data versus the reliance on RCS alone.

Design

Prospective single-center comparative study

Setting

Obstetrics and Gynecology Department, Tanta and Benha University Hospitals and Some private obstetric centers

Patients & Methods

All pregnant women who attended the obstetrics outpatient clinic were eligible for evaluation. According to the conditions of the Local Ethical Committee all women were clinically evaluated and underwent ultrasonographic imaging for evaluation for inclusion and exclusion criteria.

Exclusion criteria

Presence of pregnancy-associated medical diseases; gestational diabetes, hypertensive diseases, anemia or kidney disease, placental abnormal location, fetal congenital anomalies, coagulopathies, preconception cardiac, liver or kidney diseases. Women who refused to give birth at the participating hospital were also excluded

Inclusion criteria

Women had straightforward pregnancy course free of pregnancy-associated diseases and signed the written fully informed consent and gave birth at hospitals participating the study, either on elective or emergency basis were enrolled in the study.

Study protocol

All women fulfilling the inclusion criteria were graded at time of enrolment for the RCS classes and at time of admission for giving labor for BMI by assistants who were blinded about the study hypothesis. BMI (in kg/m2) was determined at the last visit to the clinic and women were graded according to the WHO classification of weight as underweight (BMI<18.5), average weight (BMI: 18.5-24.9), overweight (25-29.9), obese class I (BMI: 30-34.9), class II (BMI: 35-39.9) and obese class III (BMI>40), [11,12].

The decision-taking for the mode of delivery was taken by authors, who were blinded about RCS grading, according clinical judgment. The actual mode of delivery was compared as the independent variable versus the predetermined mode of delivery according to BMI and RCS grades for the following:

1. The success rate of decision-making depending on RCS grades for prediction of mode of delivery versus to the actual mode of delivery
2. The impact of BMI on the decision for the choice of the actual mode of delivery.
3. The predictability of each grading system separately and in combination on the decision concerning the mode of delivery.

Study outcome

The principle study outcome is the impact of BMI grading on decision-making concerning mode of delivery depending on RCS only

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers and percentages. The success rate was defined as the percentage of parturient that had CS in relation to the blinded diagnosis of elective CS. Correlations between studied variables were performed using Spearman's correlation of non-parametric data. Regression analysis, Stepwise method, was used to determine the predictors for CS. Kaplan-Meier regression analysis was used to determine the cutoff point of BMI that can predict CS. Statistical analysis was performed using SPSS software package, 2015. P value of <0.05 was considered significant.

Results

During the duration of study, 586 women were eligible for evaluation; 18 women were excluded for not fulfilling the inclusion criteria and 568 women signed consent to give labor under supervision of the authors. Unfortunately, 14 women could not attend and were also excluded from the study and 554 women who gave labor under supervision of the authors were included in the study (Fig. 1).

