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Acknowledgments

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

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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,

Happy New Year 2020. Very interesting subjects are included in this issue. The importance of treatment of iron deficiency anaemia after bariatric surgery and before pregnancy. There is a remarkable reduction in the level of AMH after laparoscopic cystectomy of endometrioma. The beneficial effect of sildenafil citrate in in pregnancies at high risk for fetal growth restriction. It increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries restoring a normal fetal circulation and corrects the "brain sparing" adaptive mechanism. It is recommended using electrical bipolar vessel sealing clamp during vaginal hysterectomy. It showed less pain on the first few hours after surgery but not in the following days, shorter operative time, less operative blood loss. Mini laparotomy is a suitable option for the management of benign gynecologic conditions in patients with high BMI. Treatment of adolescent PCOS patient with L-carnitine help in regaining regular cycles and proved to be efficient in decreasing BMI. We welcome your comments.

Best regards.

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Bariatric Surgery and Pregnancy deleteriously affect Women's Hematological Milieu. Is Iron Supplemental Therapy may be beneficial?

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Abstract

Objectives: to evaluate the impact of bariatric surgery (BS) on hematological status of women who got pregnant and the effect of iron supplemental therapy (IST) of these impacts.

Patients & Methods: 57 women had previous BS (group B) and 119 women (Group A) had no previous BS were evaluated at 1st trimester for their hemoglobin concentration (HB conc.) and serum levels of ferritin (SF), hepcidin and interleukin-6 (IL-6). Women had iron deficiency anemia (IDA) received IST in the form of sucrosomial oral cap 100 mg once daily. HB conc. and SF were re-evaluated at the 2nd and 3rd trimester and HB deficit was calculated. Study outcome included the impact of IST on frequency and severity of anemia.

Results: HB conc. and SF of all women decreased progressively during pregnancy course with significantly lower estimates in women of group B compared to group A. Frequency of anemic women was significantly higher in group B at the first two trimesters, but was non-significantly higher at 3rd trimester compared to group A, while frequency of women had ID was significantly higher at 1st trimester but was non-significantly higher at the 2nd and 3rd trimesters in group A than group B. At the 3rd trimester, 56 women had increased; while 116 women had decreased HB conc. with significantly higher frequency of women had increased HB conc. among women of group B. Serum hepcidin levels were significantly higher, while serum IL-6 levels were non-significantly higher in women of group B. Percentage of change of HB conc. at 3rd trimester was positively correlated with presence of BS, while negatively correlated with 1st trimester HB conc. and presence of chronic inflammatory anemia. Regression analysis defined presence of CIA, 1st trimester HB conc., the use of IST and previous BS as significant predictors for possible change of HB conc. at the 3rd trimester.

Conclusion: Women had BS were always anemic and had micronutrient deficiencies that must be corrected prior getting pregnant to avoid aggravation. IST started since 1st trimester allowed improvement of anemia especially for women had BS. Sucrosomial oral iron allowed increased HB conc. in 31.8% of studied women.

Keywords: Bariatric surgery, Pregnancy, Anemia, Iron supplemental therapy, Hepcidin, Interleukin-6.

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INTRODUCTION

Obesity originates from an imbalance between caloric intake and energy expenditure that promotes adipose tissue expansion, which is necessary to buffer nutrient excess [1]. Adipose tissue functions as an active endocrine organ, has key role in immunity and inflammation, and type 1 or type 2 immune responses and their respective cytokines have been linked to white or brown adipose tissue, respectively [2].

Obesity is associated with iron deficiency anemia (IDA) [3] and/or chronic inflammatory anemia (CIA) [4]. Bariatric surgery (BS) is considered as the most effective treatment of obesity with long lasting weight loss and improvement of metabolic disorders [5] but BS induces progressive increase of the frequency and severity of IDA, despite of decreasing the frequency of CIA [6].

Anemia is a common problem in obstetrics and perinatal care [7] and is mainly secondary to nutritional deficiencies [8]. Iron deficiency (ID) is the most common micronutrient deficiency worldwide with >20% of women experiencing ID during their reproductive lives [9]. Anemia affects about 50% of pregnant women and is associated with adverse outcomes for mother and child [10]. During pregnancy, trans-placental iron transfer systems include binding transferrin-bound iron to its receptor [11], uptake into an endosome, acidification, release of iron through divalent metal transporter 1 [12], efflux across the basolateral membrane through ferroportin and oxidation to ferrous ion [13].

Iron supplemental therapy (IST) during pregnancy is still a matter of discrepancy [14] because its clinical value for both the mother and newborn is still to some extent unclear [15], despite of the improved maternal hematological indexes [16]. Additionally, how to supply iron is also a matter of debit because high intake of heme iron was found to be associated with high risk of gestational diabetes [17], intolerability of multiple oral iron preparations and the risks and side effects of intravenous iron [18].

Hypothesis

Considering the high prevalence of iron and micronutrient deficiencies among women had BS [6], the prevalence of iron deficiency during pregnancy [10] and the low knowledge among women in childbearing period about the necessity of pre-conception medical evaluation to diagnose and treat deficiencies and systemic diseases [19], the current study hypothesized the necessity of evaluation of these deficiencies in women attending the obstetric outpatient clinic (OUC) for diagnosis or follow-up of pregnancy and the effect of IST during pregnancy on hematological measures.

Objectives

Evaluation of the impact of bariatric surgery (BS) on hematological status of women who got pregnant and the effect of iron supplemental therapy (IST) of these impacts

Design

Comparative prospective multicenter interventional study.

Setting

Gynecology & Obstetrics Department at Benha University Hospital in conjunction with multiple private Obstetric centers and clinical pathology department Benha Univerisity.

Patients & Methods

All pregnant women attending the obstetrics OUC during the 1st trimester were eligible for evaluation for inclusion criteria. Women had previous BS and fulfilling inclusion criteria were grouped as group B, while women had no previous BS were grouped as group A. Inclusion criteria included pregnancy in singleton fetus, no uterine or fetal anomalies, no history of cervical incompetence, free of indications for cesarean section, as previous CS, contracted pelvis, abnormal placental location, signed written fully informed consent to participate the study and to attend follow-up visits. Women had uncontrolled chronic systemic diseases, bleeding tendency, endocrinopathyies, maintained on immunosuppressive therapy or therapies affecting bone marrow health were excluded from the study.

According to **Api et al.** [20] iron deficiency and IDA was diagnosed according to sequential estimation of serum ferritin (SF) concentration and hemoglobin concentration (HB conc.) during the

three trimesters. HB conc. of <11, 10.5 and 11 g/dl during 1st, 2nd and 3rd trimesters, respectively indicates presence of anemia and if coupled with SF< 15 ng/ml indicates IDA but if SF was ≥15 ng/ml this points to an inflammatory state inducing iron stores depletion and indicates CIA [20]. All women with IDA diagnosed at time of enrollment or follow-up visits during 2nd and 3rd trimesters received IST using Sucrosomial Iron (Sideral Forte composed of sucrosomial iron® (Sideral® rm) 30 mg and vitamin C 70 mg; PharmaNutra, Via delle Lenze, Pisa, Italy) 100 mg cap to be taken once daily. Hemoglobin deficit at the 3rd trimester was calculated in relation to HB conc. estimated at time of enrolment was calculated.

Investigations

Venous blood samples (5 ml) were collected from the antecubital vein under complete aseptic conditions at time of enrolment and were divided into three parts:

1. The first part was put in EDTA tube (about 1.8 mg trik EDTA/ 1 ml blood) for at once HB conc. estimation by cyanomethemoglobin method [21].
2. The second part of the sample was kept in a plane container and allowed to clot then serum was separated by centrifugation at 3000 rpm for 10 min. Serum was removed and placed in pyrogen-free Eppendorf tubes and stored at -70°C until ELISA assayed by Spectrophotometer for

   a.Serum ferritin concentration using an ELISA kit from Eagle Bioscience Inc., USA (Catalogue No FER31-K01) [22].

   b.Serum hepcidin level using ELISA kit from Calbiotec, A Life Science Co, USA (Catalogue No DHP250) [23].

   c.Serum IL-6 using ELISA kit from Eagle Bioscience Inc., USA (Catalogue No IL631-K01) [24].

Study outcome

1. Primary outcome is the impact of IST on BS-induced and pregnancy-associated anemia (PAA).
2. Secondary outcome is the relation between serum levels of IL-6 and hepcidin and frequency of ID and IDA and HB deficits.

Statistical analysis

Obtained data were presented as mean±SD, numbers, percentages, median and interquartil range (IQR). Results were analyzed using paired t-test, One-way ANOVA Test and Chi-square test (X2 test). Possible relationships were investigated using Spearman's linear regression analysis. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. 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

The study included 176 pregnant women; 57 had previous BS (group B), while the remaining 119 women (Group A) had no previous BS (Fig. 1).

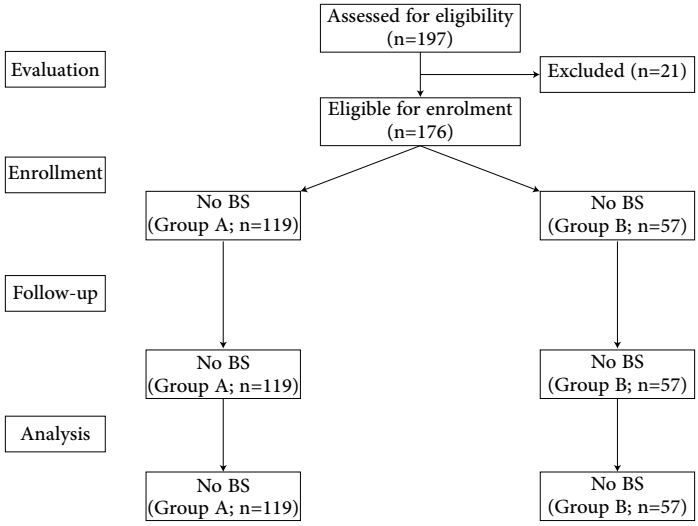

Figure 1: Consort Flow sheet

Women of Group B had significantly higher BMI with higher frequency of women had BMI>30 than women of group A. Moreover, blood pressure measures and fasting blood glucose level estimated at time of enrolment were significantly higher in women of group B compared to women of Group A (Table 1)

Table (1): Patients' data determined at time of enrolment

Data		Group A (n=119)	Group B (n=57)	P value
Age (years)		28±2.6	28.7±2.4	0.086
Body weight (kg)		80.1±5.3	88.9±4.2	<0.001
Height (cm)		169±3.4	168.2±3.4	0.729
Body mass index (kg/m^2)	<30	110 (92.4%)	38 (66.7%)	<0.001
	>30	9 (7.6%)	19 (33.3%)	
	Mean (±SD)	28.1±2	31.4±1.6	<0.001
Gravidity		2.2±0.8	2.1±0.8	0.328
Parity		1.2±0.8	1±0.8	0.119
Blood pressure (mmHg)	Systolic	115.6±4.6	119.6±8.9	0.013
	Diastolic	73.1±6.1	76.2±10.6	0.015
Fasting blood glucose (mg/dl)		108±11.5	115±7.5	0.023

Data are presented as mean±SD, numbers, percentages

HB conc. of women of group A showed progressive and significant decrease during pregnancy, while in group B, HB conc. was non-significantly higher at the 3rd trimester compared to at 1st and 2nd trimesters despite of being significantly lower than HB conc. estimated in women group A during pregnancy course (Fig. 2). On contrary, estimated levels of serum ferritin (SF) showed progressive and significant decrease in patients of both groups throughout pregnancy course with significantly lower SF levels in patients of group B than patients of group A at 1st trimester, but the difference was non-significant at the 2nd and 3rd trimester estimations. The frequency of anemic women was significantly higher in group B at the 1st and 2nd trimesters, but was non-significantly higher at the 3rd trimester compared to group A (Fig. 2). On contrary, the frequency of women had ID with SF level of <15 ng/ml was significantly higher at the 1st trimester, but was non-significantly higher at the 2nd and 3rd trimesters in women of group A than women of group B (Table 2, Fig. 3).

