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Acknowledgments

Acknowledgments should only be made to funding institutions and organizations and, if to persons, only to those
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2- Books:
(a) Personal author: Speroff L, Glass RH, Kase NO. clinical gynecologic endocrinology and infertility. 4th edition, Baltimore, Williams & Wilkins; 1988: 105
(b) Chapter in book; Wilhelmsson L, Norstrom A, Tjugum 1, Hamberger L. Interaction between prostaglan dins and catecholamines on cervical collagen. In: Toppozada M., Bygdeman '. M., Hafez ESE, Eds. Prostaglandins and fertility regulation. Advances in reproductive health care. Lancaster, England, MTP Press Ltd., 1985 : 75 - 80.

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Contents :

Letter from the Editor:

Dear esteemed colleagues,

Now that this new edition is between your hands, I sincerely hope that all the changes we have made to produce a more refined publication have been successful. Your feedback is more than welcome, and all your remarks will be taken into consideration for future updating and promotion of this respected journal.

These are very crucial, important and exciting times. we are at very difficult times, the country is deeply divided and all efforts should be done to mend the wounds and get us all serving Egypt.

The activities of our society are moving at a very fast pace despite the current turmoil in the political and security departments. The annual meeting will be held during December and we will start publishing some of the papers in the upcoming issues of the journal.
Last but not least our prayers for our beloved country to reach the prosperity and peace it deserves.
Thank you.

Mohamed Yehia
Professor of Obstetrics and Gynecology
Ain Shams University

Pelvic organs dysfunction (pod) and reconstructive surgical repair

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MD, Laila A. E. S. Mousa MD,
Ahmad G. Serour MD

ABSTRACT

Objective: By imaging with 3-dimension ultrasound (3DUS); MRI and by histopathology studies, we try to prove these three novel concepts.

Materials & Methods: We chose three hundreds women suffering from stress urinary Incontinence (SUI), fecal incontinence (FI) and vaginal prolapse. In addition, we included 30 nulliparous infertile women who have no pelvic floor dysfunction as control.
All patients and control were have their clinical history recorded, and were clinically examined and had been imaged with 3DUS and MRI. In addition, we took specimens from the IUS, IAS and the vagina and were prepared, examined microscopically, and compared to normal tissues.

Results: Imaging with 3DUS and MRI proved the novel concepts and histopathological examinations proved that the IUS, IAS are cylinders of collagen-muscle tissues that surround the urethra and the anal canal. Rupture of the collagen layer lead to weakness of the sphincters and SUI and FI ensues. In addition, rupture of the collagen layer of the vagina leads to vaginal prolapse.

Conclusion: Pelvic organs dysfunction is the main factor that leads to SUI, FI and vaginal prolapse, and not pelvic floor dysfunction. In addition, more than one trouble can be present in the patient simultaneously.

Key words: Collagen; Urinary Continence; Fecal Incontinence (FI); Vaginal Prolapse; Three Dimension Ultra Sound (3DUS); MRI.

INTRODUCTION

Urinary continence depends on high urethral pressure gained by two factors; high wall tension due to the collagen layer constituent of the internal urethral sphincter. In addition, it depends on an acquired behavior gained by learning and training in early childhood how to keep high alpha-sympathetic tone at the IUS maintaining its closure all the time until there is a need or a desire to void. In this work, we put a novel concept on the physiology of defecation.

We can divide the process of Defecation into 2 stages. The first stage, in infancy and early childhood before training: as the rectum is full, sensation of fullness travels along the pelvic para-sympathetic to the spinal cord (S. 2, 3 &4). Then efferent excitatory para-sympathetic impulses cause rectal muscle contraction pushing the rectal contents to the anal canal where the external anal sphincter relaxes finishing the defecation. Then the mother starts to teach her child how to hold up himself until social circumstance allow. Then we gain the second stage by keeping high alpha-sympathetic tone at the internal anal sphincter (IAS) maintaining its closure all the time until there is a need or a desire to empty and social circumstances allow. Sensations of rectal distension travel along the pelvic parasympathetic nerves to the CNS. Controlled by the high CNS centers, the person has the choice to retain or empty rectal contents according to social circumstances available. If he chooses to empty, this will be either for a moment only to release flatus, or for a longer time to pass stool. When social circumstances allow passage of stool, then six synergistic neuro-muscular actions take place. The IAS is a cylinder of collagen-muscular tissues that surround the anal canal, innervated with alpha-sympathetic nerves from T10-L2.

The vagina is a cylinder of collagen-elastic-muscular tissues. The strong tough collagen sheet is the one responsible for the upright position of the vagina. Childbirth trauma injuries the collagen layer due to overstretching of the vagina and leads to flabby and redundant vaginal walls with subsequent vaginal prolapse. It will also leads to lacerations in the IUS, and IAS leading to their weakness and cannot stand against rise of abdominal pressure.

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2012
Running title: Surgical repair of pelvic organs dysfunction

The female pelvis contains three major tracts that lie on and traverse the pelvic floor. These are the urinary bladder and the urethra anteriorly, the genital tract in the middle, and the rectum and anal canal posterior. We put forward three novel concepts on the pathophysiology of the anatomy and functions of these three tracts.

The urinary bladder (UB) stores the urine, which is voided through the urethra. Voiding has two stages: First stage, before training, in infancy and early childhood; sensation of bladder fullness travels along the pelvic parasympathetic nerves to the spinal cord, through spinal cord' center reflex parasympathetic activity (S 2, 3 &4) leads to contraction of the detrusor muscle voiding the urine through an open urethra irrespective of time or place.

Second stage after training: the mother starts to teach and train her infant-child how to hold up till proper social circumstances are available. This is gained by maintaining high alpha-sympathetic tone (T 10-L 2) at the internal urethral sphincter (IUS) keeping it closed all the time till favorable social circumstances allow. Urinary continence depends on a closed urethra with high urethral pressure (Pura), (Pura > 60 cm water) 5. High Pura is due to two factors: the first factor is structural or inherent, and the second factor is behavior or acquired factor.

The inherent factor is the presence of an intact and strong IUS (Figure 2, 3 & 4). The IUS is a collagen tissue cylinder that extends from the urinary bladder neck down to the perineal membrane in both sexes. It is lined with urothelium, with a muscle layer that lies on top and intermingles with the collagen fibers in the middle of the cylinder's thickness. The muscle layer, has a connection above with the detrusor muscle, and has nerve supply from alpha-sympathetic nerves (T 10-L 2). The collagen, is the strongest tissue in our body, gives the IUS the high wall tension that is responsible for the high Pura. The muscle layer is responsible for closing and opening the urethra.

We put forward a recent concept on the Patho-physiology of defecation. There are two (2) stages of the mechanism of defecation.

First Stage of Defecation:
In infancy and early childhood, before training: Stretch receptors in the rectum, impulses of rectal fullness travel along pelvic parasympathetic, S. 2, 3&4, leads to:

1- The rectal muscles contract.
2- The external anal sphincter (EAS) relaxes allowing defection to occur.

The internal anal sphincter (IAS): The IAS is a collagen-muscular tissue cylinder that surrounds the anal canal; surrounded externally by the EAS. Its nerve supply is alpha-sympathetic nerves from the hypogastric plexus.
Its function is:

1- On contraction, to keep the anal canal Closed and empty.
2- On relaxation to open the anal canal.

According to these Novel Concepts, SUI is the result of: a weak, torn IUS. Vaginal Prolapse is: a consequence of weak, flabby, redundant torn vaginal walls. FI is caused by a weak, torn IAS. Therefore, we innovated an operation to treat SUI by exposing the rupture in the IUS & mending the torn sphincter. In addition, we treat vaginal prolapse at the same time by this new operation. In addition, we treat FI at the same time by this novel operation: " Urethro-Ano-Vaginoplasty" "Al Azhar Repair operation" 7; figures 9, 10, 14 & 15. Urethro-Ano-Vaginoplasty, (Al Azhar) repair operation consists of Anterior and Posterior sections. In the anterior section, we correct the SUI and the anterior vaginal wall descent through the following steps:

1- Expose the IUS (we dissect the IUS clear from the anterior vaginal wall).
2- Mend the torn posterior wall of the IUS.
3- Strengthen the anterior vaginal wall by overlapping the two vaginal flaps, by this way; we also add extra support to the mended IUS.

In the posterior section we do:

1- Expose the IAS (by dissecting the torn IAS clear from the posterior vaginal wall).
2- Mend the torn sphincter.
3- Approximate the two levator ani muscles.
4- Strengthen the posterior vaginal wall by overlapping the two vaginal flaps; also, we add extra support to the mended IAS.
5- Repair the perineum.