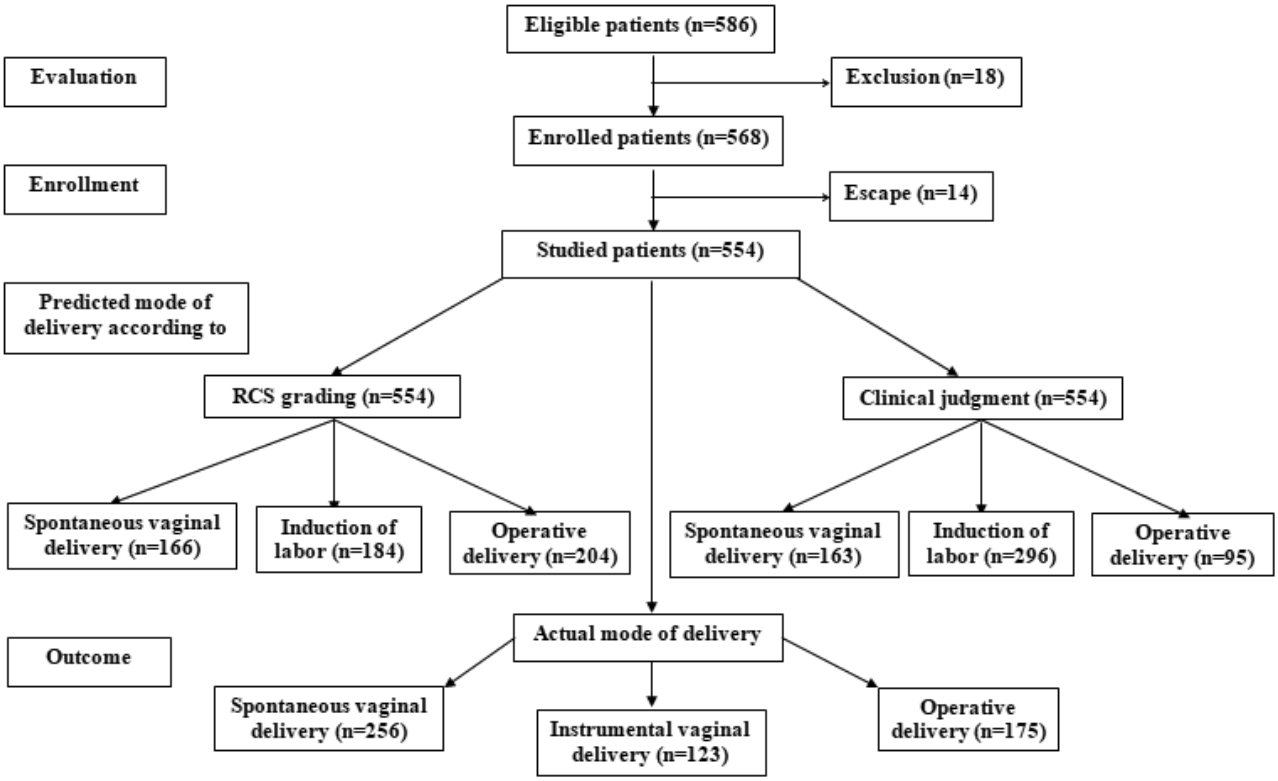

Fig. (1): Study Flow Chart

Mean age of enrolled women was 28.7±4.5 years and 90 women were younger than 25 years, 50 women were older than 35 years, and the majority of women were in range of 25-35 years. According to body weight and calculated BMI at time of admission for labor there were only 2 women (0.36%) had average BMI, 43 women (7.76%) were overweight, 386 women (66.42%) were obese grade I and 123 women (25.46%) were obese grade II. There were 283 nullipara (51%) and 271 multipara women; 105 multipara (19%) had previous CS. Twenty-four parturient had preterm labor at <37 weeks, 7 women had multiple pregnancy, another 7 parturient had a singleton fetus in oblique lie and 14 parturient had singleton fetus in breech presentation, while 502 parturient had singleton fetus in cephalic presentation and had gestational age of >37 weeks.

Table (1): Patients' enrolment data

Data		Findings
Age (years)	<25	90 (16.25%)
	25-30	265 (47.82%)
	>30-35	149 (26.9%)
	>35-40	38 (6.86%)
	>40	12 (2.17%)
	Mean (±SD)	28.7±4.5
BMI (kg/m^2)	Average (<24.9)	2 (0.36%)
	Overweight (25-29.9)	43 (7.76%)
	Obese I (30-34.9)	386 (66.42%)
	Obese II (35-39.9)	123 (25.46%)
	Mean (±SD)	26±9.6

Gravidity	Nulliparous		283 (51%)
	Multipara	Previous CS	105 (19%)
		No previous CS	166 (30%)
Number of fetuses	Singleton		547 (98.74%)
	Multiple		7 (1.26%)
Pregnancy duration (weeks)	Preterm (<37 weeks)		24 (4.33%)
	Full term (>37 weeks)		530 (95.67%)
Presentation	Cephalic		533 (96.21%)
	Breech		14 (2.53%)
	Transverse/oblique lie		7 (1.26%)

Data are presented as numbers; percentages; mean; standard deviation

According to RCS, 204 women were predicted to have elective CS, 166 women were predicted to have spontaneous delivery and 184 women were predicted to require induction of labor (Table 2).