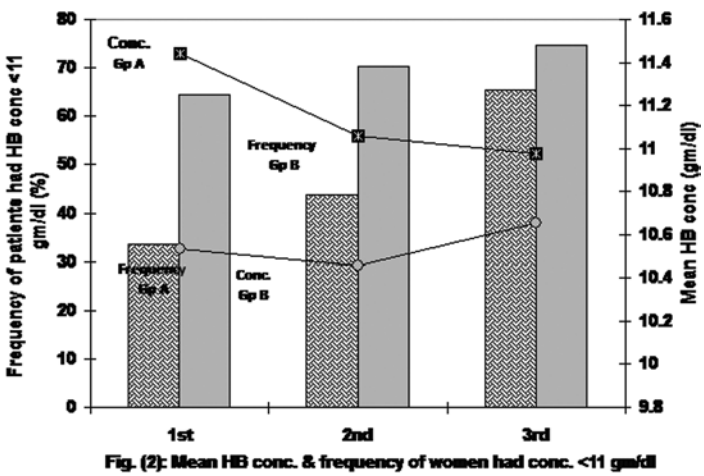

Fig. (2): Mean HB conc. & frequency of women had conc. <11 gm/dl in both groups during pregnancy

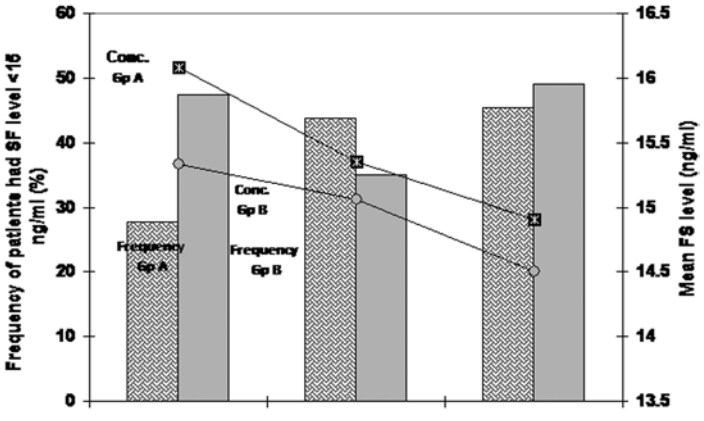

Fig. (3): Mean serum ferritin (SF) level & frequency of women had SF level <15 ng/ml in both groups during pregnancy

During course of pregnancy, 89, 67 and 36 women had no anemia/ID, at 1st, 2nd and 3rd trimesters, respectively with significantly higher frequency among women of group A at 1st and 2nd compared to women of group B, but the difference became non-significant at the 3rd trimester. Interestingly, at 3rd trimester, 56 women (31.8%) had increased; while 116 women (65.9%) had decreased HB conc. in relation to 1st trimester level and only 4 women (2.3%) had stable HB conc. with significantly higher frequency of women had increased HB conc. among women of group B. Moreover, the median value of change was -6.1 and 0.935 for women of groups A and B, respectively (Table 2). Serum hepcidin levels were significantly higher, while serum IL-6 levels were non-significantly higher in women of group B compared to women of group A (Table 2, Fig. 4)

Table (2): Laboratory findings of women of both groups determined during course of pregnancy

Time			Group A (n=119)	Group B (n=57)	P value
1st trimester	HB conc. (gm/dl)	<11	40 (33.6%)	37 (64.5%)	0.0009
		>11	79 (66.4%)	20 (35.5%)	
		Mean (±SD)	11.4±1	10.5±1.25	0.0002
	SF (ng/ml)	<15	33 (27.7%)	27 (47.4%)	0.011
		>15	86 (72.3%)	30 (52.6%)	
		Mean (±SD)	16.08±1.65	15.33±1.71	0.0061
	IDA		27 (22.7%)	23 (40.4%)	0.0005
	CIA		13 (10.9%)	14 (24.6%)	
	ID		6 (5%)	4 (7%)	
	No anemia/ID		73 (61.4%)	16 (28%)	
	Serum Hepcidin (ng/ml)		20.9±4.8	25±5.8	0.0007
	Serum IL-6 (ng/ml)		38.8±13.4	42.8±12	0.053
2nd trimester	HB conc. (gm/dl)	<11 gm	52 (43.7%)	40 (70.2%)	0.001
		>11 gm	67 (56.3%)	17 (28.8%)	
		Mean (±SD)	11.1±0.88	10.5±0.9	0.0009
	SF (ng/ml)	<15	43 (43.7%)	20 (35.1%)	0.277
		>15	76 (56.3%)	37 (64.9%)	
		Mean (±SD)	15.35±1.6	15.06±1.54	0.255
	IDA		35 (29.4%)	29 (50.9%)	0.0008
	CIA		17 (14.3%)	11 (19.3%)	
	ID		8 (6.7%)	9 (15.8%)	
	No anemia/ID		59 (49.6%)	8 (14%)	
3rd trimester	HB conc. (gm/dl)	<11 gm	78 (65.5%)	44 (74.6%)	0.117
		>11 gm	41 (34.5%)	13 (25.4%)	
		Mean (±SD)	10.9±0.9	10.65±0.58	0.028
	SF (ng/ml)	<15	54 (45.4%)	28 (49.1%)	0.641
		>15	65 (54.6%)	29 (50.9%)	
		Mean (±SD)	14.9±1.52	14.5±1.59	0.186
	IDA		41 (34.5%)	23 (40.4%)	0.453
	CIA		37 (31.1%)	21 (36.8%)	
	ID		13 (10.9%)	5 (8.8%)	
	No anemia/ID		28 (23.5%)	8 (14%)	
HB change at 3rd trimester in relation to 1st trimester		Increased	25 (21%)	31 (54.3%)	0.0005
		No change	3 (2.5%)	1 (1.8%)	
		Decreased	91 (76.5%)	25 (43.9%)	
		Median (IQR)	-6.1 (31.959)	0.935 (32.918)	0.0001

Data are presented as mean±SD, numbers, percentages, median, IQR: Interquartile range; HB: Hemoglobin; SF: Serum ferritin; IDA: Iron deficiency anemia (indicates HB conc. <11 gm/dl & SF <15 ng/ml); ID: Iron deficiency (indicates SF <15 ng/ml); CIA: Chronic inflammatory anemia; CIA indicates HB conc. <11 gm/dl & SF >15 ng/ml; No anemia/ID indicates HB conc. >11 gm/dl & SF >15 ng/ml

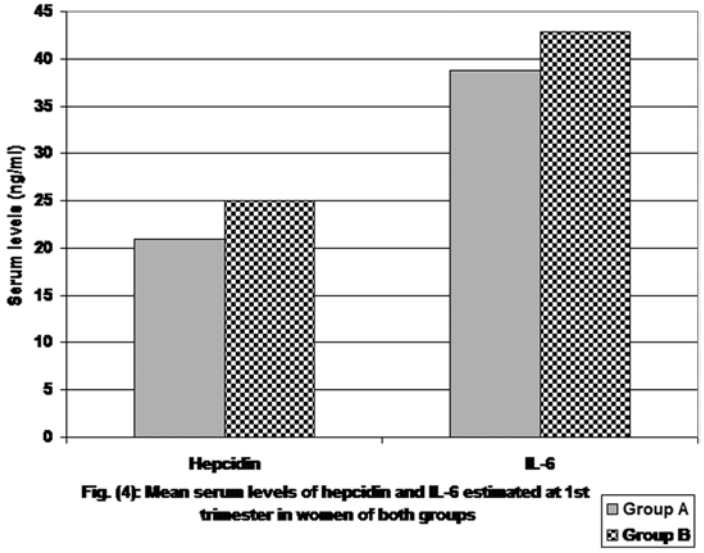

Fig. (4): Mean serum levels of hepcidin and IL-6 estimated at 1st trimester in women of both groups

Spearman correlation analysis showed a negative significant correlation between previous BS and HB conc. (Rho=-0.335, p<0.001) and SF (Rho=-0.208, p=0.006), while showed positive significant correlation with presence of chronic inflammatory anemia (Rho=0.177, p=0.019). Percentage of change of HB conc. at the 3rd trimester showed positive significant correlation with presence of previous BS, while showed negative significant correlation with HB conc. at 1st trimester and with the presence of CIA. Elevated serum hepcidin and IL-6 levels were positively correlated (Rho=0.628, p<0.001) and both showed positive significant correlation with presence of CIA (Rho=0.544 & 0.542, p<0.001), while showed negative significant correlation with HB conc at 1st trimester (Rho= -0.681 & -0.604, p<0.001). Previous BS showed positive correlation with elevated serum hepcidin (Rho=0.348, p<0.001) and IL-6 (Rho=0.137, p=0.069), (Table 3). Regression analysis defined presence of CIA (β:-0.662, p<0.001), HB conc. estimated at 1st trimester (β:-0.280, p<0.001), the use of IST (β: 0.404, p<0.001) and previous BS (β: 0.203, p<0.001) as significant predictors for possible change of HB conc. at the 3rd trimester.

Table (3): Spearman correlation between studied variables

Variables	Bariatric surgery		HB conc.		Hp		CIS anemia	
	Rho	p	Rho	p	Rho	p	Rho	p
HB conc.	-0.335	<0.001					-0.423	
SF	-0.208	0.006	0.606	<0.001	-0.405	<0.001	-0.308	<0.001
Hepcidin	0.348	<0.001	-0.681	<0.001			0.544	<0.001
IL-6	0.137	0.069	-0.604	<0.001	0.628	<0.001	0.542	<0.001
CIS anemia	0.177	0.019						
% of HB change at 3rd trimester	0.295	<0.001	-0.315	<0.001	0.169	0.103	-0.423	<0.001

HB: Hemoglobin; SF: Serum ferritin; Hp: Hepcidin, IL-6: Interleukin-6; CIS: Chronic inflammatory state

Discussion

Bariatric surgery had negative impact on patients' iron status as manifested by the significantly higher number of patients had iron deficiency anemia (IDA) with significantly lower HB conc. and serum ferritin (SF), at 1st trimester, in women had BS than control women. These results coincided with recent studies reported that iron deficiency (ID) is frequent in obese people and exacerbates by bariatric surgery [6, 25] and that reported a risk for cumulative iron, vitamin B_{12} deficiency, and anemia of 20%, 48%, and 28%, respectively after BS [26], irrespective of the undertaken surgical procedure [27].

Moreover, women who had BS had higher frequency of chronic inflammatory anemia (CIA) with significantly higher serum levels of hepcidin than control women. On the other hand, there was non-significant difference between serum IL-6 levels estimated at 1st trimester between women of both groups; a finding indicating ameliorating effect of BS on the obesity-induced inflammatory state. These results go in hand with **Coimbra et al**. [28] who found weight loss after BS is associated with an improvement in inflammation with reduction in IL-6 serum levels and **Hohensinner et al.** [29] who reported decreased serum levels of CRP and IL-6 by 83% and 55%, respectively, after BS. Also, **Askarpour et al.** [30] out of systemic review of published literature documented that BS significantly lowered serum levels of inflammatory factors; CRP, IL-6 and TNF-α.

Pregnancy also imposed a deleterious effects on patients' hematological milieu as manifested by the progressively increasing number of anemic women on the 2nd (109/176) and 3rd (140/176) trimester compared to number of anemic women determined at 1st trimester (87/176). In support of this finding, multiple recent studies documented that the prevalence of anemia in pregnant women at the 2nd and 3rd trimesters of pregnancy was higher than that at 1st trimester of pregnancy [31, 32, 33].

Interestingly, the number of patients had inflammatory anemia was 2-fold higher at the 3rd trimester than its number at 1st and 2nd trimesters. This finding indicated that pregnancy induced anemia of inflammatory state that may be attributed to iron delocalization despite of cellular/tissue overload [34] or to increased levels of inflammatory cytokines that shorten erythrocyte lifespan by activating macrophages through Toll-like receptor activation [35], prioritize leukocyte production in the marrow, and induce hepcidin to increase plasma transferrin saturation and the concentration of non-transferrin-bound iron [36].

These data points to the vicious circle affecting pregnant women who had BS where on one-side; obesity initiates a low-grade inflammatory status [37] with high hepcidin [38] and inflammatory cytokines serum levels [39, 40] with aggravation of iron and micronutrient deficiency [6, 25, 26] and also hepcidin reduces iron utilization thus aggravating the already present IDA (38). On the other side, pregnancy also induces a state of low-grade inflammation and depletion of maternal iron stores to fulfill fetal requirements [41] leading to aggrevation of both CIA and IDA.

Iron supplemental therapy provided since 1st trimester did well for the studied population of pregnant women; especially those had bariatric surgery as manifested by the increased HB conc. at the 3rd trimester compared to 1st trimester concentration and by the significantly higher number of women who developed increased HB conc. than control women. These findings illustrated the need of patients had bariatric surgery to supplemental iron therapy and go in hand with previous studies evaluated the supplemental therapy for patients had bariatric surgeries [42, 43, 44].

The IST was provided as sucrosomial oral iron for its unique structural, physicochemical and pharmacokinetic characteristics, together with high iron bioavailability and excellent gastrointestinal tolerance [45]. Unfortunately, no previous studies evaluated the use of sucrosomial oral iron for correction of pregnancy-induced anemia, however, the efficacy and safety of sucrosomial iron was approved experimentally where increased bone marrow iron availability was detected 5-hr after single dose of sucrosomial [46] and it was found to provide absorption pharomacodynamics similar to ferrous sulfate without inducing inflammatory responses [47]. Clinically, sucrosomial oral iron provides increases in HB levels and response similar to intravenous iron in cancer patients, but with higher tolerability and without risks or side effects [48]. Also, sucrosomial oral iron can provide iron effectively even in difficult-to-treat populations especially patients with IDA, inflammatory bowel disease and iron sulfate intolerance [49, 50]. Moreover, sucrosomial oral iron was used as effective alternative to parenteral iron after bariatric surgery [51].

Conclusion

Women had BS were always anemic and had micronutrient deficiencies that must be corrected prior getting pregnant to avoid aggravation of their disturbed hematological milieu. Iron supplemental therapy started since 1st trimester allowed improvement of anemia especially for women had BS for being in more need for IST. sucrosomial oral iron is appropriate form for IST that allowed increased HB conc. in 31.8% of studied women. Wider scale comparative studies are mandatory to establish the efficacy of sucrosomial oral iron than other forms of IST.

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Does Ovarian Reserve Change after Endometrioma Management? Comparison of Two Treatment Regimens

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Abstract

Background: The endometriosis-mediated damage to ovarian reserve beyond the stretching of ovarian cortex that can lead to loss of primordial follicles is supported by many studies.Laparoscopy represents the first-line treatment in sub fertile women with endometriotic ovarian cysts. The primary benefit of surgical treatment of endometriosis is the relief o f pelvic pain. The effect of laparoscopic cystectomy of an endometrioma on the antral follicle count has been conflicting.

Objective: is to estimate effects of laparoscopic ovarian cystectomy on ovarian reserve and ICSI outcome.

Methodology: 100 patients with unilateral ovarian endometrioma (size from 2.5-5 cm) were selected for ICSI, divided into two equal groups, group1 (underwent laparoscopic cystectomy) and group2 (underwent ultrasound guided cyst aspiration). Both groups were compared regarding ICSI outcome (number of oocytes, number of embryos transferred, pregnancy rate) as well as change in AMH as a marker of ovarian reserve 6 months after the procedures. Outcome measures: the outcomes were the ovarian reserve changes after the two procedures as well as the Intracytoplasmic Sperm Injection outcomes.