PATIENTS AND METHODS

Three hundreds women suffering from vaginal prolapse, SUI, and FI were chosen from the gynecology clinics at Al Azhar University hospitals for two years 2009-2010. Consent was taken, after explaining to each patient the nature of the trouble, the investigations that will be done, and the nature of the surgery she will have.

They are all multiparous women, who had vaginal deliveries, ranging from 4 to 10, average 6 labors. Their age ranged between 40 to 50 years, average 44 years. Detailed history and clinical examination were done and proved vaginal prolapse, SUI and fecal incontinence. Three Dimension Ultrasound (3DUS) was done for each patient; Magnetic Resonance Imaging (MRI) was done for 44 patients of them. 300 patients with vaginal prolapse, SUI and FI were assessed clinically and by imaging using 3DUS, and also 30 normal women not suffering from vaginal descent, nor from SUI nor from FI as a control. Three Dimension Ultrasound (3DUS) assessment of the IUS, IAS and vaginal walls was done for the 10 continent women as control and for each patient of the 300 study cases using trans-vaginal route and trans-perineal route by a vaginal probe multi-frequent 5-7.5 MHz, General Electric, integrated 3D-4D Unit (GE Volosone) 730 Pro V machine. In addition, we took specimens from the IUS, IAS and the vagina and were prepared, examined microscopically, and compared to normal tissues.

Each patient had pre-operative evaluation and all necessary investigations e.g. blood (CBC, blood sugar...etc) and urine tests…etc. Any urinary tract infection, the patient was treated according to the result of urinary culture and sensitivity lab test.

RESULTS

Imaging with 3DUS and MRI proved the novel concepts (figures 5, 6, 7, 11, 12 & 13); and histopathological examinations proved that the IUS, IAS are cylinders of collagen-muscle tissues that surround the urethra and the anal canal. Rupture of the collagen layer lead to weakness of the sphincters and SUI and FI ensues. Figures 3-12. In addition, rupture of the collagen layer of the vagina leads to vaginal prolapse. Figures 7 & 13.

Figure 1

Diagram that shows the CNS control of the steps taken in the second stage of micturition. Sensations of bladder filling travels along the pelvic parasympathetic nerves S.2, 3 &4. Controlled by the CNS, depending on the social circumstances, synergistic neuromuscular actions take place. If time and place do not allow voiding, the person will increase the alpha sympathetic tone at the IUS. He will also inhibit the pelvic parasympathetic preventing detrusor contractions. In addition, he will confirm closure of the external urethral sphincter (EUS). When social circumstances allow, he will inhibit the high alpha sympathetic tone at the IUS, thus opening the urethra. He will activate the pelvic parasympathetic inducing detrusor contractions. He will relax the EUS thus allowing voiding. The EUS tone increase to allow propulsion and ejection of the stream of urine and at the end of micturition to squeeze the urethra from the last few amount of urine.

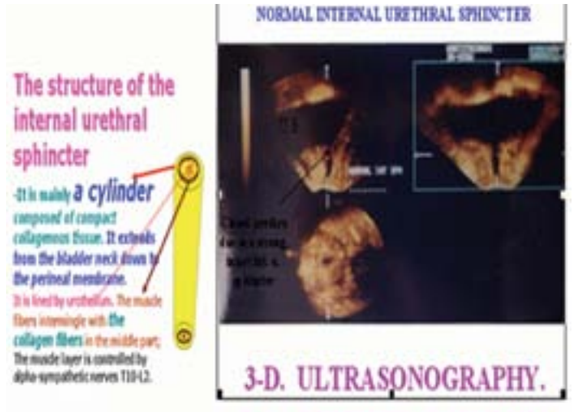

Figure 2

On the left, a diagram of the IUS as a cylinder of collagen-muscular tissue cylinder lined by urothelium is shown. On the right 3DUS image of a normal continent woman with the IUS seen as a cylinder that extends from the urinary bladder neck downwards with 2 echoes overlying each other, and a closed urethra.

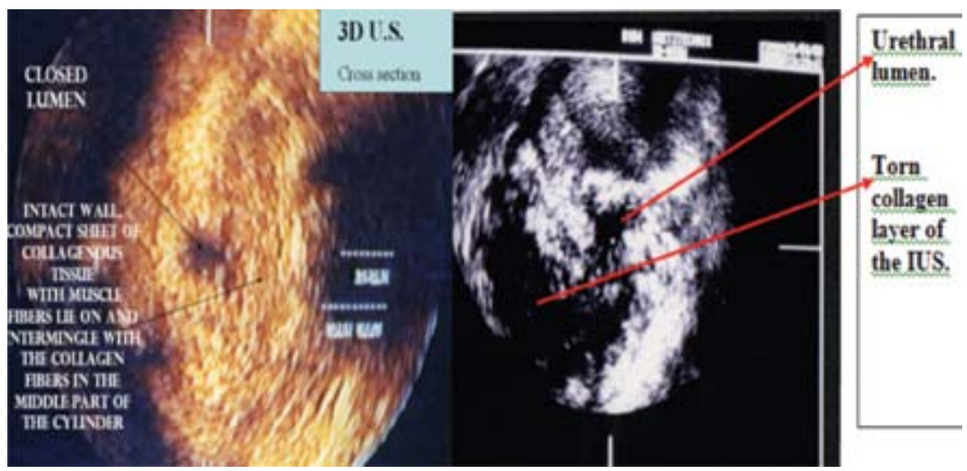

Figure 3
Cross sections of the IUS as seen by 3DUS image; on the left it shows a closed urethral lumen, surrounded by a cylinder of collagen with superimposed muscle on top and intermingling with the collagen fibers in the mid thickness of the cylinder. On the right it shows torn IUS, with wide open urethral lumen.

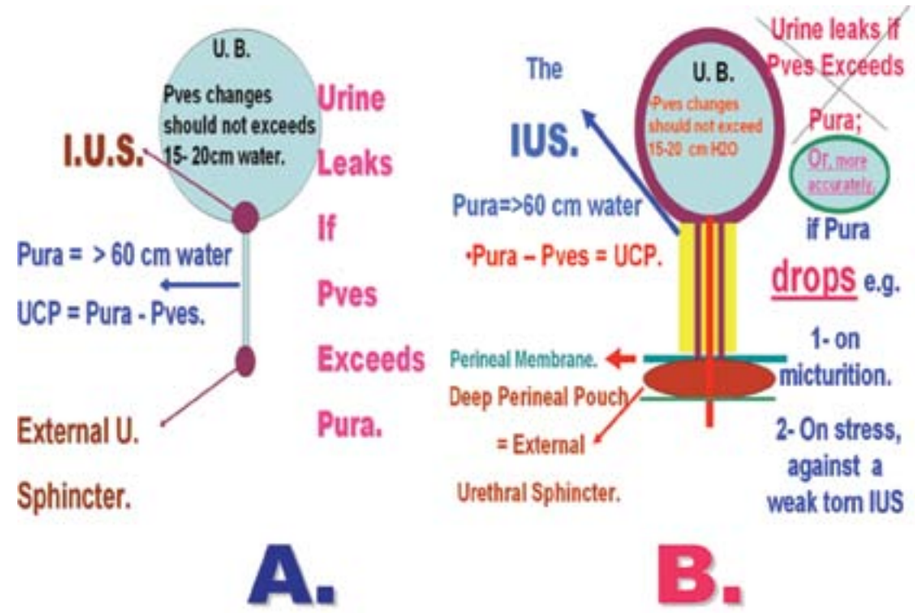

Figure 4

A diagram to explain the site, extent and structure of the IUS and the EUS. On the left, (A) the IUS is a muscular ring at the bladder neck as described classically, on the right (B), the IUS as described in the new way

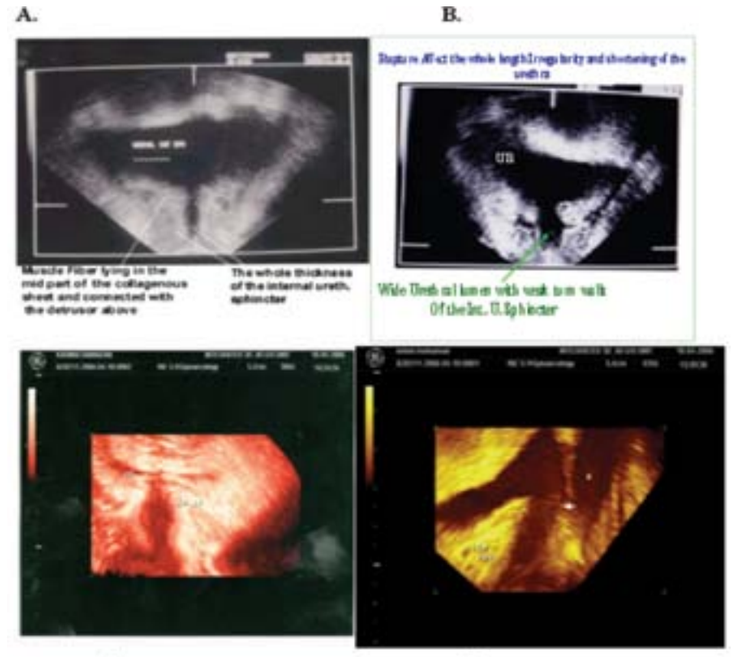

Figure 5
Images by 3DUS, picture (A) a normal IUS, compared to torn IUS (B, C & D). The whole length is torn in (B); the rupture is mainly in the lower part in (C) leading to genuine SUI and flask-shape appearance. There is a loss of Posterior U-V angle in (D) with widely open urethra.