Table (2): Patients' distribution and predicted line of management according to RCS

class	Description	Number (%)
1	Nulliparous women with a single cephalic pregnancy, ≥37 GW in spontaneous labor	95 (17.15%)
2A	Nulliparous women with a single cephalic pregnancy, ≥37 GW who had labor induced	137 (24.73%)
2B	Nulliparous women with a single cephalic pregnancy, ≥37 GW who were delivered by CS before labor	36 (6.5%)
3	Multiparous women without a previous uterine scar, with a single cephalic pregnancy, ≥37 GW in spontaneous labor	71 (12.82%)
4A	Multiparous women without a previous uterine scar, with a single cephalic pregnancy, ≥37 GW who had labor induced	47 (8.48%)
4B	Multiparous women without a previous uterine scar, with a single cephalic pregnancy, ≥37 GW who were delivered by CS before labor	22 (4%)
5	All multiparous women with at least one previous uterine scar, with a single cephalic pregnancy, ≥37 weeks gestation	94 (17%)
6	All nulliparous women with a single breech presentation	11 (2%)
7	All multiparous women with a single breech presentation, including women with a previous uterine scar	3 (1.26%)
8	All women with multiple pregnancy, including women with a previous uterine scar	7 (1.26%)
9	All women with a single pregnancy with a transverse or oblique lie, including women with a previous uterine scar	7 (1.26%)
10	All women with a single cephalic pregnancy <37 GW, including women with a previous uterine scar	24 (4.33%)

According to clinical judgment, 163 women (29.42%) were predicted to have spontaneous vaginal delivery and 95 women (17.15%) to have elective CS, while 296 women (53.43%) were predicted to require induction of labor. Induction of labor resulted in 164 unaided vaginal delivery, 23 instrumental vaginal delivery and 109 women required CS. Thus, 327 women had unaided vaginal delivery, 23 had instrumental vaginal delivery and 204 required CS.

Thus, the predicted rate of CS as the mode of delivery was significantly higher (p<0.0001) if decision was taken according to RCS grading system in comparison to the that based on clinical judgment with respecting age and BMI (Fig. 2).

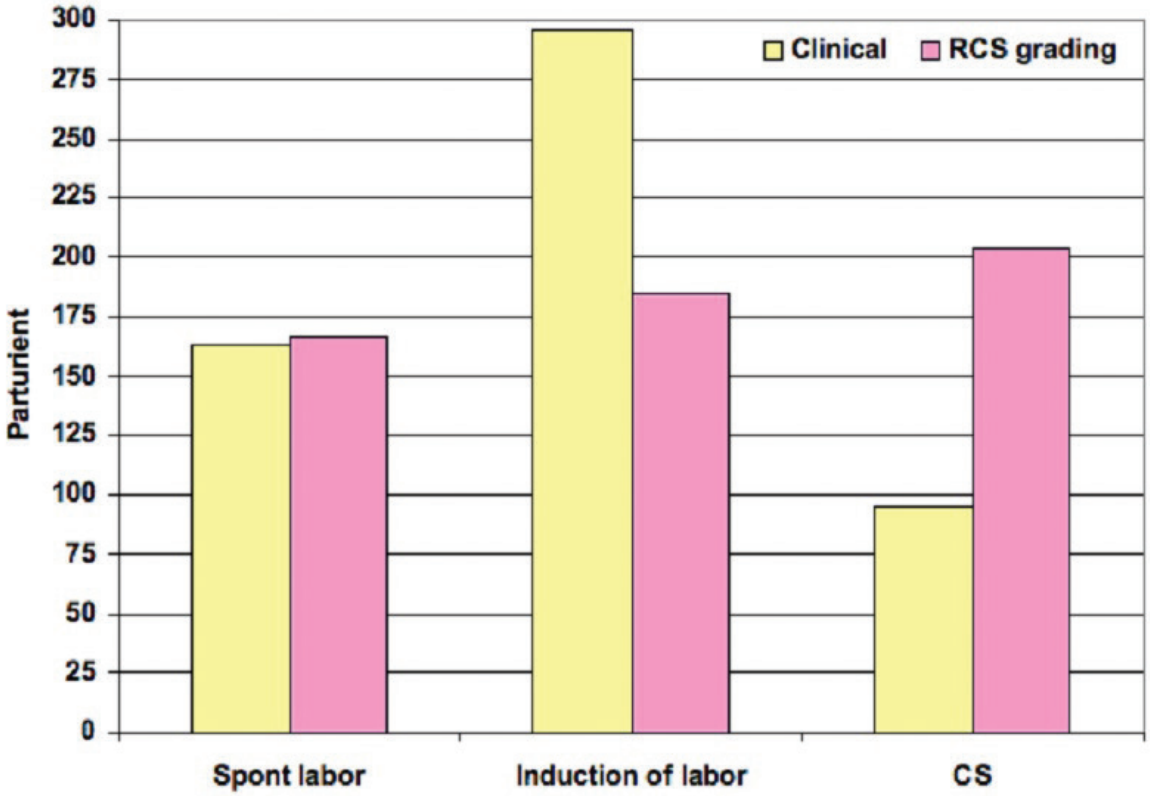

Fig. (2): Parturient's distribution according to the predicted mode of delivery according to clinical judgement and RCS grading