Results: There is a remarkable reduction in the level of AMH in group1(43% reduction) compared to group2 (5.7%) with no significance (P=0.393).

Conclusion: In view of the hazardous effect of laparoscopic ovarian cystectomy on ovarian reserve, ultrasound guided aspiration may be a good alternative procedure for treatment of endometrioma in view of preserving the ovarian tissues without compromising ICSI outcomes.

INTRODUCTION

The pathogenesis of typical ovarian endometriosis is a source of controversy. Hughesdon demonstrated, by serial section of ovaries containing an endometrioma, that 90% of typical endometriomas are formed by invagination of the cortex after the accumulation of menstrual debris from bleeding of endometrial implants, which are located on the ovarian surface and adherent to the peritoneum [1].

It was recently demonstrated that decreased follicular density, associated fibrosis, and deterioration of normal structure of ovarian cortex in ovaries that are affected by endometriomas[2]

The endometriomas themselves are the cause of diminished ovarian

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reserve in women with endometriosis. Deterioration of ovarian reserve may precede surgery and destructive surgery may exacerbate their reproductive potential further [2]

Endometriomas often present on ultrasound as cystic structures with low-level homogenous internal echoes consistent with old blood, and occasional thick septations, thickened walls, and echogenic wall foci [3]

Laparoscopy is the gold standard for the diagnosis of endometriosis[4]

In addition to perfect diagnosis of endometrioma, laparoscopy can identify the pelvic endometriosis that could not be diagnosed by ultrasound. However, laparoscopy is an invasive technique.

Whether the presence of endometrioma affecting the oocyte quality or not is a matter of controversy. In the study by Filippi et al., they showed that the presence of ovarian endometrioma does not affect oocyte quality[5]

Despite that, and in view of the follicular number, several studies have shown that there is a loss of follicular density in ovaries with endometriomas compared with unaffected ovaries [6],[7]

Many publications have raised concern over the deleterious effects of laparoscopic ovarian cystectomy on ovarian reserve, specifically as reflected by anti-Mullerian hormone (AMH) levels [8]

Ultrasound guided aspiration of endometriomas has an application in patients who are not good surgical candidates or who have experienced in vitro fertilization (IVF) failure, it is considered relatively safe and noninvasive [9]

Even in patients who are good surgical candidates for laparoscopy, this study was conducted to test the hypothetical value of ultrasound guided cyst aspiration as an alternative option for laparoscopic cystectomy in view of preserving the ovarian tissue without compromising the intra cytoplasmic sperm injection (ICSI) outcome.

Methodology

This is a retrospective cohort study that performed in ART unit, Al-Azhar University and including 100 patients with endometrioma and indicated for ICSI in the period from July 2013 to September 2015. They were divided into two equal groups, group1 (no.=50 patients) underwent laparoscopic ovarian cystectomy (LC) and group2 (no.=50 patients) underwent ultrasound guided aspiration followed by a proper antibiotic to guard against pelvic infection. The study was approved by the University Medical Ethical Committee. The patients have the following criteria:

Inclusion criteria

- Patients age less than 35 years,
- Body mass index (BMI) ≤30
- Unilateral endometrioma with size between 2.5 – 5 cm.
- Basal hormonal levels of FSH, LH in the early follicular phase of < 10 IU

Exclusion criteria

- Patient with other pelvic pathology as uterine myoma or other ovarian cysts.
- Patients with history of previous ovarian surgery or exposure to radiation or chemotherapy for malignant conditions.

In group I, under general anesthesia, laparoscopic cystectomy was performed at midcycle(KARL STORZ SE & Co. KG, Tuttlingen, Germany).After inspection of the intra-abdominal area and obtaining peritoneal washing, mobilization of the ovaries was done. The utero-ovarian ligament is taken with a 5-mm atraumatic grasper. Lysis of the adhesions is performed with the use of sharp dissection to fully mobilize the ovaries. Adhesiolysis was performed by scissor and in some cases cauterization with scissor was needed. In most cases, the cyst was ruptured during mobilization of the ovary, which required the liquid to be aspirated immediately to prevent pelvic contamination .The cysts were enucleated with their capsules (with cauterization of the bleeding points by bipolar electrocautery when needed). Ovarian stimulation was conducted in the next cycle.

In group II, and after intravenous sedoanalgesia using a combination of 25 mg of pethidine hydrochloride and 50 mg of fentanyl,ultrasound guided cyst aspiration(using Cook aspiration needle 16 gage ,30 cm length, single lumen needle,Cook Group Company,Indiana,USA)and under 200 mm Hg negative vacuum pressure was carried out premenstrual just before stimulation.

Ovarian stimulation: Patients in both groups were received short protocol with short acting s.cGnRH agonist (0.1 mg triptoline) daily starting from the first day of the cycle. 225 IU of recombinant fsh (rec.fsh) was administered from the second day of the cycle. Treatment with rec-fsh and GnRH agonist continued daily. The dose of stimulation was adjusted after Day 5 of stimulation, depending on the ovarian response, as assessed by estradiol (E2) levels and ultrasound. As soon as at least three follicles reached a mean diameter of >17 mm, 10000 IU of human chorionic gonadotrophin (hCG) was administered i.m.

Oocyte retrieval, embryo transfer, luteal support: Oocyte retrieval was performed 35-36 hours after the hCG injection by transvaginal ultrasound-guided double lumen needle aspiration under 100 mm Hg vacuum pressure. Ultrasound guidance was used for all embryos transfer, which was performed 2 or 3-days post-oocyte retrieval. Oocyte quality and embryo grading were determined.

Ultrasound and laboratory assays: All ultrasound measurements were performed using a 7.5 or 6 or 5 MHz vaginal probe. AMH, FSH, LH, E2 and prolactin levels were measured at the preceding cycle day2 using ELFA technique (Enzyme linked Fluorescent Assay, VidasBiomerieux) and AMH was repeated 6 months after the procedure in both groups for the non-pregnant cases

Outcome measures: the primary outcome measure was the ovarian reserve changes presented by the changes in estimated AMH levels in both groups. Secondary outcome measures were the clinical pregnancy rate per patient randomized, numbers of oocytes retrieved, number of metaphase II oocytes, fertilization rate, pregnancy rate and recurrence rate. AMH was measured before the procedures and 6 months after the ICSI trials for non-pregnant cases.Data was collected and refined using Microsoft Excel 2013 (Microsoft Corporation, USA).Data were analyzed using the Statistical Program for Social Science (IBM SPSS Statistics 20). Quantitative data were presented by mean± standard deviation (SD) and qualitative data were presented by frequency and percentage. P value was considered significant if < 0.05.Student-t test was used for estimating the difference between 2 independent quantitative samples .Chi-square test was used for comparison of qualitative data. Sample size was calculated using Epi-info 7 for Windows with the power of the study =80%, the level of significant to be 5% and the effect size that gave the minimal clinical difference reported from previous reviews.

Results

Table (1): The basal characteristics of the studied patients.

	Group I (n = 50)		Group II (n= 50)		
	Mean	**±SD**	**Mean**	**±SD**	**p-value***
Age (years)	29.8	3.1	29	3.9	0.326
BMI	28.1	2.1	27.3	2.8	0.088
FSH	5.6	1.6	6.2	2.4	0.175
AMH	3.2	0.8	3.5	0.6	0.814
LH	4.2	1.7	4.5	2.1	0.400
re FSH dose	3625	1299.3	3423	1168.6	0.416
Duration of stimulation	10	2	10	1.6	0.869

*Independent Sample t-test was used for comparison between quantitative variables.

This table shows no statistically significant difference between groups according to age, BMI. Basal hormones (FSH and LH), re FSH dose and duration of stimulation

Table (2) Comparisons between both groups regarding the secondary outcomes.

Parameter	Group1	Group2	P-value
Number of oocytes retrieved(mean ±SD)	6.7± 2.7	5±2.8[1]	**0.003***
Number of MII oocytes(mean ±SD)	2.8± 1	1.9±0.7	**0.370**
Number of Embryos transferred(mean ±SD)	1.8± 0.7	1.7± 0.9	**0.750**
Fertilization rate (%)	53.1%	50%[2]	**0.857**
Pregnancy rate (%)	34%(17/50)	38% (19/50)	**0.842**
Recurrence rate (%)	12%(4/33)	38%(12/31)	**0.6292**

[1] Independent Sample t-test was used for comparison between quantitative variables.
[2] Chi-square test was used for comparison between qualitative variables.
*The level of significance if p-value ≤.05

There is statistically significant differences between groups in view of number of Oocytes retrieved, it is higher in group 1 than 2.On the other hand there are no statistically significant differences between groups in view of number of MII oocytes, number of embryos transferred, fertilization, pregnancy and recurrence rates.

Table (3): The levels of AMH estimated in the same group before and after procedures.

AMH	Before procedure	After procedure	P-value*
Group I (laparoscopic ovarian cystectomy) (no=33)	3.2± 0.8	1.8±0.6	0.394
Group II (ultrasound guided cyst aspiration) (no=31)	3.5 ± 0.6	3.3 ± 0.9	0.842

*Paired t-test was used for comparison

There is no statistically significant difference according to (AMH) estimated before and after procedure in both groups with (mean ±SD 3.2±0.8 vs 1.8±0.6 with p =0.394) for group1 and (mean ±SD 3.5±0.6 vs 3.3±0.9 with p =0.842) for group2.

From the above table we can calculate the reduction rate for AMH in both groups as shown in figure(1).

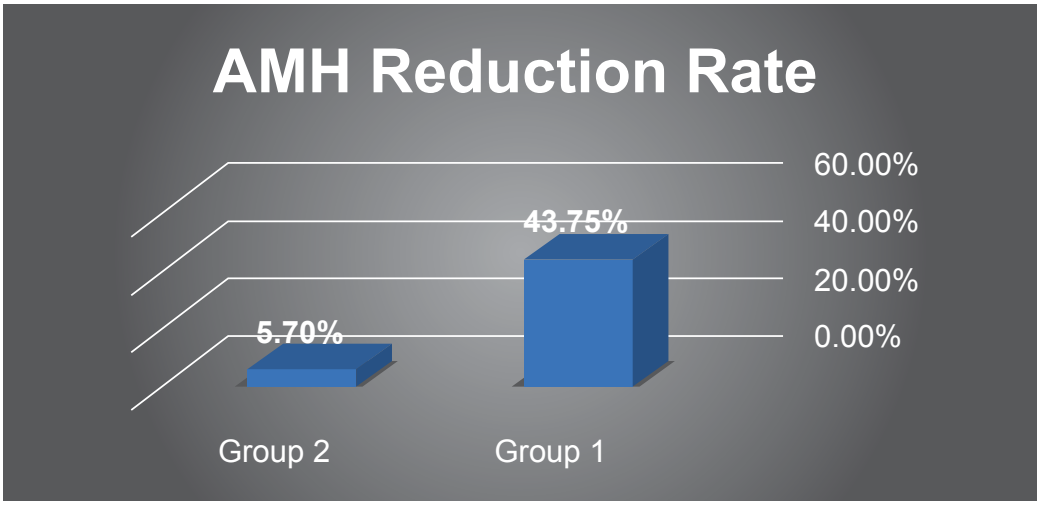

Figure (1): Bar chart presents AMH reduction rate in both groups, 6 months after the ICSI trials in non-pregnant cases.

The reduction rate was calculated by estimating the change in AMH levels before and after the procedures in both groups.

Table (4) comparison of AMH (in both groups) estimated 6 months after the procedures.

Parameter	Group1(no.=20)	Group2(no.=22)	P-value*
AMH (mean ±SD)	1.8±0.6	3.3 ± 0.9	**.187**

*Independent sample t-test was used for comparison.

There is no statistically significant difference between the two groups in view of the levels of AMH estimated after procedures, with p-value =0.187

Discussion

The detrimental effects with endometriosis-associated infertility patients offered ART present poor ovarian response [10], [11] ,lower fertilization rates[11] ,[12], decreased endometrial receptivity [13], and poor implantation rates[14]. It has also been suggested that oocyte and embryo quality [15],may be compromised in patients with endometriosis. It has also been reported that the incidence of aneuploidy is significantly higher in patients with endometriosis [16]

This study was designed to evaluate the ovarian reserve changes after two treatment regimens for 100 patients with ovarian endometrioma with sizes from 2.5-5cm (laparoscopic ovarian cystectomy, and ultrasound guided cyst aspiration) in addition to the estimation of outcomes of ICSI.Patients with endometrioma>5 cm was excluded from the study because of the higher recurrence rate reported by many studies.

Two groups were compared (50 patients in each group) and the data was analyzed anonymously.

The study showsno significant difference between groups in view of the basal characteristics (Age,BMI, FSH,AMH, LH, stimulation dose, duration of stimulation).

There is a significant difference between both groups in view of the numbers of oocytes retrieved(mean ±SD 6.6±2.7.and 5.0. ± 2.8 with P-value=0.0.03).This is may be explained by the relieve in the ovarian tissue produced by the excision of the cyst that allow the ovary to be more responsive and not compromised by the recurrent cysts or the remaining endometrial tissues.However, there is no significant difference between both groups in view of Oocyte quality (mean ±SD 2.8±1.and 1.9. ± 0.7 with P-value=0.370), for numbers of metaphase II (MII) Oocytes in group1 and group 2 respectively.

In addition to that, the study reported no significant difference between groupsin view of the numbers ofembryos transferred(mean ±SD 1.8±0.7.and 1.7± 0.9 with P-value=0.0.455), in both groups. The pregnancy rates did not differ significantly between the two groups (34% versus 38% with P-value=0.677).