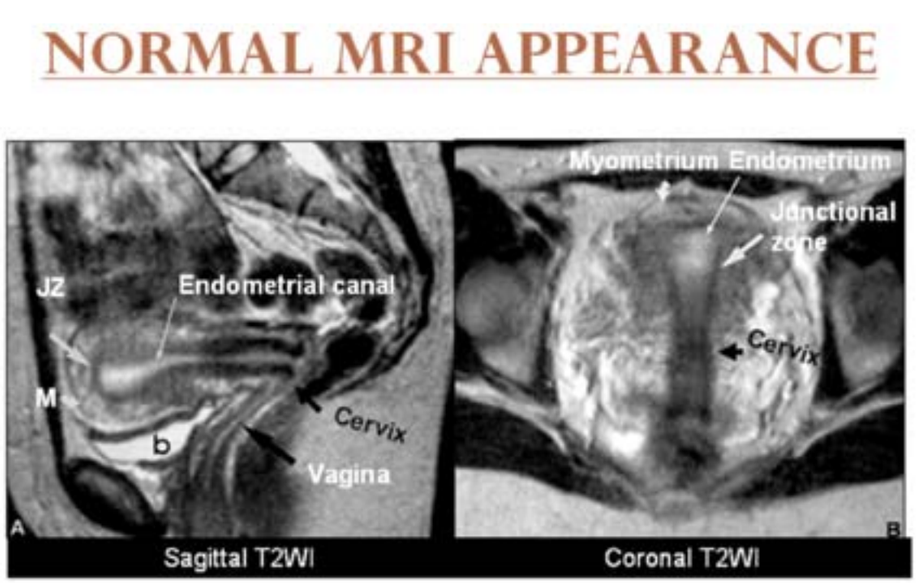

Figure 6

MRI pictures, sagittal and coronal sections, of the urinary bladder, the urethra and the uterus and the vagina. Kindly notice the uniform thickness of the IUS that extends from the bladder neck down to the perineal membrane. Kindly notice the vaginal wall thickness, it is standing up due its tough collagen sheet. Collagen also constitutes the organ capsules, like the urinary bladder and the uterus.

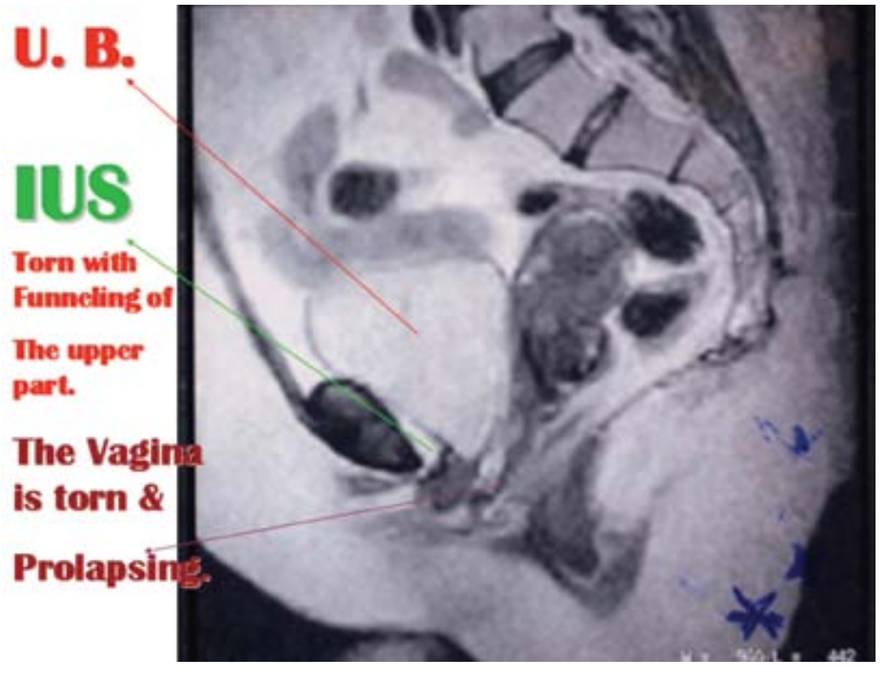

Figure 7

MRI, sagittal view of a patient with DO that shows torn upper part of the IUS with funneling. The IUS is seen clearly as a compact tissue cylinder that extends from the bladder neck downwards.

Figure 8

Diagrammatic representation of the physiology of defecation and its nervous control

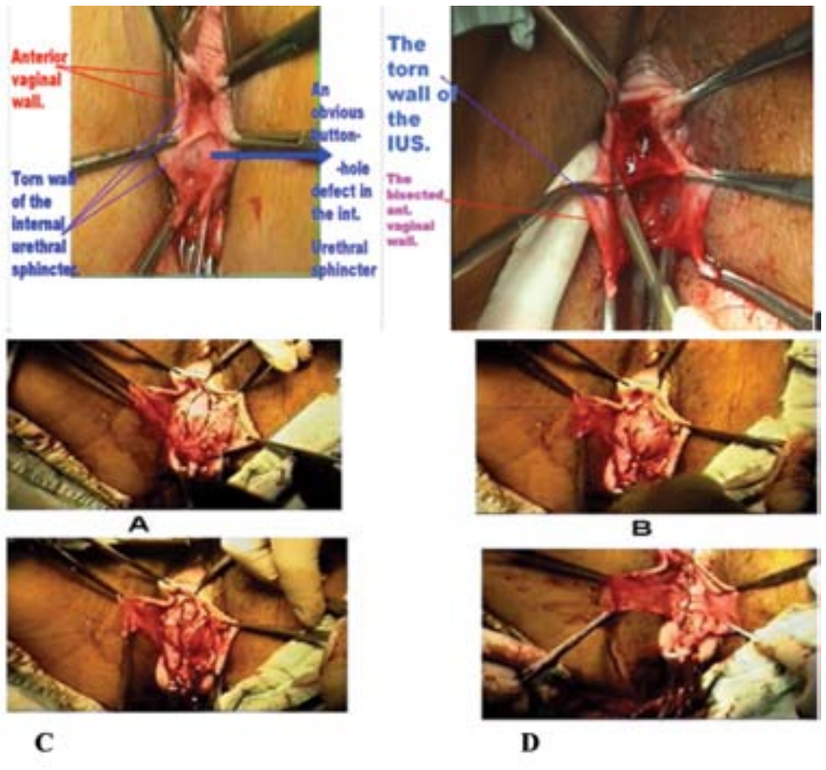

Figure 9

Kindly notice there are 2 edges, first is the edge of the bisected vagina; the second is the edge of the torn IUS. After carefully dissecting and separating the torn posterior wall of the torn IUS, it is mended with simple interrupted sutures.

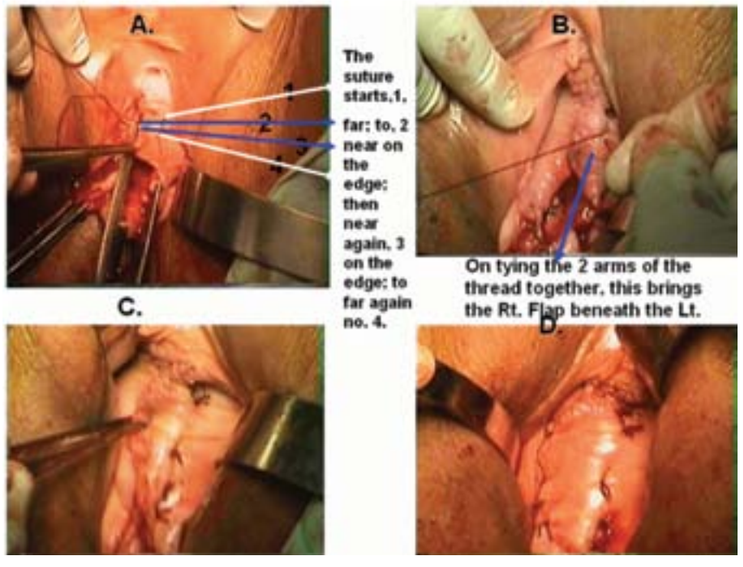

Figure 10

Overlapping the two vaginal flaps is done by a new "dragging" suture that brings the right flap beneath the left one. Then the free edge of the left flap is sutured as far laterally as possible on the right. This will narrow the vagina, preserve the natural collagen to keep the vagina in its upward position and add extra support to the mended IUS.