The actual number of women had CS showed positive significant correlation with nulliparity (Rho= 0.129, p=0.002), history of previous CS (Rho= 0.118, p=0.005), high BMI (Rho= 0.490, p<0.0001) and with RCS grading (Rho= 0.097, p=0.022). Regression analysis, defined older age (β=0.086, p=0.029), RCS grade (β=0.098, p=0.012) and high BMI (β=0.462, p<0.0001) as the significant predictor for CS as the mode of delivery. ROC curve analysis of these variables defined nulliparity as the significant sensitive and high BMI as the significant specific predictor for the mode of delivery to be operative delivery (Fig. 3).

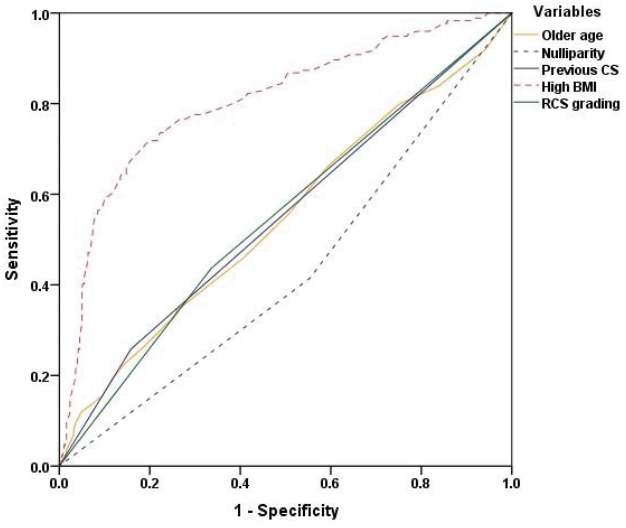

Fig. (3): ROC curve analysis of variables evaluated as predictors for oncoming CS as a decision for mode of delivery

Kaplan-Meier regression analysis for BMI values of studied parturient as a risk factor for having CS as a mode of delivery defined minimal cumulative risk of having CS at BMI up to ≤32 kg/m2. However, in comparison to women had BMI of ≤32 kg/m2, the cumulative hazard for having CS increased by about 10% in women had BMI in range of >32 to 34 kg/m2 by 45% in women with BMI in range of 34-35 kg/m2 and by 100% at BMI≥ 36.5 kg/m2 (Fig. 4).

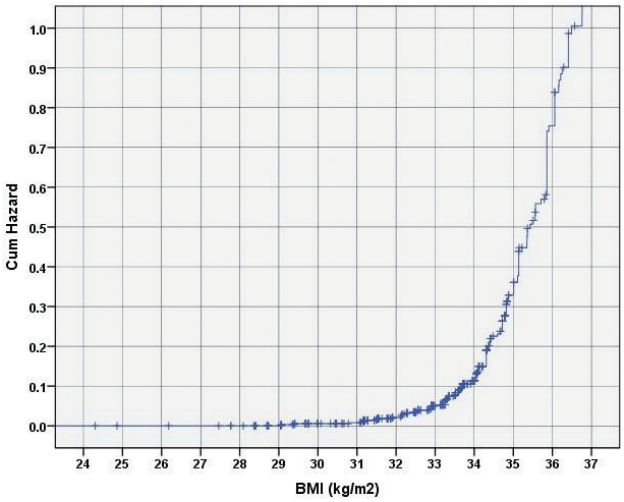

Fig. (4): Kaplan-Meier Regression analysis for cumulative hazard of for CS as a mode of labor stratified according to BMI of parturient

Discussion

Obesity of the studied parturient seriously affected the decision-making about the predicted mode of delivery. Moreover, BMI showed positive significant correlation with the actual mode of delivery applied for the studied women and statistical analyses defined BMI as a determinant parameter for the decision-making about the mode of delivery. Furthermore, Kaplan-Meier regression analysis showed progressively increasing cumulative hazard for CS with BMI of >32 kg/m^2 reaching a maximum of 100% cumulative hazard at BMI of 36.5 kg/m^2.