For that, the need for effective treatment that can eliminate the associated negative effect of endometriomas on the ovaries as well as relieving the distressing symptoms associated with them i.e. dysmenorrhea, dyspareunia and non-menstrual pelvic pains is of mandate.

Surgery for the ovarian endometrioma is efficacious when pain or infertility is present [17]

Many studies consider Laparoscopy as the gold standard for treatment of ovarian endometriomasin many aspects associated with a shorter hospital stay, faster patients' recovery, decreased costs and a lower incidence of post-operative adhesion formation.

The presumptive benefit of LC to reduce or reverse the inherently damaging effects of endometriomas on the ovarian cortex is more controversial. The endometriosis-mediated damage to ovarian reserve beyond the stretching of ovarian cortex can lead to loss of primordial follicles[18]

Despite that, electrocoagulation after laparoscopic excision of ovarian cysts is associated with a statistically significant reduction in ovarian reserve, which is partly a consequence of the damage to the ovarian vascular system [19]

Because the preservation of the vascular blood supply to the ovary is vital for the preservation of ovarian volume and antral follicular counts. Meticulous surgical techniques, avoiding the compromise of ovarian blood supply and healthy ovarian tissue are of great importance.

In the study by Donnez et al, they described a new mixed technique for the laparoscopic management of endometriomas that can preserve the damaging effects following the removal of endometrioma, summarized in the following steps:

1. The endometrial cyst is opened and washed out with irrigation.
2. The inner lining of the cyst is stripped from the normal ovarian tissue.
3. If the excision provokes bleeding, or if the plane of cleavage is not clearly visible, the cystectomy is stopped because of the risk of removing normal ovarian tissue containing primordial, primary, and secondary follicles along with the endometrioma.
4. The cyst wall should be removed up to the hilus (partial cystectomy)
5. CO2 laser is used to vaporize the remaining 10%–20% of the endometrioma close to the hilus.
6. Don't close the ovary after the operation[20]

The possibility of a reduced ovarian reserve should be discussed with the patient, but this issue should not however change the well-defined indications for surgery.

The advantages of U/S guided aspiration of endometriomas, it is easily performed, and patients can return to normal activities shortly following the procedure [21]

In agreement with the results of the current study except for the number of oocytes retrieved, a meta-analysis by *Tsoumpou et al.,* found no significant difference in the dosage of gonadotropins used, oocytes retrieved, embryos available for transfer, or clinical pregnancy rates between ultrasound guided cyst aspiration and surgical intervention[22]

In a study by *Hamdan et al*, includedwomen with endometrioma underwent laparoscopic cystectomy compared with who had transvaginal aspiration. They reported that women had a similarclinical pregnancy rate (CPR)and similar total (FSH dose)[23].This also matched with the results of the current study.

In contrary to the results of this study, a prospective study comparing operated and aspirated ovaries in women who previously underwent laparoscopic cystectomy of endometriomas, Ragni et al., did find a lower number of developing oocytes and retrieved oocytes from the operated ovary. However, there was no difference in fertilization rates or high-quality embryos in these women [24]

AMH is considered the most reliable non-invasive methods of ovarian reserve evaluation [25].In the meta-analysis performed by ***Raffi et al.*** 2012[26] a statistically significant fall of 38% for AMH levels was reported after excisional surgery, with a weighted mean difference of −1.13 ng/ml

In the current study, AMH was measured before and 6 months after the procedures to allow for complete resolution and restoration of the ovarian functions, so the comparison could be meaningful. After exclusion of pregnant cases in both groups, the number of patients who submitted to follow up by AMH level estimation were 33 cases in *group 1* and 31 cases in *group 2*.

There is a non-significant difference in means of AMH estimated before ICSI and 6 months after (means ± SD, 3.2± 0.8 Vs 1.8±0.6 with p-value=0.394) after LC.

Also after ultrasound guided cyst aspiration, there is a non-significant difference in means of AMH estimated before ICSI and 6 months after, (means ± SD, 3.5 ±0.6 vs 3.3 ± 0.9 with p=0.842).

There is a great reduction in the level of AMH in group1(43.75% reduction) if compared to the reduction in group2 (5.7%) with no statistically significant difference (P =0.393). The non-significant difference may be explained by the low number of cases in both groups who were submitted to follow up.

Whether this reduction is consistent and true is a matter of controversy. Rustamov et al reported that the association between surgery and decreased ovarian reserve as evaluated by AMH,is still inconclusive[27]

Muzii et al, ***2011***, [28]alsoreported that the damage to ovarian tissue is already present before surgery due to the disease itself, and not due to the surgical procedure.

Systematic reviews on AMH as a marker for the reduced ovarian reserve have highlighted the heterogeneity of the published studies and the difficulty in pooling the data[26]

In addition to that, AMH may reflect an immediate insult to the residual ovarian tissue after surgery, which sums up with the ovarian damage provoked by the endometrioma itself[29]

Although, the risk of surgery on endometrioma is rising, it may be to a certain extent, only temporary, and, in fact, a partial recovery has been reported by some authors at longer follow-up times[30]

AMH may recover 3 months postoperatively or may be sustained up to 6 months, even in the hands of experienced laparoscopic surgeons[31]

In a contradiction to the above studies, Uncu et al. demonstrated that surgical excision of endometriomas leads to a decline in AMH that appears progressive[32]

Recurrence rates among both groups after 6 months were 12 % (4 cases out of 33) for group1 and 38 % (12 cases out of 31) for group2 with P-value=0.0.6292) without significant difference between both groups.

This recurrence may be explained by incomplete removal of the cyst bed or with high grades of endometriosis or effect of ovarian stimulation in both groups.

The main problem related to the cyst aspiration is the high rate of recurrence following the procedure. For prevention of the recurrence, measures in the form of post-operative hormonal therapy was suggested by many authors, but the results were inconclusive as reported by the study of Sesti et al 2009[33]

Recurrent endometriomas, as detected by TVS, can remain asymptomatic and do not necessarily progress in size with or without medical treatment. The decision to re-operate depends less on the endometrioma's size than on symptoms. However, such patients are also more likely to have signs of deep nodules and adnexal/bowel adhesions and larger endometriomas on TVS scan, thus predisposing them to require a second procedure [34].

In spite of all these results, debate will continue regarding the decision for endometrioma management especially that with sizes more than 3 cm. We think that this debate is logic and may be explained by the differences in patients´ history, symptoms and indications for treatment. All these factors should be taken in considerations before decision. We think that large randomized controlled trials in the futures with further reviewing may give an evidence that may resolve this conflict. Also the pain assessment after both procedures should be discussed in the future studies because it may give a good hint about which procedure may be superior in view of symptoms management.

Conclusion

The oocyte yield after laparoscopic cystectomy for endometrioma is shown to be significantly better than ultrasound guided cyst aspiration. Also the tragic effect of laparoscopic ovarian cystectomy on ovarian reserve is not evident and more clinical trials were recommended to evaluate this effect. However, the cyst aspiration may be a good alternative tool that can replace the laparoscopic cystectomy, in view of preservation of ovarian tissues without compromising the ICSI outcomes.

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Effects of sildenafil citrate on impedance to flow in the umbilical and fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction

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Objective:

To assess whether sildenafil citrate improves blood flow in fetal umbilical arteries and middle cerebral arteries in pregnancies at high risk for fetal growth restriction.

Methods:

A quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital in Ismailia over the period from June 2017 to April 2018. Trans-abdominal obstetric ultrasonography (U/S) was done for 30 pregnant women aged24 to 35 years, gestational age ranged between 33- 36 weeks, at high risk for fetal growth restriction (mild pre-eclampsia, diabetes mellitus, history of previous pregnancy with a small for gestational age, stillbirth, severe pre-eclampsia or pregnancies with abnormal umbilical artery indices-above 90th centile). Fetal umbilical and middle cerebral artery blood flow Doppler indices were determined before and 2 and 6 hours after ingestion of sildenafil citrate 20 mg tablet.

Results:

There was a statistically significant decrease in umbilical artery Doppler indices before, two hours and six hours following sildenafil citrate therapy in the studied patients ($P<0.05$) and a statistically significant increase in middle cerebral artery Doppler indices before, two hours and six hours following sildenafil citrate therapy in the studied patients ($P<0.05$).

Conclusions:

Sildenafil citrate significantly increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction thereby restoring a normal fetal circulation and corrects the "brain sparing" adaptive mechanism.

Key words:

Sildenafil citrate, FGR, High-risk pregnancy, Doppler ultrasound, Umbilical artery, iddle Cerebral Artery

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INTRODUCTION

Excluding fetal anomalies, after prematurity, fetal growth restriction (FGR) is the second common cause of perinatal morbidity. It has been long recognized that in preeclampsia, a severe maternal endothelial dysfunction must be identical placental pathology to that underlying fetal growth restriction. Pregnancies with fetal growth restriction are associated with elevated peripheral resistance in the maternal arterial system as seen in pregnancies with preeclampsia[1], [2].

Several maternal demographic factors have been associated with FGR as maternal race, lower socioeconomic status, and living in a developing country also smoking in pregnancy is associated with a 3.5-fold increased risk of SGA compared with nonsmokers. Up to 19 % of term low birth weight (LBW) has been attributed to smoking during pregnancy. Fetal factors can vary from genetic causes, congenital malformations, fetal infection, or other causes, including multiple pregnancies. Placental insufficiency accounts for many cases of FGR and can affect up to 3 % or more of all pregnancies. The pathogenesis of FGR is not well defined; defects in the placental circulation and transport can affect the nutrient transport to the fetus, resulting in FGR. The relative decrease in placental mass and function can result in the development of FGR[3]–[5].

A fetus with FGR may be born small for gestational age (SGA) or appropriate for gestational age (AGA) according to population reference charts. Additionally, in developing countries, there is a direct correlation between the incidence of low birth weight (<2500 g) and FGR because in developing countries, the high incidence of low-birth-weight (LBW) infants is almost exclusively due to the incidence of FGR. Data from developed countries show the opposite, rates of low birth weight being explained almost exclusively by prematurity rates[6], [7].

Sildenafil citrate is a selective inhibitor of cyclic guanosine mono phosphate (cGMP)–specific phosphor-diesterase (PDE)-5 and enhances the relaxation and (cGMP) accumulation elicited by exogenous and neural-released nitric oxide in corpus cavernosum. The most common adverse reactions reported in clinical trials are headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash[1], [2].

Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction and it could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR) [1], [4].

Reduced flow increased resistance in uterine and umbilical arteries, indicative of reduced uteroplacental flow in pregnancies with fetal growth restriction, has been documented by noninvasive Doppler ultrasound velocimetry. This adaptive mechanism, termed “brain sparing”, is reflected on arterial Doppler ultrasound by increased impedance in the umbilical arteries and decreased impedance in the middle cerebral arteries. As metabolic deterioration occurs and the fetus loses the ability to adapt to hypoxemia, the middle cerebral artery Doppler indices will normalize, with an evident decrease in end-diastolic flow in the cerebral circulation[5], [8], [9].

Dastjerdi et al.determined whether the phosphodiesterase type 5 inhibitor, Sildenafil citrate, affects uteroplacental perfusion. They concluded that velocimetry index values reflect decreased placental bed vascular resistance after Sildenafil. Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction[1]. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR) [9].

PATIENTS AND METHODS:

A quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital, Ismailia, Egypt. Thirty pregnant women with fetal growth restriction were included in the study. The patients were recruited from the prenatal outpatient clinicover the period from March 2018 to December 2018.Inclusion criteria were as follows:

- Maternal age ranged between 24 to 35 years
- Gestational age between 28- 37 weeks
- Singleton pregnancy
- Low risk pregnant women with ultrasound evidence of fetal growth restriction

- Pregnant women at high risk for fetal growth restriction:
  - Mild pre-eclampsia
  - Diabetes mellitus
  - History of previous pregnancy with; small for gestational age, stillbirth, severe pre-eclampsia
- Elevated umbilical artery Doppler indices above 90th percentile of norm
- Normal non-stress test at time of admission. Intact membranes.

Approval of the Ethics Committee of the Faculty of Medicine, SCU was obtained. A signed informed consent for participation in the study was also obtained from each of the enrolled patients.

Investigations: Trans abdominal Obstetric Ultrasonography (U/S) was done for 30 pregnant women in a semi-recumbent position (before and 2- and6-hours after of ingestion of sildenafil citrate 20 mg tablet) using a PHILIPS, ClearVue350 with a C5-2 Active Array transducer.

The ultrasound criteria for FGR included:

- Fetal body weight below 10th percentile.
  - An elevated ratio of Head Circumference (HC) to Abdominal Circumference (AC).It is normally drops almost linearly from 1.2 to 1.0. The ratio is normal in the fetus with symmetric growth restriction and elevated in the infant with asymmetric growth restriction.
  - An elevated ratio of femoral length to abdominal circumference. Growth retardation = >24% **(Crang-svalenius, 1991)**.
- Oligohydramnios.

Umbilical artery Doppler is identified at the fetal end, the free-floating loop of the umbilical cord at the apparent entrance point into the placenta.Absent or Reverse End-Diastolic Velocity (AREDV) was noted and the following waveform indices were determined;Systolic/Diastolic (S/D) ratio, Pulsatility Index (PI) and Resistance Index (RI).

Middle cerebral artery Doppler was found overlying the anterior wing of the sphenoid bone near the base of the skull in the transverse plane of the fetal head at the apparent entrance point into the Circle of Willis. The Systolic/Diastolic (S/D) ratio, Pulsatility Index (PI) and Resistance Index (RI) were determined. Doppler studies were done by the same investigator in all the patients.

Cerebroplacental ratio was calculated by dividing the Doppler pulsatility index of the middle cerebral artery (MCA)by the umbilical artery (UA) pulsatility index.