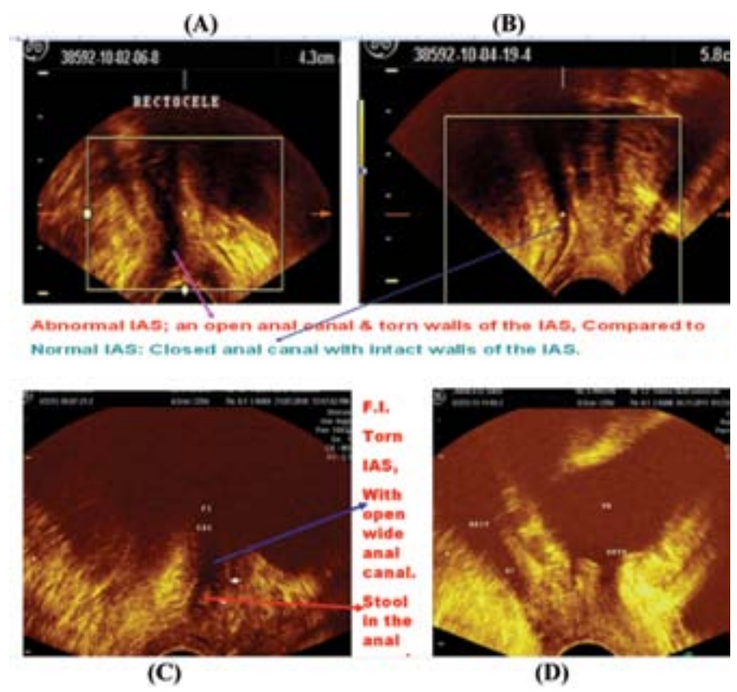

Figure 11

Comparison between torn IAS with an opened anal canal (A), as compared with an intact IAS with a closed anal canal (B) as seen by 3D US images. The anal canal is open and contains stool (C) as is seen by 3DUS; D shows an image by 3DUS of a patient suffering from SUI & FI at the same time with torn IUS and IAS.

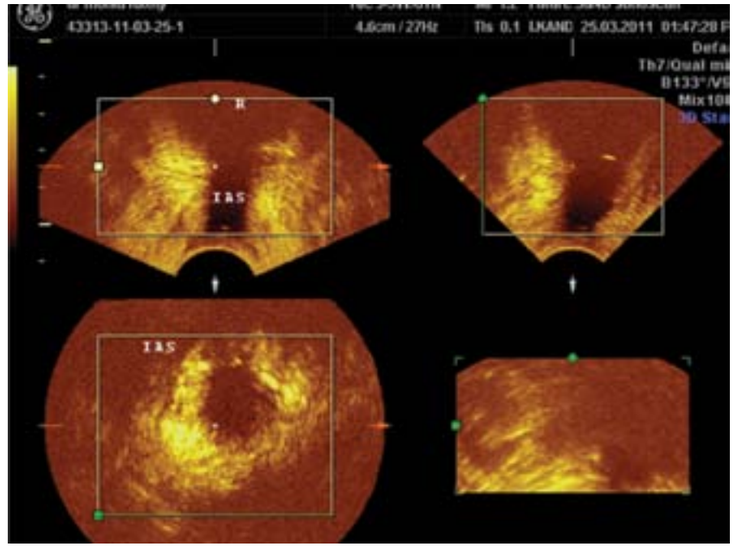

Figure 12

An image with 3DUS of a patient with FI, that show an open anal canal with torn IUS, the cross section looks like a horse-shoe appearance of defective IAS.

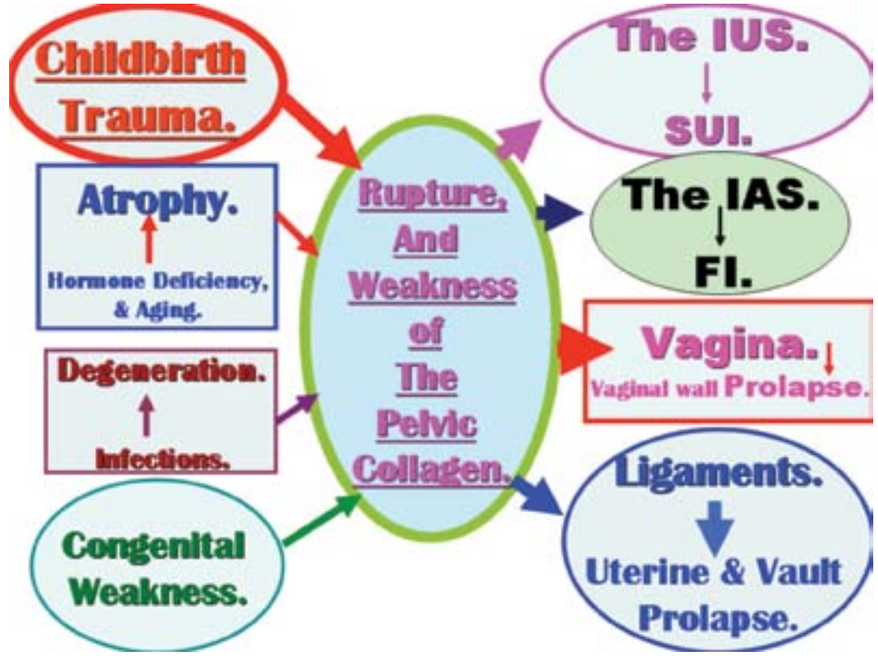

Figure 13

Diagrammatic representation of causes of weakness of the pelvic collagen and its sequels.

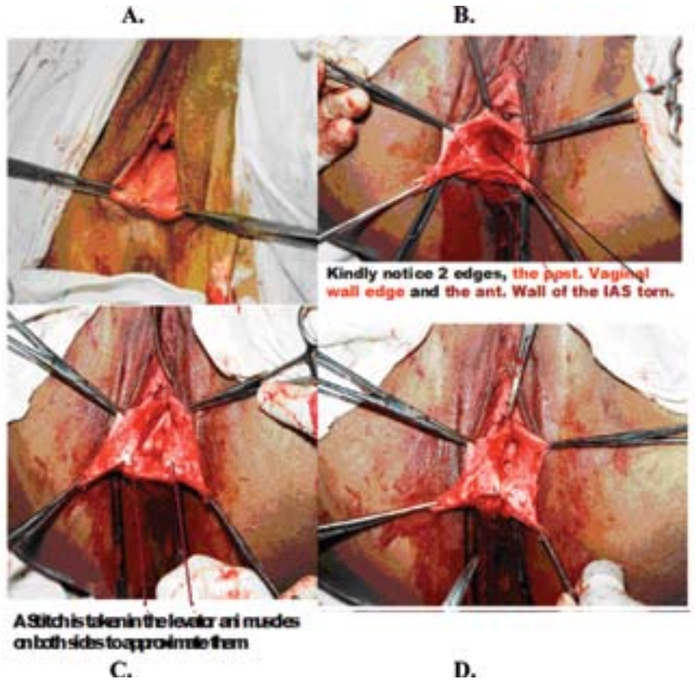

Figure 14

The IAS is torn with its torn anterior wall attached to the posterior vaginal wall. After carefully dissecting and separating the IAS from the posterior vaginal wall, simple interrupted sutures mend it. The sutures are taken in the collagen layer, which is very tough and thick. Sutures, 2-3, are taken in the levator ani muscles and left untied till finishing the mending of the torn IAS, and overlapping the vaginal flaps.

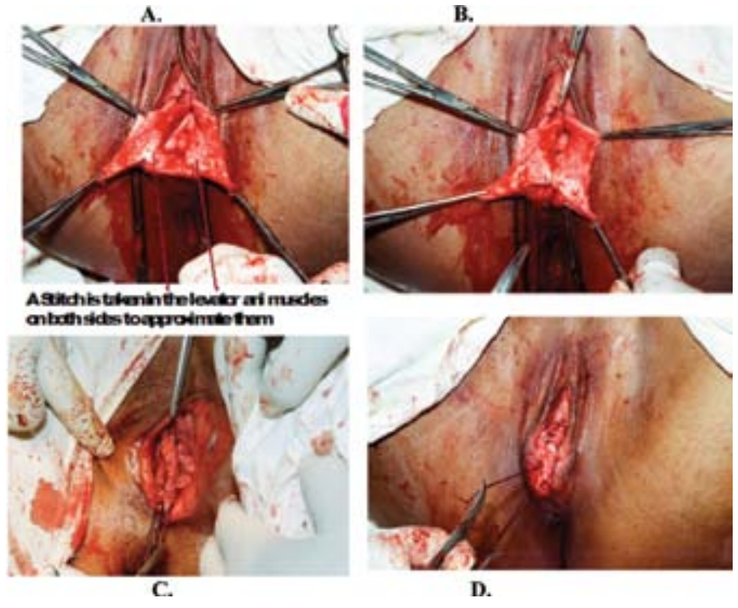

Figure 15

The vaginal flaps are overlapped by " dragging" sutures bringing the right flap beneath the left one then suturing the left flap as far laterally as possible. The two levator ani muscles sutures are then tied and the perineum repaired.