These results illustrate the contribution of BMI in the decision-making for the mode of delivery. Similarly, Szewczyk et al., [13] reported that higher BMI was associated with increased odds of CS and obese women in class II had significantly higher odds of CS than normal weight women. Also, Carlhäll et al., [14] found the time from admission until start of active labor increased successively with maternal obesity and women with BMI ≥40 kg/m2 had significantly longer duration of active labor, but if this occurs the chance for spontaneous vaginal delivery equals that of normal weight women, despite of the higher rate of CS. Moreover, Girault et al., [15] documented those nulliparous obese women had significantly lower odds of having a shorter labor than women with BMI of less than 25 kg/m^2.

In support of the impact of BMI on decision-making, de Góes Salvetti et al., [16], studied follow-up data of 1,574 at-risk pregnant women and found 43.1% preferred normal delivery, but only 17.3% had normal delivery and found CS was associated with overweight/obesity, physical inactivity and age and ICU admission was associated with age and BMI. Also, Stafford et al., [17] studied 11,369 of low-risk women across all BMI classes and found the rate of induction and birth weight increased across BMI.

In line with respecting BMI as a determinant factor for decision-making, Gadeer et al., (18) detected a significant association between post-CS wound infection and BMI. Moreover, Otero-Naveiro et al., [19] found obese women showed higher rates of prenatal complications and Stafford et al., [17] reported higher risk of NICU admission with increasing maternal weight class.

Nulliparity was another determinant for decision-making especially for obese nulliparous women and the need for CS showed positive correlation with nulliparity. In line with this finding, Valente et al., [20] found labor induction was significantly more frequent among obese nulliparous women who showed significantly prolonged latent phase and this group of parturient had a significantly higher

rate of CS in comparison to normal weight nulliparous women.

According to the RCS grading of parturient at time of hospital admission, 204 women (36.8% of total number) had to have CS, but of these 76 parturient (13.72%) required elective CS as a first-line decision and 99 parturient had CS after trial of induction, while 29 had vaginal delivery for a success rate of decision-making depending on RCS grade of 85.8%. Such figure for success depended on the inclusion of parity and previous CS as determinant variables of the scoring system as evidenced by the negative significant correlation between nulliparity and positive significant correlation between previous CS and decision to have CS. Interestingly, decision according to RCS showed non-significant correlation with BMI; a finding that point to the possibility of increasing the predictive values of the RCS grading system for the need for elective CS if grades were corrected and adjusted according to BMI.

In line with the necessity of adjustment of RCS classing of parturient according to BMI, Crequit et al., [21] found the overall CS was significantly higher for multipara obese women (Robson group 5) than multipara women without obesity with a significant association between maternal obesity and intrapartum CS. On the other side, Dalbye et al., [3] detected increased risk of intrapartum CS in obese nulliparous women with higher risk of intrapartum CS by increases of obesity class. Moreover, Dalbye et al., [3] found obese nullipara had increased risk of epidural analgesia, use of continuous fetal cardiac monitoring, amniotomy, oxytocin augmentation, obstetric anal sphincter injuries and postpartum hemorrhage, and so concluded that obese women in Ten-Group Classification System group 1 had increased risks of obstetric interventions and maternal complications.

Depending on the obtained data, the outcome of the work undertaken by Alsulami et al., [22] who considered Robson Class 1-4 as low-risk classes for CS and did not take into account the impact of obesity might be inadmissible, because the prevalence of obesity among Saudi women especially those in childbearing period was recently documented in published Saudi literature (23,24).

Conclusion

The Robson Ten-Group Classification System had good negative, but high false positive predictive values for CS. Adjustment of the decision-making for the mode of delivery according to BMI grading within Robson groups significantly reduced the need for CS and thus may improve the decision for augmentation, instrumental and operative delivery.

Recommendation

Multicenter studies for evaluation of the impact of pregnancy-associated diseases on the decision-making for the mode of delivery according to Robson classification.

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