- Sildenafil was given orally 20 mg tablets/ tdsuntil delivery.
- Doppler studies were performed (before and at 2- and 6-hours after giving sildenafil) to assess its effectiveness and note any adverse reactions.
- Patients were asked about drug adverse reactions such as nausea, dizziness, headache, flushing, back pain, nasal congestion and asked about fetal movement changes after ingestion of the drug and weekly thereafter until delivery. Mild dizziness and headache were the only adverse side effects reported and sildenafil appeared to be well tolerated by our patients at the above-mentioned dosage.

Statistical Analysis

Data were analyzed by Statistical Package of Social Science (SPSS), software version 240.0 (SPSS Inc., 2016). Continuous data were presented as the Mean±SD or Median (Range). Normality of distribution of data was checked by Shapiro-Wilk test. Categorical data were presented by frequency and percentage.The one-way repeated measure ANOVA: was used to test for differences between groups when the dependent variable is normally distributed continuous variable. Post hoc analysis with a Bonferroni adjustment: is used for multiple comparisons following one-way repeated measure ANOVA to detect which occasion in particular differs from other occasions.

RESULTS

Table 1: Demographic characteristics of the studied patients (n=30)

Variables		
Maternal age (years)		
Mean ± SD	30.5±3.5	
Median (Range)	30(26-35)	
Gestational age at delivery (weeks)		
Mean ± SD	34.1±1	
Median (Range)	34(33-36)	
Maternal parity, n, (%)		
Multipara	N	%
2	9	30%
3	15	50%
4	3	10%
6	3	10%
Maternal risk factors:n, (%)		
• Mild pre-eclampsia	13	43%
• Diabetes mellitus	5	17%
• History of previous FGR, stillbirth or severe pre-eclampsia	9	30%
• Elevated umbilical artery indices above the 90th percentile of norm	3	10%

This table shows that mean age of studied population was Mean ± SD (34.1±1), and shows that 43% wereMild pre-eclampsia,17% werer diabetics and 30% had History of previous FGR, stillbirth or severe pre-eclampsia and only 10% of the participants had Elevated umbilical artery indices above the 90th percentile of norm.

Table 2: Umbilical artery Doppler indices before (baseline), 2 hours and 6 hours following sildenafil citrate therapy in the studied patients

Umbilical Artery Indices	**Baseline Indices** n=30	**2-hours post sildenafil** n=30	**6-hours post sildenafil** n=30	**Repeated measure ANOVA**	**P-value**
S/D ratio	3.3±0.49	3.0±0.39	2.7±0.22	F=23.8	<0.001
Pulsatility index	1.2±0.36	1.12±0.1	0.9±0.11	F=10.7	0.001
Resistance index	0.79±0.2	0.70±0.1	0.60±0.2	F=7.5	0.003

UA= umbilical artery

This table showed statistically significant differences in umbilical artery Doppler indices before sildenafil and2 and 6 hours following sildenafil citrate therapy in the studied patients (P<0.05).

Table 3: Post hoc analysis assessing umbilical artery pulsatility index at different time points (Pre-sildenafil, 2- and 6-hourspost sildenafil) in the studied patients

UA pulsatility index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		> 0.99	**0.004**
2-hourspost-sildenafil			**<0.001**

Post hoc analysis with a Bonferroni adjustment revealed that umbilical artery pulstality index was not statistically significantly differentbetween pre-sildenafil therapy to two hour-post therapy (p>0.99). However, the pulsatility index was statistically significantly decreased in the6-hour post therapy as compared to pre-sildenafiland2-hour post-therapy were the probability values were 0.004 and 0.001 respectively.

Table 4: Post hoc analysis assessing umbilical artery resistance index at different time points (Pre-sildenafil, 2-hoursand 6-hourspost- sildenafil) in the studied patients

UA resistance index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		.33	**0.008**
2-hours post-sildenafil			**0.022**

Post hoc analysis with a Bonferroni adjustment revealed that umbilical artery resistance index was not statistically significantly different between pre-sildenafil therapy to 2-hourspost therapy (p=0.33). However, the resistance index was statistically significantly decreased in the6-hour post therapy as compared to pre-sildenafil and the2-hour post therapy were the probability values were 0.008 and 0.022 respectively.

Table 5: Post hoc analysis assessing middle cerebral artery Systolic/diastolic ratio at different time points (Pre-sildenafil, 2- and 6-hourspost sildenafil) in the studied patients

MCA S/D ratio	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		0.003	**<0.001**
2-hours post-sildenafil			**0.006**

Post hoc analysis with a Bonferroni adjustment revealed that middle cerebral artery systolic/diastolic ratio was statistically significantly higherinthe 2-hourspost therapy, and 6-hourspost therapycompared-to pre-sildenafil therapywere the probability value was0.003 and<0.001 respectively. Also, the middle cerebral artery systolic/diastolic ratio was statistically significantly higherin the6-hourspost therapy as compared to 2-hourspost therapy (p= 0.006).

Table 6: Post hoc analysis assessing middle cerebral artery resistance index at different time points (Pre-sildenafil, Two hours-post sildenafil and Six hours-post sildenafil) in the studied patients

MCA resistance index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		**0.002**	**0.01**
2-hours post-sildenafil			>0.99

Post hoc analysis with a Bonferroni adjustment revealed that middle cerebral artery resistance index was statistically significantly higherinthe 2-hourspost therapy, and 6-hourspost therapy comparedto pre-sildenafil therapy were the probability value was<0.002 and<0.001 respectively. Also, the middle cerebral artery resistanceindex was not statistically significantly higherin the6-hourspost therapy as compared to 2-hourspost therapy (p>0.99).

Table 7: Cerebro-placental ratio before, two hours and six hours following sildenafil citrate therapy in the studied patients

Variable	Baseline n=30	2-hours post-sildenafil n=30	6-hours post-sildenafil n=30	Repeated measure ANOVA	p-value
Cerebro-placental ratio	**0.88±0.22**	**1.1±0.10**	**2.7±0.92**	***F=99.3***	**<0.001**

This table showed a statistically significant increase in cerebroplacental ratio before, two hours and six hours following sildenafil citrate therapy in the studied patients (P<0.001).

Table 8: Post hoc analysis cerebroplacental ratio at different time points (Pre-sildenafil, 2- and 6- hourspost-sildenafil) in the studied patients

Cerebroplacental ratio	Pre-sildenafil n=30	Two hourspost-sildenafil n=30	Six hourspost-sildenafil n=30
Pre-sildenafil			**<0.001**
2-hours post-sildenafil		**<0.001**	**<0.001**

Post-hoc analysis with a Bonferroni adjustment revealed that cerebro-placental ratio was statistically significantly increased from pre-sildenafil therapy to two hours post-therapy (P<0.001), and from pre-sildenafil therapy to six hourspost-therapy (P<0.001). Also, cerebro-placental ratio was statistically significantly increased from two hours post-therapy to six hours post-therapy (P<0.001).

Table 9: Birth weight of the babies

Variables	
Birth weight (g)	
Mean ± SD	2573.3±146.1
Median (Range)	2550(2400-2900)

DISCUSSION

This quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital, Ismailia, Egypt. Thirty pregnant women with risk factors for fetal growth restriction were included in the study. The patients were recruited from the prenatal outpatient clinicover the period from June 2017 to April 2018.

In our stud y, mean age of studied women is 30.5 years, with range from 26 to 35 years old.

Sildenafil, as a vasodilator, should be an alternative in the treatment of fetal growth restriction (FGR) and preeclampsia by later normalization in velocimetric profile. As a therapeutic agent in FGR gestations by promoting myometrial small artery vasodilatation, reducing in maternity peripheral resistance and increasing flow within the uteroplacental bed, can improve uteroplacental perfusion. PDE-5 inhibitors can reduce vasoconstriction and improve relaxation of FGR myometrial small arteries[1], [10].

Not only an extensive report of the preclinical evaluation could not demonstrate any evidence of teratogenicity by Sildenafil, even at doses much higher than that evaluated in the present study but also for preeclampsia treatment, Sildenafil in the escalating dose regimen 20-80 mg tid was well tolerated, without increasing in maternal or fetal morbidity or mortality. It might safely reduce perinatal morbidity and mortality by increasing uteroplacental impaired perfusion[10], [11].

The current study findings consistent with those of Dastjerdi et al. which was conducted on 59 women with fetal growth restriction were divided into two groups, 30 in the placebo and 29 in the Sildena-

fil group .Unfortunately,3 patients in the placepo and 15 in the sildenafil group refused to undergo Doppler velocimetry for the second time. Among the41 pregnancies, there were 6 with oligohydramnios (4 in the case and 2 in the control group), 3 with hypertension (all in the control group) and 1 with previous stillbirth (in the placebo group). This study included 38 asymmetric and 3 symmetric fetuses with growth restriction. All symmetric ones were in the control group. No significant improvement was detected in the perfusion of umbilical and middle cerebral arteries in the control group before and after placebo[1], [9].

Two hours after tablet ingestion, 1 in the Sildenafil and 2 in the placebo group expressed headache and 1 in the placebo group reported flushing but there was no report of nausea, myalgia and arthralgia. However, nine in the placebo and 3 in the Sildenafil group reported better fetal movement. The means of the umbilical artery (UA) pulsatility index (PI) and Systolic/Diastolic ratio (S/D) significantly decreased 2 hours after Sildenafil ingestion as compared to the placebo group. Mean umbilical artery systolic/diastolic ratio (UA S/D) significantly decreased in the Sildenafil group as compared to the placebo group. Mean umbilical artery pulsatility index (UA PI) significantly decreased in the Sildenafil group in comparison with the placebo group. In middle cerebral arteries, a significant increase was noted in mean Pulsatility Index (PI), resistance index (RI) and Systolic/Diastolic ratio (S/D) after Sildenafil administration. Mean Middle Cerebral Artery Pulsatility Index (MCA PI) significantly increased in the Sildenafil group [12], [13].

Maharaj et al. studied the effects and mechanisms of action of sildenafil citrate in human chorionic arteries ex vivo. In a series of pharmacologic studies, the effects of sildenafil citrate in pre-constricted chorionic plate arterial rings were determined. They showed that phosphodiesterase-5-mRNA and protein was demonstrated in human chorionic plate arteries. Sildenafil produced dose dependent vasodilatation. They concluded that sildenafil citrate vasodilated the fetoplacental circulation via a cGMP dependent mechanism involving increased responsiveness to nitrous oxide[14].

Von Dadelszen et al. studied the role of sildenafil citrate therapy for severe early onset intrauterine growth restriction. Women were offered sildenafil citrate 25 mg three times daily until delivery if their pregnancy was complicated by early onset IUGR (AC\5th centile) and either the gestational age was less than 25 weeks or the fetal weight was 600 g. They found that sildenafil citratewas associated with increased AC growth. They suggested that Sildenafil treatment offer a new opportunity to improve perinatal outcomes for women whose pregnancies are complicated by severe early-onset IUGR [15].

Panda et al. stated that sildenafil, as a vasodilator has also emerged as a potential management option in the treatment of FGR and preeclampsia by later normalization in velocimetric profile[16].

This study is consistent with a study was conducted in Ain shams University hospital and Kafr Aldwwar main Hospital in El-Behera governorate showed that Sildenafil treatment was associated with a significant increase in length of pregnancy and a significant increase in estimated fetal weight by ultrasound , and was associated with a significant decrease in neonatal ICU admission and neonatal mortality[17].

CONCLUSION

Sildenafil citrate significantly increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction in late.

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VAGINAL HYSTERECTOMYUSING VESSEL SEALING CLAMP VERSUS CONVENTIONAL SURGERY; A RANDOMISED TRIAL

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Abstract

Objective: To compare the effects of electrical bipolar vessel sealing clamp and conventional suturing on postoperative pain, operative time, blood loss, and costs, in women undergoing vaginal hysterectomy.

Patients and Methods: 20 women scheduled to undergo vaginal hysterectomy for prolapsed and non prolapsed uterus with benign indication of hysterectomy. Women were randomizedrandomly into two groups;Conventional vaginal surgery Groupand a Group using vessel sealing Erbe machine.Ten patient in each group. Operative time, intraoperative assessment of blood loss, postoperative pain, and estimated cost were evaluated and compared between both groups.

Results: Pain was evaluated few hours post-operative.Patients in the vessel-sealing clamp group showed statisticallysignificant less pain (5.7 versus 4.5 on a scale of 0–10, P= 0.03), but this followed by comparable pain in both groups later. Operative time wasshorter in vessel sealing clamp group (39 versus 61 minutes = P< 0.05). Amount of Blood lostwas also less vessel sealing clamp group.However, regarding the estimated coast, no significant difference between both groups (2903 versus 3102, P=0.26).

Conclusion: Using electrical bipolar vessel sealing clamp during vaginal hysterectomy showed less pain on the first few hours after surgery but not in the following days, shorter operative time, less operative blood loss, with no statistically significant differences in costwere found between the two groups. **(Pictures and videos available)**.

Introduction

Hysterectomy is the commonest gynecological operation done for many indications including benign conditions as abnormal uterine bleeding.*FLORY ET AL, (2005) AND VAN DEN ET AL (1998)*. Hysterectomy done to treat such conditions aims to improve patient's life and of course, this involve avoidance of possible side effects of the operation. Vaginalhysterectomy is the preferredroute with many advantages including fewer complications, shorter hospital stay and lower costs.*VAN DEN ET AL (1998) AND JOHNSON ET AL (2006)*. Vaginal hysterectomy carries the difficulty of gaining access to the vascular pedicles, *HEFNI ET AL (2015)*. To overcome such difficulty more traction on the pedicles is needed which may cause nerve injury, urinary bladder dysfunction and increase post-operative pain. *LAKEMAN ET AL (2010) AND (2011)*.Electrosurgical bipolar vessel sealing clampis used to obliterate tissue bundles andblood vessels up to7mm in diameter. The clamp allow occluding blood vessels and cutting the tissues at the time which shorten the operative

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time and may reduce the post-operative pain by applying less traction on the pedicles of the uterus. In addition, using electrosurgical bipolar vessel sealing clamp enable surgeons to cut tissues close to the uterus preserving the nerves extensively located in the supporting uterine ligaments.