DISCUSSION

High urethral pressure (Pura) which is much higher than vesical pressure (Pves) is the cause of urinary continence (figures 1 & 4). The main causes of high Pura are:

1- The tough constituent of the IUS that have abundant collagen, which creates the high wall tension necessary for keeping high urethral pressure (Pura).
2- The acquired high alpha-sympathetic tone at the IUS that keep it closed all the time.

Drop of one or both factors leads to leak of urine. This drop in Pura happens:

1- Physiologically when we voluntary inhibit the high alpha-sympathetic tone at the IUS that leads to opening the urethra and voiding occurs.
2- Pathologically because of rupture, atrophy and degeneration of the collagen sheet of the IUS. The weak IUS will not stand against sudden rise of abdominal pressure as on cough, sneezing, jumping, coitus, or sometimes getting up.

Childbirth trauma causes rupture of the collagen layer of the IUS leading to its weakness. Drop in estrogen level causes atrophy of the pelvic collagen and subsequent weakness. Chronic and or repeated genito-urinary infections cause degeneration of the collagen of the IUS and of the vagina that lead to it's weakens causing SUI and vaginal prolapse, figure 13. 3DUS and MRI we can see the rupture in the IUS clearly. The level of the rupture along the cylinder of the IUS and its extent will determine the type of SUI (DO, genuine SUI or mixed type of incontinence) and the morphological shape of the urethra seen on imaging. If the rupture affects mainly the upper part of the IUS, detrusor over activity (DO) ensues, and funneling of the bladder neck with loss of urethra-vesical angle is seen on imaging. When the main damage is in the lower part of the IUS, it will lead to genuine SUI, and a "flask-shape" appearance is seen on imaging. If the damage affects the entire length of the IUS, then mixed type of urinary incontinence is the result, and a collapsed, apparent short urethra with irregular walls is seen on imaging figures 5 & 7.

Normally, the anal canal is empty and closed with intact IAS, and strong intact EAS. Figure 11.

In patients with FI the IAS is torn and the anal canal is wide and open, as is seen by imaging with 3DUS figures 11 & 12.The EAS can be assessed clinically, in addition to imaging with 3DUS. Many studies have shown that on ultrasound, fecal incontinence is strongly associated with anal sphincter defects; patients most often have a combined external and internal sphincter defect, or an EAS defect alone; isolated IAS defects are rare 9, 17. We believe that isolated IAS defects are much more prevalent than recorded, and it is a major cause of FI.

The vagina is standing up due to its own strong collagen sheet, which gives it strength and stout upright position. Childbirth trauma injuries its collagen sheet leading to flabby, redundant vaginal wall which collapse, prolapse. The injury affects, more the transverse diameter leading to patulous vagina. Clinically we can prove this as well, in nulliparous women the vagina is H-shape, which changes with parity to transverse slit.
There had been trials to evaluate the role of 3DUS in urinary continence and surgical treatment of SUI; 9, 10 & 11.

3DUS has been used in the assessment of patients with urinary incontinence by imaging the urethral morphology and measuring the urethra and its sphincter. 3DUS imaging had shown that women with SUI have urethral sphincters that are shorter, thinner, and smaller in volume 8. There had been debate about the urinary continence mechanism, whether it is related to an extrinsic mechanism such as a sling that is located under the urethra that is pulled upward and compresses the urethra during pelvic floor contraction, 9. Alternatively, whether it is related to an intrinsic mechanism such as striated sphincter that contracts down on the urethral lumen when the pelvic muscles contract 20. With use of 3DUS there was a trial to elucidate the urethral continence mechanism 10 &11. With use of a transrectal transducer, the morphology of the urethra was recorded and the urethral diameters, sphincter, and smooth muscle lengths as well as their thickness and volumes were measured. Those investigators found that urethral diameters and sphincter thickness were smaller during pelvic floor contraction compared with pelvic floor relaxation. In addition, total urethral and sphincter volumes are smaller during contraction compared with relaxation. The smooth muscle complex of the urethra did not change in thickness or volume during contraction periods compared with relaxation periods. Those investigators concluded that the urethral continence mechanism was extrinsic and occurs because of external compression by paraurethral tissues rather than intrinsic contraction of the urethral sphincter 10 &11.

Conclusions

We demonstrated that urinary continence depends on high urethral pressure (Pura). Intact and strong collagen sheet of the IUS creates the high wall tension necessary to have high urethral pressure. In addition the acquired behavior gained by learning and training in early childhood of keeping high alpha-sympathetic tone at the IUS confirm its closure all the time and add to the high urethral pressure.

Again, strong and intact collagen of the IAS, in addition to maintaining high alpha-sympathetic tone at the IAS is extremely important factor of preventing FI. Pelvic collagen is the most important factor of maintaining the shape, state, position and functions of the pelvic organs. It is hormone dependent and loss of steroid hormones causes its atrophy and weakness. Childbirth trauma is the main cause of its injury and weakness. Cumulative effects of injury, hormone deficiency plus degenerations from chronic or repeated infections lead to its weakness and pelvic organs dysfunction.

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Cardiovascular status and metabolic syndrome among young women with polycystic ovarian syndrome in a rural area in Egypt

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Abstract

Objective: To evaluate the cardiovascular status and risk factors among active non smoker young PCOS women, in a rural community in Egypt, with or without features of MS. Materials & Methods: A case control study comprised of 312 PCOS women who were recruited from the Outpatient Clinics, Mansoura University Hospitals fulfilling the Rotterdam consensus criteria (2003) of PCOS. They comprised of 122 women who fulfilled the definition criteria of MS according to National Cholesterol Education Program and the Adult Treatment Panel III, 2001.The remaining 190 cases did not fulfill the definition criteria (non- MS PCOS). A healthy age-matched control group of 50 women free of PCOS were also included. All cases and control underwent ECG-QTc interval analysis, echocardiography for interventricular septum diameter (IVSD) and ejection fraction (EF) estimation, and carotid intima media thickness (cIMT) by ultrasound Doppler study.

Results: Cardiovascular abnormalities were significantly higher among the MS-PCOS cases compared to non- MS PCOS, significant prolongation of QTc interval (P 0.03) with evident QT dispersion (P 0.018), significant increase in IVSD (P 0.03), insignificant decrease in EF and significant increase in cIMT (P 0.046) in PCOS cases with MS. On the other hand, the non- MS PCOS cases showed significant prolongation of QTc interval (P 0.049), significant increase in IVSD (P 0.004) significant decrease in EF (P 0.039) and significant increase in cIMT (P 0.018) when compared to the healthy control women.

Conclusion: Many cardiovascular risks are frequent and evidence of premature atherosclerosis is existent among young women with PCOS, being even more exaggerated if there is associated MS. Early intervention to ameliorate cardiovascular risks for these cases is an important health care demand.

Keywords: Polycystic ovary syndrome, metabolic syndrome, cardiovascular risks.

Introduction

The new millennium has brought intense focus on the risk of cardiovascular disease (CVD) in women especially those with features of metabolic syndrome (MS) (1). PCOS is the most common endocrine disorder worldwide being not only a reproductive disorder but a multifaceted syndrome with insulin resistance (IR), substantial metabolic and long term cardiovascular (CV) consequences (2). Serial CV risk factors in MS are present at early age in PCOS women and IR appears to be the key factor linking these risk factors (3). Ehrmann and coworkers (4) reported that MS and PCOS have many features in common and usually have the same pathogenesis. However, Cusson et al (1) reported that the real increase of CVD in PCOS women remains unclear and definitive data are lacking and more studies are needed to define the magnitude of CV risk and CV disease in PCOS with or without MS (3). The aim of this work was to detect the CV risk factors and the CV manifestations present in women with PCOS with and without MS in a case control study.

Patients & methods

The studied cases included 312 women who were enrolled from patients attending the outpatient clinics, Mansoura University Hospital because of obesity, oligomenorrhea, amenorrhea and/or hirsutism after confirmation of the presence of PCOS according to the Rotterdam criteria (5). The study protocol was approved by the ethical committee and informed consents were obtained.