The advantages of vessel sealing clampwere evaluated by few randomized studies, which reported safety, efficacy, short operative time and less post-operative pain *Hefni et al 2015, Elhao et al 2009 and Silva et al 2009*.The effect on postoperative recovery and on the costs of the operationwas not evaluated before.Although Vaginal Hysterectomy (VH) has many advantages,it represent a surgical challenge for surgeons where a narrow space to perform a major surgery and difficult hemostasis.

This study iscarried out compare electrical bipolar vessel sealingclamping and conventional suturing regarding pain after surgery, operative time, blood loss, and costs, in vaginal hysterectomy

Patients and Methods

Thisrandomized controlled trialwas performed in a private hospital Alkhobar, Saudi Arabia to comparing electrical bipolar vessel clamp sealing with conventional suturing in vaginal hysterectomy.

The study was preceded by a pilot study done upon 10 women at a private hospital in Mansoura Egypt using the same inclusion criteria assessing the value of vessel sealing clamping in vaginal hysterectomy on postoperative pain, operative blood loss and duration of surgery.

Casesdiagnosed with benign lesions in the uterus and scheduled for hysterectomy vaginallywere collected between April 2017 and March 2018. All cases were included after general, abdominal and local examination as well as pelvic ultrasound. The uterine size ranged from normal size to10wks. Exclusion criteria were suspected adnexal pathology or pelvic adhesions. Thestudy was approved by the medical ethical committee. After signing the informed consent,womenwere randomized to one of the treatment groups by computerizedrandomization. Conventional vaginal surgery Group and a Group using vessel sealing Erbe machine. Ten patient in each group

The ERBE BiClamp BVSS are insulated forceps with an automatic coagulation completion. The technique has similar anatomical principles to conventional technique of vaginal hysterectomy. It uses only two instruments with easy access and lower risk of trauma. We investigated the use of ERBE BiClampBVSS in VH with possible advantages over conventional suture ligation, namely less post-operative pain, reduced blood loss, shorter operative time and cost of surgery.

Surgical procedure:

Vaginal hysterectomy was donefollowing steps of the standardizedtechnique. Vaginal wall was incised circumferentially anteriorly below the bladder base. The Douglaspouchwas incised posteriorly and a retractor was used to retract vaginal wall. The urinary bladder was then dissected from the vagina wall. The uterosacralligaments were clamped, cutandligatedbyVicryl No. 1sutures thatkept long to be fixed to the vault later. In cases of conventional surgery, the rest of pedicles were clamped, cut and ligatedbyVicryl No. 1 sutures. In casesof the vesselsealing clampgroup the pedicles were clamped, transected and sealed using the Erbybiclampvessel-sealing device. Vault closure was done in the same manner in both groups byVicryl No. 1 sutures.

The amount of lost bloodwas calculated by the amount collected by a suction machine during the surgery and the total number of gauzes used during the procedure. This amount was estimated by the operation assistant and nurse.

Pain management:

Analgesics included morphine and nonsteroidal anti-inflammatory drugs as indicated combined with paracetamolfor 3 days postoperativewere given according to a standard protocol.

Outcome measurements:

We used the visual analogue scale (VAS) to measure postoperative pain as a primary outcome during the first week after surgery. Operative time, amount of blood loss and estimated total cost were the Secondary outcomes.

Results

TABLE 1: Basline Characteristics Of Women According To Surgical Approach.

PARAMETER	CONVENTIONAL SURGERY GROUP	VESSEL SEALING GROUP
NUMBER OF WOMEN	10	10
AGE	49.1	50.0
PARITY(MEDIAN,RANGE)	2.0(1-5)	2.0(0-6)
BODY MASSINDEX KG/M2	27.6	26.9
PREVIOUS ABDOMINAL SURGERY INCLUDING CS	3	2
MEDICAL DISORDERS		
DIABETES	3	1
HYPERTENTION	4	2
MAIN INDICATION FOR VH		
ABNORMAL UTERINE BLEEDING	2	2
POSTMENUPOSAL BLEEDING	1	2
PELVIC PAIN	3	1
UTERINEPROLAPSE	4	5
THYROID DISORDERS	1	2

TABLE 2:Duraion And Average Intraoperative Blood Loss:

OUTCOMES	CONVENTIONAL SURGERY GROUP	VESSEL SEALING GROUP	P VALUE
DURATION OF SURGERY/ MINUTRS	**61.3**	**39.6**	**< 0.05** S.SIG.
BLOOD LOSS/ML	**427.7**	**231.0**	**< 0.05** S.SIG.

Operative duration was shorter for vessel sealing group (39.6 versus 61.3 = P< 0.05) **statistical-lysignificant**. Blood loss was less in vessel sealing group (231.0 versus427.7 = p<0.05) **statistically significant.**

Women in the vessel-sealing group showedsignificantly less pain few hours after surgery (5.7 versus 4.5 on a scale of 0–10, **P= 0.03**)which was **significant**, but after that pain scores were similar in both groups

TABLE 3: Estimaatedcost Of Surgery (SR) *:

COST PARAMETER	CONVENTIONAL SURGERY GROUP MEAN COST	VESSEL SEALING GROUP MEAN COST	P VALUE
INPATIENT HOSPITAL CARE	**2903(2651-3225)**	**3102(2958-3250)**	**0.26 NS**
OUTPATIENT HOSPITAL CARE	**57(37-79)**	**115(71-167)**	**0.037**
TOTAL	**2943(2692-3264)**	**3188(3040-3341)**	**0.18 NS**

*SR :SAUDI RIYALS

Outpatient hospital costs (i.e. care by medical staff the GP, physiotherapist and company physician) of the vessel-sealing group were significantly higher compared with conventional surgery. Fourcasesneededmultiple outpatient clinic visits because of different complaints: constipation, pain and urinary tract infection. All of them were in the vessel-sealinggroup, which increased the cost. However, the total cost was similar in both groups

Discussion

This randomized controlled trial evaluated the effects of using electrical bipolar vessel sealing on postoperative pain, operative time, blood loss, and cost. Vessel sealing machine group showed less Postoperative painfew hours after surgery, but pain was similar in both groups after that. Operative time and blood loss was lower in electrical bipolar vessel sealing group.Total coats were similar in both groups with no statistically significant differences.

Both cases as well as the medical staff following them after surgeries remained blinded to the used technique. As a result, bias in the counseling on experienced pain, based on the cases' or the nurses' preferenceswasavoided. A validated questionnairewas usedbefore and after surgery to evaluate pain and analgesia effects.

One of the most important outcomes was the postoperative pain. In accordance with two previous clinical trialsshowingthat pain waslessfew hours after vaginal hysterectomy when using vessel-sealingclamp CRONJE ET AL (2005) AND SILVA ET AL (2009). The current study found the decreased postoperative pain few hours after operation in the vessel-sealing group, which became similar in both groups after the first day of surgery. The overall low pain scores found in both studied groups after the first postoperative day probably explain this.

Comparing the results of the our study with previous studiesincluded women scheduled for abdominal hysterectomyLAKEMAN ET AL (2008), theoverall pain scores weresignificantly highfollowing abdominal hysterectomy owing to pain of the abdominal incision JONSON ET AL (2006).

The mean hospital stay was slightly long in this study in contrast to previous studiesCRONJE ET AL(2005), SILVA ET AL(2009) AND DING ET AL(2005). However, when compared with hospital stay in other studies for cases of vaginal hysterectomy, it was within average rangeJONSON ET AL (2006).The large difference in of hospital stay durationcould be explained by local cultural factors, and by surgeon, as well as participant expectations matched with a meta-analysis done by KROFT ET AL (2011). Hospital stay in our study was shorter, but not statistically significant among women in the vessel-sealing group.

Our study results regarding the operative time were similar to previous studies comparing vessel sealing with conventional method. All reported reduced operation timeHEFNI ET AL (2015), ELHAW ET AL (2009), LEVY ET AL(2003),SILVA ET AL(2009) AND DING ET AL (2005). This could be explained by the ability of the vessel-sealing clamp to rapidly seal ,coagulate and cut the pedicles in one hand held tool LAMBERTON ET AL (2008).

Reduction of the operative time is a matter of discussion. Although the reduction was as high as 40%, it does notmean a quicker recovery or shorter hospital stay. However, reduction in the operative time reduced the cost of the operation.

Decrease in blood loss using vessel sealing was found by many studiesLEVY ET AL(2003),SILVA ET AL(2009) AND DING ET AL (2005).Results of the current study are in agreement with these studies. However,studieson larger scaledid not find significant difference in estimated blood lossELHAW ET AL (2009).

Vessel-sealing technique cost was expected to be higher than the conventional method owing to the cost of the device. The cost was slightly higher in the vessel-sealing cases (2903 versus 3102 SR P=0.26), which is explained by the added cost of the ERBE BICLAMP device , However, this is compensated by shorter operative time (conventional surgery 688SR versus vessel sealing 616SR) ,and shorter hospital stay after vessel sealing (conventional surgery 1852SR versus vessel sealing 1713SR).

Conclusion

It seems that ERBE BiClampBVSS is a safe, effective techniquefor vaginal hysterectomy compared to conventional method. The technique resulted

in less pain,shorter operative times, less blood loss,shorter hospital stay and lower total cost. The reduced post-operative pain observed allowed rapid mobilization and recovery.

Recommendations

Further studies with more number of patients is recommend, as well as studies concerning the effects of the two different methods for vaginal hysterectomy on the urinary bladder function and pelvic floor function.

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Minilaparotomy for benign gynecologicconditions in patients with high body mass index: is it a suitable approach?

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Abstract

Objectives: to assess the efficacy and outcome of minilaparotomy for management of benign gynaecologic conditions in patients with high body mass index.

Patient and methods: A retrospective study conducted on 64 patients at Mansoura university hospital. We analysed the outcome, perioperative and postoperative complications of minilaparotomy for benign gynaecologic conditions. All patients have a high BMI(more than 25 kg/m^2).

Results: The mean operative time was60.5±16.7 ranging from 30 to 90minutes.The mean time for ambulation andpostoperative hospital stay was 10.53±4.4hours and2.59±0.66 days respectively. The overall complications were 10.9% with no major complications. Conversion tolaparotomy occurred in 3 patients due to adhesions in 2 patients and suspicion of malignancy in the third one. None of the patients required blood transfusion..

Conclusion: Minilaparotomy is a suitable option for the management of benign gynaecologic conditions in patients with high BMI.

Keywords: minilaparotomy, hysterectomy, myomectomy and ovarian cystectomy

Introduction

Laparoscopy has been widely used in the management of benign adnexal masses andfor hysterectomy (1-4). This is attributed to short hospital stay, early recovery and less postoperative pain .However, it is associated with highcost, long learning curve, the needof special experienceand long operative time (5).Moreover, pneumoperitoneumcould be contraindicated in morbidly obese patients and in some medical disorders(6).

In this context, Minilaparotomy could be an alternative to laparoscopyand also in places where the economic issue is of importance or lacks expertise in laparoscopy. It relies on the simplicity of traditional laparotomytechnique avoiding the drawbacks of laparoscopy (7). It is well establishedtechniquefor tubal sterilization (8).Many studies proved it as an accepted approach for hysterectomy for benign gynecological conditions (9, 10).

In this study we tried to explore the feasibility and outcomes of minilaparotomy for benign gynecologic condition in patients with high body mass index (BMI)

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Patient and methods

This retrospective observational study was conducted on 64 patients over a period of 56 months from June 2014 to February 2019. Inclusion criteria were mobile uterus with a size up to 12 weeksand or benign ovarian masses in patients with high body mass index (more than 25kg/m^2)

Exclusion criteria were suspected malignancy and suspected pelvic adhesions. Written informed consent was obtained from all the patientsand the Departmental Ethical Committee approved the study. History taking, general, abdominal andpelvic examination were done for all patients.All patients followed the same standard preoperative protocol. All the operations were performed by at least one of the surgeons included as authors in this study.All surgeries were performed under general anesthesia with endotracheal intubation. Data that included age, parity, body mass index(BMI), diagnosis, size of the lesion on imaging or by examination, criteria of the lesion by ultrasonography, associated medical disorders and previous operations were collected. The data including duration of surgery, intraoperative blood loss, uterine weight, organ injuries, and conversion to laparotomy and relaparotomywere collected. Postoperative pain, need for analgesia, postoperative complications, time till the patient became ambulant and the duration of hospital stay were also collected.All patients received anticoagulant in the early postoperative period in addition to elastic stockings applied on both lower limbs.

Surgical technique: the surgery was started in supine position.

A transverse skin incision 4 to 6 cm was made 2 cm above the symphysis pubis. The subcutaneous fat was incised to expose the rectus sheath which was incised larger than the original skin incision. The recti muscles were retracted from the midline. The peritoneum was incised vertically and extended upwards and downward. The abdominal wall was then retracted using thin Deaver retractors. The uterus, adnexaewere then examined todetermine the extent of any unexpected pelvic pathology oradhesions. Theoperative table was then tilted to the tarendelenberge position of 30 degree and gentle packing was done to gain additional exposure.