Clinical examination and laboratory investigations were carried out stressing on symptoms and signs of MS according to National Cholesterol Education Program and the Adult Treatment Panel III (NCEP- ATP III) (6); namely 3 or more of the following conditions; waist circumference >88 cm, BP >130/85mmHg, TG >150 mg/dl, FPG >110 mg/dl, HDL-C <50 mg/dl.

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Waist circumference was assessed in the standing position midpoint between the highest point of iliac crest and the lowest point of the costal margin in the mid axillary line. BMI was calculated as weight (kg)/height (meter)2. Blood pressure was measured twice at 30 minutes intervals by using a standard mercury manometer and the mean of two readings was used for analysis (7).

Secondary causes of hyperandrogenism were excluded by appropriate clinical and laboratory tests. Women with known diabetes mellitus, hypertension, hepatic or renal disorders and women receiving antihypertensive, lipid lowering drugs were also excluded. The studied women were not desiring pregnancy and were not receiving oral contraceptives. Fasting plasma glucose level was measured by autoanalyzer by the glucokinase method. Insulin measurements were performed by using a polyethylene glycol accelerated double antibody radioimmunoassay method. TG was measured enzymatically on a chemistry autoanalyzer and free testosterone was assessed together with HDL-C estimation (8). Twelve lead electrocardiographies were undertaken with stress on ischemia, arrhythmia, QTc, QTd. Echocardiographic assessment was carried out with stress on IVSD, EF, together with measurement of cIMT for the studied cases and the reference groups.

Statistical analysis

Statistical analysis was performed by using SPSS statistical package for social science program version "16". The qualitative data were presented as frequency and percentages. The quantitative data were examined by using Kalmogrov-Smirnov test to test for normal distribution of the data when parametric, expressed as mean and standard deviation. Student t test was used, to test for difference in normally distributed quantitative data between the two groups. Mann-Whitney-μ test was used for comparison between two groups when data were not normally distributed. Significance was considered when P value was less than 0.05.

Results

Out of the 312 women with PCOS, 122 cases fulfilled the NCEP and the modified ATP III for the diagnosis of MS making the prevalence of MS among PCOS women to be 39.11%. The prevalence of MS increased significantly with age, BMI, IR and free testosterone plasma level (table II). The most dominant component of MS was the increased waist circumference (>88 cm) being present in 77.87% of PCOS women, followed by lowered HDL-CL plasma level (75.41%). Hypertriglyceridemia was present in 28.69% and BP elevation was present in only 20.5%. Elevated FPG was detected in only 17.21% of women with PCOS (table III).

Among the studied CV variables, QTc and QTd were significantly higher among the MS PCOS cases compared to non- MS PCOS: significant increase in IVSD, insignificant decrease in EF and increase in cIMT in PCOS cases with MS. On the other hand, the non- MS PCOS cases showed significant prolongation of QTc interval, significant increase in IVSD and significant increase in cIMT (P 0.018) when compared to the healthy control women (table IV). In the present study higher left ventricular mass (LVM), higher left atrium size, and lower LVEF and early to late mitral flow velocity were observed in both groups of PCOS in comparison to control (table IV).

Table (I): Demographic characters of the studied PCOS women.

	No. of cases	Percentage
Age		
≤30 years	125	40.07%
>30 years	187	59.94%
BMI		
< 25	125	40.07%
25-30	94	30.13%
>30	93	29.81%
Insulin resistance		
FBG/FI ≤4.5	190	60.9%
FBG/FI >4.5	122	39.11%
Free testosterone		
< 2 mmol/L	78	25%
≥2 mmol/L	234	75%

Table (II): Prevalence of metabolic syndrome according to age, BMI, IR, free testosterone

Risk parameters		PCOS without MS (n=190)	PCOS with MS(n=122)	P
Age	≤30 years	95 (50%)	30 (24.59%)	<0.001
	>30 years	95 (50%)	92 (75.41%)	
BMI	<25	120 (63.1%)	5 (4.09%)	<0.001
	25-30	64 (33.6%)	30 (24.5%)	
	>30	6 (3.1%)	87 (71%)	
Insulin resistance	FBG/FI ≤4.5	98 (51.6%)	92 (75.41%)	<0.001
	FBG/FI >4.5	92 (48.4%)	30 (24.59%)	
Free testosterone	≥2 mmol/L	134 (70.5%)	100 (81.9%)	0.023
	<2 mmol/L	56 (29.5%)	22 (18.1%)	

Table (III): Prevalence of individual components of metabolic syndrome in PCOS patients

Components of metabolic syndrome.	PCOS withMS (total no. 122 cases)	% of cases
HDL <50 mg/dl	92	75.4%
Waist circumference ≥88 cm	95	77.87%
TG ≥150 mg/dl	35	28.69 %
BP≥130/85 mmHg	25	20.5%
FPS ≥110 mg/dl	21	17.21%

Table (IV): Demographic characters of studied groups versus the control group.

(mean ± SD)	PCOS with MS (n=122)(1)	PCOS without MS (n=190) (2)	Control (n=50) (3)	P(1- 3)	P(2- 3)	P (1- 2)
Age	29.2± 4.3	28.9± 4.5	29.91± 3.3	0.80	0.244	0.55
BMI	28.4± 2.2	28.8± 2.5	28.5± 2.1	0.389	0.780	0.138
Insulin resistance (FBG/FI)	3.9± 1.7	4.3± 1.8	4.6± 0.1	0.023	<0.001	0.048
Free testosterone (mmol/L)	1.8± 0.9	1.6± 0.8	1.1± 0.6	<0.001	<0.001	0.046
HDL(mg/dl)	45.5± 12.9	48.8± 13.5	54.7 ± 11.2	<0.001	<0.001	0.031
Waist circumference(cm)	88.5± 01.2	75.5± 1.1	74.5± 2.4	0.004	<0.001	<0.001
TG (mg/dl)	126.8± 12.9	121.8±20.1	116 ±16.2	0.033	<0.001	0.007
SBP(mmHg)	125± 15.5	120 ± 13.6	116 ± 9.2	0.015	<0.001	0.003
DBP(mmHg)	83± 9.9	80 ± 8.8	76.6 ± 9.9	0.028	<0.001	0.006
FPS (mg/dl)	95.1± 9.8	93.2± 9.9	89.2± 8.9	0.006	<0.001	0.097

Table (V): Cardiovascular abnormalities in studied groups versus the control group.

(mean ± SD)	PCOS with MS (n=122) (1)	PCOSwithout MS(n=190) (2)	Control (n=50) (3)	P(1-3)	P(2-3)	P(1-2)
QTc interval (ms)	456± 30	445± 50	435± 20	<0.001	0.031	0.016
QT dispersion (sec)	0.05±0.04	0.04 ±0.03	0.03±0.02	0.005	<0.001	0.018
IVSD	11.1 ± 0.8	10.9 ± 0.8	10.5 ± 0.9	0.004	<0.001	0.03
EF	69.8± 2.9	70.2± 2.8	71.2± 3.1	0.039	0.006	0.229
cIMT(cm)	0.845± 0.21	0.798±0.19	0.765±0.01	0.018	<0.001	0.046

Discussion

The prevalence of MS among women with PCOS in the present study is 39.11. This is nearly similar to many previous studies (4, 9), but lower than the findings of Dokras et al (10), Carmina (11) who reported that nearly 50% of women with PCOS have MS. While the results of Hahn et al (12) are much lower (31.5%). The differences in the prevalence of MS among women with PCOS could be due to racial or ethnic characteristics and/or differences in the diagnostic criteria adopted for the diagnosis of PCOS and MS. Carmina and coworkers (13) utilizing the ATP III criteria found the prevalence of MS to be 8.2% and by using the WHO criteria to be 16% in Italian women with PCOS.

The prevalence of MS increased with age from 24.59% in the group below 30 years to 75.41% in the group >30 years (P <0.001). This is contradictory to Dokras et al (10), Trevor et al (7) and Orchard et al (14) who found that the incidence of MS did not vary substantially by age. However, the present findings are in agreement with the result of Grant and Meigs (15) which revealed an increasing prevalence of IR in elderly populations.

The prevalence of MS in the studied women was positively related to BMI. This confirms the results of Coviello et al (9) who found none of the girls of normal BMI having MS, whereas 63% of obese PCOS were having MS.

The increased IR in the studied group of PCOS is in agreement with Orio et al, (16), Carmina et al (13). In Hahn et al (12) study, IR was the most common metabolic abnormality in PCOS being present in 71%. In our series IR was present in 75.4%.

The present results illustrated that the prevalence of MS is increased in PCOS cases having higher free testosterone. This is in accordance with Apridonidze et al (17) who concluded that women with PCOS and MS differ from their counterparts lacking the MS in terms of increased hyperandrogenemia and more severe IR.