For hysterectomy or myomectomy the uterus was exteriorizedby applying gentle traction on the fundus by a tenaculum forceps and a double stitch was taken in the uterine fundus then gentle traction until delivery of the uterus through the wound was achieved. The hysterectomy or myomectomy was the done in the traditional way. For hysterectomy, a straight Kocher's was applied on one side ofthe uterus including the origin of the tube and the round ligament.A Kocher's clamp is applied on the round ligament about 2 centimeters from the uterine end. The round ligament was then divided in between the 2 Kocher's and ligated. A window was done for application of an artery forceps on the infundibulopelvic ligament which is then sutured with a 1 polyglactin 910 suture .The dissection was then carried out between the two leaves of the broad ligament after gentle traction on ligated distal part of the round ligament to reach the peritoneal reflection on the upper surface of the bladder which was then incised.

The same technique was repeated on other side. Agauzewas used to push the vesicocervical fascia down to expose the cervix, thereby pushing the ureters laterally. Next, the uterine pedicle is transfixed, and ligated.

At this point of dissection much of the uterus gets out of the surface. The lateral cervical ligaments were then divided and ligated figure (1).An incision was then carried out at the cervico-vaginal junction which was opened and the vaginal vault was held by a Kocher's clamp till the uteruswas removed figure (2). The vaginal vault was repaired with polyglactin 910and hemostasis wasachieved. Figure (3)

For the large ovarian cysts which could not be extracted from the wound due to large size were deflated first. This was achieved through a burse string suture in the surface of the cyst, afterpacking, avoiding piercing the wall, then a small incision 1 cm was done in the cyst wall while the tip of the suction catheter was introduced inside the cyst through the small incision and tightening of the opening around the catheter was done though tractionof the two ends of the threads which then ligated to avoid escape of the cyst content into the peritoneal cavity. After deflation of the cyst it could be easily extracted from the wound where cystectomy and reconstruction of the ovary could then be performed.

The parietal peritoneum was closed and therectus sheath was closedwith continuous suture. The skin incision was closed by applying interrupted or sub -cuticular sutures. A dressing over theincision was applied for 48 hours.All specimens were sent for histopathological examination. Intraoperative blood loss was estimatedby the number of soaked packs and the amount in the suction bottle.

Blood transfusion wasconsidered if the estimated blood loss was more than 500 ml. Patients were encouraged to become ambulatory as early as they can.Injectable antibiotics were given for 48 hours post-operatively andthen replaced by oral tablets. Injectable non-steroidal anti-inflammatory drugs were given on demand for post-operativepain relief (3 doses in 24 hours at the most) and oral fluids were started on hearing the intestinal sounds, followed by semi-solids after another 12 hours.

The patients were discharged when ambulatory, passing urine normally, had normal bowel motion and had no complications.

Figure (1): ligation of lateral cervical ligament

Figure (2):opening the vaginal vault

Figure (3): the vaginal vault is closed

Figure (4): the removed uterus

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the 0.05 level and all tests were 2 tailed.

One Way ANOVA testwas used for parametric quantitative variables, to compare between more than two studied groups with Post Hoc Tukey test for pairwise comparison .Monte Carlo test was used to compare qualitative variables when more than 25% of cells have count less than 5.

Results

Sixty four patients were enrolled in our study. The patient's characteristics including age, parity and BMI in addition to associated medical diseases, previous surgery were described in table 1.the mean age was 39.1±9.9 ranging from19 to 58 years.The mean BMI was 33.63±4.58 ranging from 28.1 to 39.2. Nineteen patients had previous surgery and 14 had an associated medical disorder the majority are diabetic or hypertensive.

The most common presenting symptom is abnormal vaginal bleeding and the most common indication for surgery was uterine fibroids. Table (2)

The operative data are presented in table 3.The mean size of ovarian cysts was 9.13±4.53, ranging from 5 to 25 cm. The mean uterine weight was283.0±33.65ranging from 210 to340 gm. Mean operative time was60.5±16.7 ranging from 30.0 to 90.0minutes, being least in ovarian cystectomy (table 4).

Estimated blood losswas <500 cc and no patient requiredintraoperative blood transfusion. Estimated blood loss was less in the ovarian cystectomy group(table 4). Conversion to laparotomy occurred in 3 patients; 2 for extensive pelvic adhesions and one for suspicion of malignancy. No organ injury in our study population .

Table 4illustrated thecomplications. The overall complication rate was (7/64)10.9%.one case needed relaparotomy for parietal hematoma. Superficial wound infection was reported in 4 cases. Two cases developed fever (38.5c) 2 days after surgery. No reported cases with DVT.

Discussion

The laparoscopic surgery is increasinglyreplacing the conventional laparotomy.However, to establish laparoscopic unit is costly. Moreover its practice needs special experience with long learning curve. Also laparoscopy carries a risk in patients with high BMI due to pneumoperitoneum.Learman(11) reported that the rate of major complications is higher in laparoscopic than abdominal hysterectomy(11.1% versus 6.2%).Again Aarts et al reported that laparoscopic hysterectomy isassociatedwith more urinary tract injuries (12).

The results of our study showthat minilaparotomy is a suitable surgical option for management of benign gynecological conditions in patients with high BMI. It can be done withaccepted blood loss, reasonable operative time without serious complications.

Many studies demonstrated the feasibility and safety of this technique (9, 10, 13, and 14) which relies on the simplicity of the traditional laparotomy and avoids the drawbacks of laparoscopy.

The stitch in the uterine fundus or the cyst wall allows the traction on the organ to be delivered through the small wound (4-6 cm) thus avoids introducing the hand inside the abdomen that decreases the capacity of the operative field. The advantages of this small skin incision are many including the small wound which acts as a tourniquet around the organ so avoids the exposure of the intestinal loops, thus decreasing the chance of intestinal injury and diminishes the possibility of postoperative ileus. Furstenberg has documented that avoiding repeated handling of the intestinal loops reduces the duration of postoperative ileus (15).Moreover getting the uterus outside through a small wound helps to avoid accidental injury of the ureters. This could explain the absence of organ injury in our patients.

Again a small wound decreases postoperative pain which allows early postoperative ambulation so decreases the risk of postoperative DVT being the complication of special importance in the population of our study.

Superficial wound infection was the most frequentcomplication in our patients. This may explained by high BMI of the population of our study.All of them were managed conservatively with no need for resuturing.

Conversion to traditional laparotomy was done in 3 patients; 2 due to extensive pelvic adhesions and one for suspicion of malignancy that necessitated widening of the wound.

In the present study the mean operative time, time to ambulate were accepted. Blood loss was also accepted and there was no perioperative blood transfusion. No major complications were noticed in any of the patients, and the overall 10.9 percent complication rate could be considered low.Results of our study are comparable to other (9, 14).However, in our study the mean operative time for hysterectomy is longer than that reported by Mahendru et al (9). This couldbe explained by the higher

BMI of our study population which take longer time during opening and closure of the abdominal wall.

In our study minilaparotomy is a valid option for myomectomyand ovarian cystectomy.Other studies proved its feasibility for myomectomy (16, 17) and management of benign adnexal masses (1)

The disadvantage of the small wound is the difficulty to deal with adhesions due to the narrow window that does not allow optimal adhesiolysis. This explains the need to widen the incision in 2 cases due to the extensive adhesions.

This study is limited by its retrospective nature which might lead to possible bias but this was overcomed by the performance of surgery by at least one of the two consultants included as authors in this study.

Conclusion

Minilaparotomy for the management of benign gynaecological diseases in patients with high BMI can be safely done .it has an accepted operative time and reasonable blood loss with no serious intra or postoperative complications. Of importance is the associated tolerable postoperative pain and early ambulation that deceases the chance of developing postoperative DVT which is a complication of importance in obese patients. It is easy to learn than laparoscopy but has limitations in cases with extensive adhesions.

Conflict of interest statement: we declare that we have no conflict of interest.

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Table (1): patient characteristics and indications for surgery

Patient characteristics	n=64	%
Age/years Mean±SD (Min-Max)	39.19±9.9 (19.0-58.0)	
BMI (Kg/m^2) Mean±SD (Min-Max)	33.63±4.58 (28.1-39.2)	
Parity Mean±SD (Min-Max)	2.53±1.18 (0.0-5.0)	
Previous surgery no yes	 45 19	 70.3% 29.7%
Associated medical disease • No • DM • Hypertension • DM and hypertensive • Portal hypertension • RHD-MR	 50 6 5 1 1 1	 78.1% 9.37% 7.8% 1.5% 1.5% 1.5%

Table (2): presenting symptoms and indications for surgery

	n=64	%
Presenting symptoms		
• Abdominal pain	25	39.1
• Chronic pelvic pain	6	9.4
• Menorrahgia	23	35.9
• Metrorrhagia	6	9.4
• Postmenpausal bleeding	4	6.2
Indications for surgery		
• Adenomyosis	5	7.8
• Dermoid cyst	3	4.7
• Endometrioma	3	4.7
• Endometrial hyperplasia without atypia	8	12.5
• Simpeovrian cyst	15	23.4
• Intramural fibroid	17	26.6
• Subserousfiboid	8	12.5
• Submucusfibrid	5	7.8

#Categories are not mutually exclusive

Table (3): operative and postoperative data

	n=64	%
Size of ovarian cyst/cm Mean±SD (Min-Max)	9.13±4.53 (5.0-25.0)	
Uterine weight /gm Mean±SD (Min-Max)	283.0±33.65 (210-340)	
Operation done Myomectomy Ovarian cystectomy TAH TAH& BSO	 9 20 4 31	 14.1 31.3 6.20 48.4
Estimated blood loss <100 100-250 >250-450	 10 21 33	 15.6 32.8 51.6
Patients need blood transfusion	0	0.0
Operative time /minutes Mean±SD (Min-Max)	60.5±16.7 (30.0-90.0)	
Organ injury	0	0.0
Primary bleeding	0	0.0
Conversion to laparotomy	3	4.7
Analgesics dose Mean±SD	2.36±0.48	
Post operative ambulation time (hours) Mean±SD (Min-Max)	10.53±4.4 (6.0-24.0)	
Post operative hospital stay(days) Mean±SD (Min-Max)	2.59±0.66 (2-4)	

Table (4): Comparison of estimated blood loss, operative time and time for ambulation between types of operations

	Myomectomy N=9(%)	Ovarian cystecto-my N=20(%)	Hysterectomy N=35 (%)	test of significance
Estimated blood loss <100 100-250 >250-450	 0 3(33.3) 6(66.7)	 9(45.0) 11(55.0) 0(0.0)	 1(2.9) 7(20.0) 27(77.1)	 MC P<0.001*†
Operative time /minutes Mean±SD	51.67±15.0	43.25±6.34	72.63±9.64	F=62.87 P<0.001#†
post operative ambula-tion time/ hours Mean±SD	10.22±4.1	10.20±4.9	10.80±4.3	F=0.14 P=0.87

*Statistically significant difference between Myomectomy & Ovarian cystectomy ,# Statistically signif-icant difference between Myomectomy & hysterectomy , † Statistically significant difference between Ovarian cystectomy &hystrectomy
F:One Way ANOVA test , MC :Monte Carlo test

Table (5): complications

	Number	**%**
Blood loss > 500 ml	0	0
Need for re-laparotomy	1	1.6
Post-operative DVT	0	0.0
Fever	2	3.1
Superficialinfections	4	6.2
Prolonged ileus	0	0
total	7	10.9

The effect of L-carnitine on adolescent polycystic ovary syndrome patients with irregular cycles

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder that affects women in their reproductive age. L-Carnitine (LC) is a small water-soluble molecule that plays a basic role in the normal mitochondrial oxidation of fatty acids and generation of energy. Consequently LC is expected to play a positive role in enhancing ovarian functions. This work was primarily designed to assess those positive effects of treatment with LC among adolescent PCOS patients.

Objective: To assess the effect of treating adolescent PCOS patients with LC, in terms of improvement in menstrual irregularities, hormonal imbalance and body weight.

Setting: Department of Obstetrics and Gynecology, Suez Canal University Hospitals, Ismailia.

Patients and Methods: This prospective randomized clinical trial included 25 adolescent PCOS patients with menstrual irregularity between the age of 14 and 19 years. They were given LC in a dose of 1 g daily for three months. Hormonal profile, menstrual pattern and body mass index (BMI) were assessed before and three months after treatment.

Main outcome measures: Changes in menstrual cycle, hormonal profile and body weight.

Results: The mean BMI decreased significantly after treatment from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03). Prior to treatment, all the participants complained of menstrual irregularity, the most common form of menstrual irregularity was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32% , n = 8) ,and finally secondary amenorrhea (12% , n =3).After treatment with LC for 3 months 36% (n=9) of the study population regained regular cycles.

Conclusion: Treatment of adolescent PCOS patient with LC help in regaining regular cycles and proved to be efficient in decreasing BMI and further large scale studies may be needed with larger sample sizes and more longer treatment period to elude all potential beneficial effects of LC in this age group.

Keywords: L-carnitine, PCOS, adolescent

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Introduction

Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in child bearing period as well as during adolescence. (1).

PCOS is characterized by a heterogeneous symptoms and signs, including a variable intermingling features of ovarian dysfunction (oligo-ovulation or anovulation or menstrual irregularity and/or character-

istic polycystic ovarian morphology) and androgen excess (hirsutism and/or hyperandrogenemia) , with the exclusion of other endocrine disorders such as hyperprolactinemia and non-classic congenital adrenal hyperplasia.(2)

The prevalence of PCOS ranges from 6% to 20% according to the criteria used for diagnosis, which may broaden or narrow the inclusion of patients.(3,4) In the past PCOS was considered as a disorder of adult women, but recent evidence suggests that PCOS is a lifelong syndrome, with variable manifestations and late complications. The exact prevalence of the disease during childhood is still considered unknown (5).

The external features of PCOS are primarily due to androgen excess. Any adolescent with persistent menstrual irregularities or features of hyperandrogenism should be suspected of having PCOS. Hyperandrogenism is due to ovarian thecal cells overproduction of testosterone. Hyperandrogenism manifests as hirsutism, acne, temporal balding, deepening of voice, increased muscle mass, decreased breast size. It has been noted that one third of women presenting with acne are diagnosed as having PCOS. Premature adrenarce and the occurrence of hirsutism before puberty have been associated with PCOS in adolescents. (6)

L-Carnitine is a water-soluble molecule with important role in fat metabolisms. It also plays a crucial role in mitochondrial oxidation processes of fatty acids and energy production through generation of Acyl-CoA esters. Some studies showed that supplementation with LC improves PCOS through several mechanism including decreasing blood glucose levels ,regulating production of gonadotropins and antagonizing insulin resistance, which could perhaps be attributed to LC-induced increase in beta-oxidation of fatty acids and basal metabolic rates .(7)

Women with PCOS also have hormonal imbalance with possibility of ovarian production of excess androgens. One study suggested that hyperandrogenism and/or insulin resistance in women with PCOS may be associated with decreased total serum LC levels, denoting that a normal serum level of LC may play a crucial role for preventing insulin resistance and hyperandrogenism.(8)

From the previous view we can deduct that LC is expected to play a positive role in enhancing the ovarian function and improving features associated with PCOS. Review of literature showed very few data about using LC in adolescents with PCOS. This work was primarily designed to assess those positive effects of LC in adolescent PCOS patients with irregular cycles.

Patients and methods

Patients

This is a prospective randomized clinical trial which was performed at the department of Obstetrics and Gynecology, Suez Canal University hospital. This study was approved by the faculty ethical committee board, and informed consent was given by the patient as well as parents before inclusion in the study. This study included 25 patients with PCOS between the age of 14 and 19 years with documented menstrual irregularities. Although the diagnosis of PCOS was based on the 2003 Rotterdam criteria for diagnosis of PCOS, but the following recommendations were considered:

- A detailed history was taken from each participant as well as from her mother regarding the sustainability and pattern of menstrual irregularity, because the overlap between normal pubertal development and characteristic features of PCOS may confound an accurate diagnosis of PCOS among adolescent girls.
- Other disorders associated with irregular menses or hyperandrogenism need to be excluded from diagnostic consideration, so patients with any endocrine abnormality, medical disorders, hyperprolactinemia, ovarian pathology, or running on any hormonal or chronic medications were excluded from the study.
- Oligomenorrhea or any other form of menstrual irregularity has to persist for more than 2 years when diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism , to avoid misdiagnosing physiological pubertal changes as PCOS features.(8)
- Insulin resistance, hyperisulinemia and obesity were excluded as criteria for diagnosis in adolescent.
- Less weight is given to ultrasound criteria, especially follicular count, since all cases were done through trans-abdominal route which is less sensitive than tran-vaginal in detailed follicular counting.

Methods

After obtaining informed consent all the participants in the study were subjected to detailed history taking with emphasis on menstrual history. General and local examinations. Hormonal profile assessment included basal day 3 FSH, basal day 3LH, TSH, prolactin, and total testosterone. Pelvic ultrasound

was done for assessment of the uterus and both ovaries. As was mentioned before the diagnosis of PCOS was based on the 2003 Rotterdam consensus for diagnosis of PCOS, putting in consideration the recommendations discussed above due to the more complexity of diagnosis among adolescent, at least 2 of the following three criteria were needed for diagnosis; menstrual irregularities or anovulation and/or clinical or biochemical hyperandrogenism and/or characteristic ultrasound morphology.

In this study we emphasized on the criteria of menstrual irregularity to be included in all cases and persisted for at least more than 2 years after menarche to avoid false diagnosis of normal pubertal incidental changes as PCOS. A cycle length between 22 days to 35 days was recognized as regular cycles. Secondary amenorrhea was defined as a cycle length more than 180 days or 6 months. Irregular cycles were defined as overlapped repeated occurrence of cycles less than 21 days or more than 41 days, and finally Oligomenorrhea was defined as a cycle length of 42 -180 days .

Clinical features of hyperandrogenism included persistent acne and hirsutism (assessed through Ferriman and Gallawy score),total serum testosterone more than 70 ng/dl was used as a biochemical marker for hyperandrogenism .

A count more than 12 follicles of the 2-9mm cohort per single ovary and/or ovarian volume more than 10 ml were considered as ultrasound criteria for PCOS. Much weight was given to ovarian volume then follicular count since all cases were done through trans-abdominal route which is less sensitive than tranvaginal in detailed follicular counting.

LC was given in a dose of 1 g per day (1 g tab) for 3 successive months. After the 3 months of the treatment a detailed menstrual history was taken again. BMI recording, hormonal profile and pelvic ultrasound were repeated.

Diet control was offered for all the participants in order to avoid the confounding effect of excess high caloric food intake, this was done through prescribing high protein, low carbohydrate diet, at least three meals per day which are low in sugar and fat and high in fruit, fresh vegetables and salad. Light sustained exercise such as walking, cycling or swimming for at least an hour at a time several times per week.

Results

The mean age among the study population was 16.52±1.58 years. The mean FSH was 4.92 ± 0.94 iu/l , while the mean LH was 6.04 ± 1.56 iu/l .Mean ovarian volume was 9.32±2.48 ml, while the mean BMI was 29.34 ± 1.73 kg/m2. Finally, the mean total testosterone was 60 ± 27.1 ng/dl. (Table 1)

The most common form of menstrual irregularity was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32%, n = 8), and finally secondary amenorrhea (12%, n =3). (Table 2)

After the treatment with LC for 3 months there was a significant decrease in BMI from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03). (Table 3)

Following the treatment with LC for 3 months 36% (n=9) of the study population regained regular cycles. (Table 4)

Discussion

Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in child bearing period as well as during adolescence. PCOS is characterized by heterogeneous symptoms and signs, including variable intermingling features of ovarian dysfunction and/or androgen excess. (2)

The prevalence of PCOS ranges from 6% to 20% according to the criteria used for diagnosis, which may broaden or narrow the inclusion of patients.(3,4) In the past PCOS was considered as a disorder of adult women, but recent evidence suggests that PCOS is a lifelong syndrome, with variable manifestations and late complications . The exact prevalence of the disease during childhood is still considered unknown (5).

The external features of PCOS are primarily due to androgen excess. Any adolescent with menstrual irregularities or features of hyperandrogenism should be suspected of having PCOS.(6)

Although many studies have been conducted to demonstrate the beneficial role of LC in fertility and improvement of variable health parameters among PCOS, but there is very few data about such beneficial role among adolescent PCOS patients. The aim of this work was to test such positive effects of LC supplementation among adolescent PCOS patient with menstrual disorders.

This study included 25 patients with PCOS between the age of 14 and 19 years with documented men-

strual irregularities. All the patients in the study were subjected to detailed history taking with emphasis on menstrual history. General and local examinations. Hormonal profile assessment included basal day 3 FSH, basal day 3LH, TSH, prolactin, and total testosterone. Pelvic ultrasound was done for assessment of the uterus and both ovaries. LC was given in a dose of 1 g per day (1 g tab) for 3 successive months. After the 3 months of the treatment a detailed menstrual history was taken again and followed for the next 3 months. BMI recording, hormonal profile and pelvic ultrasound were repeated.

The mean age among the study population was 16.52 ± 1.58 years. Prior to treatment, the mean FSH was 4.92 ± 0.94 iu/l ,while the mean LH was 6.04 ± 1.56 iu/l. The mean ovarian volume was 9.32±2.48 ml, while the mean BMI was 29.34 ± 1.73 kg/m2. Finally, the mean total testosterone was 61 ± 27.1 ng/dl.

The most common form of menstrual irregularity among the study population was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32%, n = 8), and finally secondary amenorrhea (12% , n =3).

The distribution of menstrual irregularities among adolescents in this study differed from that of Bhavana V. 2017, In his work 80 adolescent PCOS patients with menstrual irregularities between 10 and 20 years were allocated into 2 groups, one group was treated with metformin for 6 months while the other group with placebo. The main form of menstrual irregularity in his work was irregular periods representing 83.75% (n=67) , followed by secondary amenorrhea (5% , n = 4), then menorrhagia (8.75% .n=7). The differences in the pattern of menstrual irregularity between both studies may be due to different ethnic background, sample size and the different age ranges as Bhavana V. extended the age range down to 10 years which may be confounded with dysfunction uterine bleeding that may commonly intercepted in the first 2 to 3 years following menarche.(10)

In this work, After the treatment with LC for 3 months there was a significant decrease in BMI from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03).Several studies documented such weight reducing effect of LC among PCOS. In a prospective, randomized, placebo-controlled, double-blind trial to determine the effects of oral LC supplementation on weight loss and lipid profiles in women with PCOS, it was found that the supplementation of LC in a dose of 250 mg per day orally for 12 weeks lead to significant reduction in body weight, BMI, waist and hip circumference in women with PCOS. Increase in the basal metabolic rates and excess beta-oxidation of fatty acids were the proposed mechanisms for the LC-moderated effects. (11)

As for the hormonal profile before and after the treatment, none of the hormones measured showed any significant change following LC treatment for the 3 months of the study, but still the only hormonal change that was close to significance was the decrease of total testosterone from 61 ± 27.1 to 58 ± 23.9 (p value =0.08) . Such decrease in biochemical hyperandrogenism was suggested by Some authors who concluded that hyperandrogenism and/or insulin resistance in the non-obese women with PCOS may be associated with decreased total serum LC levels and that normal serum levels of LC may be mandatory for normal ovarian function. They measured the serum total LC levels in non-obese women with PCOS and compared it to normal control. They found that PCOS patients have significantly lower total LC (40.5 ± 5.7 μmol/L vs. 91.1 ± 15.2 μmol/L), higher levels of dehydroepiandrosterone (DHEA), testosterone, luteinizing hormone (LH), low-density lipoproteins (LDL) and fasting insulin compared to control. (9)

From that point it is proposed that the close to significance decrease in total testosterone in this work might have been significant if the sample size was larger or if the treatment was continued for longer time.

The main outcome of the study was the significant change in menstrual pattern before and after the treatment. As was mentioned before it was assured during selection of patient that a persistent menstrual irregularity was documented for at least 2 years, so generally speaking 100% of the study population showed menstrual irregularity (oligomenorrhea representing 56% (n=14) followed by irregular cycles (32% , n = 8) ,and finally secondary amenorrhea (12% , n =3)) .

Following the treatment with LC for 3 months, 36% (n=9) of the study population regained regular cycles. The percentage of oligomenorrhea decreased from 56% (n= 14) to 32 % (n= 8) ,while irregular cycles decreased from 32% (n = 8) to 24% (n=6), and finally secondary amenorrhea decreased from 12% (n =3) to 8% (n=2).

Such positive improvement in cycle pattern among PCOS adolescents treated with LC for three months in this work confirms the consistency of the variable favorable actions of LC on female fertility (specially PCOS).

This improvement following LC treatment is caused through both direct and indirect actions. The direct action on ovarian cells and oocyte specially include an increased energy production by transferring palmitate into mitochondria and maintaining acetyl CoA/CoA ratio, it promotes cellular growth and maturation by decreasing the rate of apoptosis, and finally reducing oxidative stress by scavenging free radicals and removing excess palmitate. (12)

LC acts indirectly through affecting the HPG axis to regulate reproductive hormone secretion. The highest LC concentration in neuronal cells is in the hypothalamus where it decreases neuronal cell death. It is reported that LC cause K+-induced depolarization in hypothalamic neuronal cells thus increasing its secretory activity. it is proposed that treatment with LC increases serum levels of other reproductive hormones, like estradiol, progesterone, LH and decreases prolactin. Through this indirect effect, it prevents PCOS, amenorrhea and other problems related to the female reproductive cycle. (13,14)

Conclusion

Treatment of adolescent PCOS patient with LC may help to regain regular cycles and proved to be efficient in decreasing BMI and further large scale studies may be needed with larger sample sizes and longer treatment period to elude all potential beneficial effects of LC in this age group.

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Appendix

TABLE (1) : Basic characteristics of the study population

Characteristic	Mean ± SD	RANGE
Age (years)	16.52±1.58	14-19
FSH (iu/l)	4.92 ± 0.94	3.7-7
LH (iu/l)	6.04± 1.56	4-9
PROLACTIN(ng/ml)	7.08±1.7	3-12
TSH(mu/l)	2.51 ± 0.57	1.6-3.8
BMI (kg/m^2)	29.34 ± 1.73	26.4-32
OVARIAN VOLUME(ml)	9.32±2.48	6-15
TOTAL TESTOSTERONE(ng/dl)	61±27.1	20--120
Hyperandrogenic features	**n**	**percentage**
Acne	7	28%
Hirsutism	4	16%

TABLE (2) : Different patterns of menstrual irregularities among the study population prior to treatment

Menstrual pattern	n	percentage
oligomenorrhea	14	56%
irregular cycles	8	32%
secondary amenorrhea	3	12%

Table (3) : Basic characteristic of the study population before and three months after the treatment

Characteristic	Before	After	P value
FSH (iu / l)	4.92 ± 0.94 3.7-7	4.76 ± 0.87 3.9-6.8	0.13
LH (iu / l)	6.04± 1.56 4-9	5.72 ± 1.94 4-10	0.38
OVARIAN VOLUME (ml)	9.32±2.48 6-15	9.12 ± 1.86 7-14	0.19
BMI (kg/m^2)	29.34 ± 1.73 26.4-32	27.88±1.45 26-31	0.03*
Total testosterone(ng/dl)	61±27.1 20-120	58 ±23.9 20-110	0.08

*significant p value

TABLE (4) Different pattern of menstrual irregularity 3 months after treatment

Menstrual pattern	n	percentage
Normal cycles	9	36% (n=9)
oligomenorrhea	8	32% (n=8)
irregular cycles	4	24 % (n=4)
secondary amenorrhea	2	8% (n=2)