The significant elevation of free testosterone plasma level in women with PCOS (75%) are confirmatory to those of Chang et al (18) who found that the clinical phenotypes of PCOS have frank hyperandrogenemia and also in agreement with the Consensus Development Conference ADA in 1998 (19). The latter stressed on the biochemical criteria particularly hyperandrogenemia to diagnose PCOS.

Despite the known association between PCOS and glucose intolerance (20), the present study shows that abnormalities in both HDL-C and TG together are more common than FPG. Dokras et al (10) found similar results on white females with PCOS. The common presence of lipid abnormalities over FPG abnormalities emphasizes the greater importance of screening for dyslipidemia together with FPG in women with PCOS. The infrequent "hyperglycemia" in the present series is against the WHO criteria for diagnosing MS (21), where DM, impaired glucose tolerance (IGT) are prerequisites plus any two clinical or biochemical abnormalities (high BP, dyslipidemia, central obesity, microalbuminuria).

In spite of the significant increase in CV risk factors in PCOS with MS and those without MS in relation to matched control groups, there was no clinical manifestation of CV changes. Dokras (22) described PCOS as a silent preclinical CV disorder that has to be screened and managed early to guard against manifest atheroscle-

rosis. Increased cIMT which is a surrogate marker of early subclinical atherosclerosis (23) was observed more in the group of PCOS with MS than PCOS alone groups and both in relation to the control group. Although the present finding is confirmatory to many previous studies (24, 25, 26), yet it is not in accordance with Meyer et al (27) who found no difference in the mean cIMT between PCOS and control in spite of significant increase in CV risk factor, lipids, insulin resistance and increased pulse wave velocity (PWV). Also it is not in agreement with Costa et al (28) who found no difference in PCOS versus control. However, Talbott and coworkers (29) found that the PCOS remained associated with increase cIMT independent of insulin resistance or visceral fat. Lackhani et al (25) advised the development of new strategies like cIMT for screening PCOS cases even in young aged women < 35ys.

Calculating the QTc interval and the QTd which is the difference between the maximum and the minimum QTc interval revealed significant prolongation in PCOS with MS followed by PCOS group in comparison to the control groups and the QTd was significantly more frequent among the two groups in relation to the control group. These results are in accordance with Seyfeli et al (30), who found that obese women had higher maximum P wave duration and QTd and concluded that obese women may not only be at risk of ventricular arrhythmia but also at atrial arrhythmia.

The prolonged QTc and increased QTd could point to silent CVD dysfunction. However, Orio et al (31) reported the lack of electrocardiographic changes in women with PCOS and the QTc, QTd were not significantly different in relation to the controls. Meden Vertovec et al (32) found that the QTc intervals were even shorter. Shroff et al (33) concluded that young obese women with PCOS have a high prevalence of early asymptomatic coronary atherosclerosis compared with obese control and they advised to screen and aggressively counsel and treat PCOS women to prevent symptomatic CVD.

Echocardiographic study revealed that all systolic function parameter were comparable in the PCOS with or without MS to the control group except that patients with PCOS had significantly lower ratio between the early and late peak mitral flow velocities and longer isovolumic relaxation time representing a trend for non restrictive type of diastolic dysfunction with higher LVM. Our results are confirmatory to Tiras et al (34). On the other hand, Yarali et al (35) showed evidences of restrictive cardiomyopathy.

Conclusion

Many cardiovascular risk factors are frequent with evidence of premature atherosclerosis which exists among young women with PCOS being more exaggerated if there is associated MS. Early intervention to ameliorate the CV risks for these cases is an important health care demand.

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Clampless vaginal hysterectomy in women with nonprolapse: evaluation of a new technique

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ABSTRACT

Background: Vaginal hysterectomy is the least invasive method of removal of uterus. Most of hysterectomies can be performed vaginally. The lower rate of vaginal hysterectomy is not only due to the relative contraindications to the vaginal route of hysterectomy but also due to the technical barriers in the mind of most surgeons to deal with inadequate accessibility, poor visibility and effective hemostasis even after considerable experiences. I aim to evaluate a clampless technique for vaginal hysterectomy in comparison to the standard technique in patients without genital prolapsed.

Methods: After ethical approval, 46 women admitted to Gynecology Department, Mansura University Hospital for hysterectomy for benign lesions during the period from May 2009 to November 2011 had been divided to 2 groups; group (A): comprised 21 women in whom a clampless technique used, and group (B) comprised 25 women in whom the standard technique using clamps has been used.

Results: The study comprised 46 women assigned for vaginal hysterectomy for benign indication mostly abnormal uterine bleeding. They were divided randomly into 2 groups; group- A (21 women), for whom a clampless vaginal hysterectomy was performed, while the other group- B (25 women) used as a control (standard) group for whom the standard technique for vaginal hysterectomy was performed.

There were no statistically significant difference between both groups regarding the demographic data (p- value > 0. 05) in all. The mean age for both groups was 51.7 and 52.0 years respectively. The mean gravidity was 4.14 and 4.92 respectively. Mean parity for group A was 3.47 and that for group B was 3.16. T he BMI was 29.28 kg/m2 for group A while 29.16 kg/m2 for group B.

No statistically significant differences were found between both groups as regards the preoperative uterine volumes 232.8 mL vs. 213.0 mL respectively. The mean operative time (in minutes) for vaginal hysterectomy in group A was 92.3±7.45 while it was 94.0± 5.86 with no significant difference between both groups. The mean values of pre and postoperative hemoglobin concentrations were not significantly different in the two study groups (Figure 1).

Conclusion: Finally we can conclude that clampless vaginal hysterectomy is a technique that can be practiced as alternative to traditional technique using clamps.
Keywords: clampless, vaginal, hysterectomy

INTRODUCTION

Vaginal hysterectomy is the least invasive method of removal of uterus. Most of hysterectomies can be performed vaginally. The lower rate of vaginal hysterectomy is not only due to the relative contraindications to the vaginal route of hysterectomy but also due to the technical barriers in the mind of most surgeons to deal with inadequate accessibility, poor visibility and effective hemostasis even after considerable experiences (1).

There is considerable evidence from observational and uncontrolled studies showing that vaginal hysterectomy is associated with several advantages over abdominal hysterectomy . Apart from the cosmetic benefit , complications are less frequent , recovery is faster and overall treatment costs are reduced (2). The advent of laparoscopic hysterectomy has not altered these conclusions (3).

Non-descent vaginal hysterectomy is a more skilled procedure and has a learning curve; however, it can be mastered provided the correct approach and technique is adopted (4). In this study, I tried to evaluate a new technique in which I ligate the uterine pedicle without clamping them first using a pair of aneurysm needles a right and a left aneurysm needles.

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Patients & Methods

The study was approved by Mansura medical research ethics committee. Women admitted to Gynecology Department, Mansura University Hospital for hysterectomy for benign lesions during the period from May 2009 to November 2011 had been divided to 2 groups; group (A): comprised 21 women in whom a clampless technique used, and group (B) comprised 25 women in whom the standard technique using clamps has been used.

For all women included, complete physical examination was performed to exclude the non appropriate cases included in the exclusion criteria. Trans vaginal ultrasound was performed to each woman to confirm the data of local gynecologic examination and to estimate the uterine volume using the formula (uterine volume= length x width x depth x 0.542) . These measurements excluded the cervix. Cases with uterine volumes more than 400cm3 were excluded from the study. An informed consent was taken from each woman included.

Exclusion criteria included those with uteri larger than 12 weeks gestational size, uterine volume>400 cm3, presence of adnexal masses > 8cm, fixed uterus on bimanual examination, previous pelvic operations (including cesarean section), suspicion of malignancy, narrow sub-pubic angle : less than 2 finger breadth, presence of genital prolapse.

The technique:

For both groups; the patient is put in lithotomy position, with regional or general anesthesia according to the choice of the anesthetist, sterilization and draping with sterile towels. Vagina and cervix swapped with gauze soaked in 10% povidone iodine solution, insertion of urinary catheter, bimanual examination to confirm the uterine size, mobility, and presence of any adnexal or pelvic masses. Two of multi-toothed volsellum will be applied to the cervix one for each cervical lip for traction. Cervical circumcision performed with scalpel, then dissection of an area of 3cm all around the cervix. The volsellum applied the posterior cervical lip is lifted up to expose the posterior fornix. The cul-de-sac is opened with a scissors .The the right uterosacral ligament is palpated between the thumb and index of the right hand making sure the no adhesions in the vicinity.

In group A: A right aneurysm needle loaded with double strand polyglycolic acid suture number 1 is passed around the right uterosacral pedicle, after loosing the suture material each strand will make a ligature, thus we will have 2 proximal ligatures; the second should be cut long leaving an adequate length of suture material for the purpose of vault suspension. The same aneurysm needle with a single strand polyglycolic acid suture is re-inserted half a centimeter distal to the last knot to make a distal ligature. The pedicle is cut with a scissor between the proximal 2 ligature and the distal one. The same is done on the left side using a left aneurysm needle. The index finger is inserted adjacent to the cervix to get around the mackenrodt-uterine pedicle with anterior retractor to elevate the bladder. An ipsilateral aneurysm needle with double strand polyglycolic acid suture number 1 is passed through the course of the finger applying 2 proximal ligatures to the mackenrodt-uterine pedicle the 2nd ligature is left long for vault suspension. A distal ligature is placed a centimeter distal by reinsertion of the appropriate aneurysm needle. The pedicle is divided between the 2 proximal and the distal ligature.
The peritoneum of the uterovesical pouch is opened over the uterine fundus after pushing the fundus anteriorly by 2 fingers in the cul-de-sac, then the infundibulopelvic pedicle is ligated & divided using the same technique as with the other 2 pedicles. The uterus is removed, pedicles checked up for bleeding, ovaries inspected, then the peritoneum closed, and suspension suture tied in a criss-cross pattern, the vaginal vault closed.

In group B: the pedicles are divided between two proximal and one distal clamps, the ligature is applied; the first (most proximal) is simple ligature, the second is transfixation with round needle. The other steps are the same.

Both techniques are compared regarding operative time, exposure during operation, suture material consumption, intra-operative bleeding, post-operative bleeding, bladder injury, ureteric injury, postoperative pain

Statistical analysis

Data was tested for normality using Kolmogorov-Smirnov test. An unpaired Student's t test was used to compare the parametric values of the two groups; Mann-Whitney U test was performed to compare the non-parametric values of the two groups. Serial changes in data were analysed with repeated measures analysis of variance. Chi square test was used to compare categorical data in the studied groups. Data was expressed as mean (SD) or numbers (percent). A value of $P<0.05$ was considered to represent statistical significance.

Results

There was no significant difference regarding the patients' demographic data (table-1). There were no significant differences in the preoperative data between both groups regarding the uterine volume, type of anesthesia, indication for hysterectomy, pre-operative hemoglobin concentration and preoperative endometrial histology (table-2, figure-1).
Regarding the postoperative (outcome) data, there was no significant difference between both groups in duration of surgery, post-operative uterine weight or postoperative hospital stay (table-3)

Table (1): Patients' demographics.

	Clampless vaginal delivery (n = 21)	Standard vaginal hysterectomy (n = 25)
Age (yrs.)	51.7 ± 3.22	52.0 ± 2.87
Gravidity	4.14 ± 1.19	4.92 ± 1.18
Parity	3.47 ± 1.07	3.16 ± 0.74
BMI (kg/m²)	29.28 ± 2.96	29.16 ± 1.84

Data are presented as mean ± SD. Abbreviation: BMI; body mass index. Significant when $P<0.05$

Table (2) Preoperative data:

	Clampless VH (n = 21)	Standard VH(n = 25)
Preoperative uterine volume (mL) Type of anesthesia	232.8 ± 43.56	213.0 ± 36.74
Spinal	13 (61.9%)	17 (68%)
General	8 (38.1%)	4 (1.6%)
Indications of hysterectomy		
Peri-menopausal bleeding	20 (95.2%)	19 (76%)
Post-menopausal bleeding	1 (4.8%)	3 (1.2%)
Preoperative endometrial histology		
Simple Endometrial Hyperplasia without atypia	13 (61.9%)	11 (44%)
Regressive endometrium under hormonal therapy	2 (9.5%)	3 (1.2%)
Secretory Endometrium	3 (14.3%)	4 (1.6%)
complex hyperplasia without atypia	2 (9.5%)	0 (0.0%)
Proliferative endometrium	1 (4.8%)	3 (1.2%)

Data are presented as mean ± SD. Abbreviation: BMI; body mass index. Significant when P <0.05.

Table (3) Outcome data

	Clampless vaginal delivery (n = 21)	Standard vaginal hysterectomy (n = 25)
Duration of surgery (min.)	92.3 ± 7.45	94.0 ± 5.86
Postoperative uterine weight (gm.)	202.1 ± 52.61	186.6 ± 43.61
Postoperative hospital stays (hrs.)	30.9 ± 5.61	28.9 ± 2.95

Data are presented as mean ± SD. Abbreviation: gm.; grams. Significant when P <0.05.

Disscussion

The study comprised 46 women assigned for vaginal hysterectomy for benign indication mostly abnormal uterine bleeding in Mansura university hospital. They were divided randomly into 2 groups; group- A (21 women) , for whom a clampless vaginal hysterectomy was performed, while the other group- B (25 women) used as a control (standard) group for whom the standard technique for vaginal hysterectomy was performed.

There were no statistically significant difference between both groups regarding the demographic data (p value > 0. 05) in all. The mean age for both groups was 51.7 and 52.0 years respectively. The mean gravidity was 4.14 and 4.92 respectively. Mean parity for group A was 3.47 and that for group B was 3.16. T he BMI was 29.28 kg/m2 for group A while 29.16 kg/m2 for group B.

No statistically significant differences were found between both groups as regards the preoperative uterine volumes 232.8 mL vs. 213.0 mL respectively. Furthermore, there was no statistically significant difference between both groups regarding other preoperative data such as indication of hysterectomy, preoperative hemoglobin concentration, preoperative endometrial histology, type of anesthesia whether spinal or general.

The mean operative time (in minutes) for vaginal hysterectomy in group A was 92.3±7.45 while it was 94.0± 5.86 with no significant difference between both groups. The mean operative time was no much longer the reported by Ottosen et al 5 who reported a similar operative time for vaginal hysterectomy for non-prolapse in prospective study comparing three methods for hysterectomy.

The mean values of pre and postoperative hemoglobin concentrations were not significantly different in the two study groups indicating insignificant difference in intra-operative blood loss. There was no need for blood transfusion in either group.

There were no intra-operative complications reported in either group. This may be explained by minimizing technical difficulties by proper selection of our cases according to the 1989 American College of Obstetrician and Gynecologists guidelines for hysterectomy route state that the choice "depends on the patient's anatomy and the surgeon's experience" and that it is usually accomplished in women with mobile uteri that are not larger than a uterus at 12 weeks of gestation (280 g.).

Finally It can be concluded that clampless vaginal hysterectomy is a technique that can be practiced with no disadvantages than the traditional technique using clamps. Moreover, placing of the ligature on the uterine pedicle seemed easier with the aneurysm needle than with the claps as it required less space so the clampless method may be beneficial with larger uteri and this may require another study to prove or disprove.

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Comparative study between the effects of metformin monotherapy in obese and non-obese patients with polycystic ovary syndrome

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ABSTRACT

Objective: To compare the efficacy of metformin montherapy in improvement of the clinical and biochemical parameters, ovulation and pregnancy rates in obese and non obese patients with polycystic ovary syndrome.

Materials & Methods : A prospective comparative study in Minia University infertility clinic comprised of 100 infertile women who were diagnosed as clomiphene citrate resistant polycystic ovary syndrome at the period starting from November 2009 to August 2010.. The patients were divided into 2 groups: Group (O); included 50 patients with BMI ≥30 kg/m2 and Group(N); included 50 patients with BMI ≤30 kg/m2. Both groups received metformin 850 mg tablet twice daily for 12 weeks. The primary outcomes were the ovulation rate, the degree of menstrual regularity , the change of the patients' clinical and biochemical profile after three months of metformin treatment; including the changes in LH/FSH ratio.The secondary outcome was the pregnancy rate.

Results : There was a statistically significant improvement as regards pre-and post-treatment concerning regularity of the cycle (p<0.0001) , acne (p<0.001) and LH: FSH ratio (p= 0.015) and no statistically significant improvement as regard hirustism between both groups .In addition,there was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle (p=0.0001 & 0.0002) , acne (p=0,028 & 0.033) and LH:FSH ratio(p=0.038 & 0.495) and no statistically significant decrease as regard hirustism in both groups. However, there were no statistically significant differences between the two groups concerning the ovulation and pregnancy rates after treatment.

Conclusions : Metformin alone may be an effective drug for restoration of menstrual irregularities, LH: FSH ratio, treatment of acne, inducing ovulation and increase pregnancy rates in clomiphene citrate resistant polycystic ovary syndrome. Non obese patients responded better but statistically non significant than obese patients. Further randomized controlled studies on large number of patients are required to compare efficacy of metformin in obese and non obese PCOS patients.

Key Words : Metformin,Polycystic ovary syndrome,Obesity.

Introduction

Polycystic ovary syndrome is a common reproductive and metabolic disorder in which patients will benefit for early recognition and treatment. The prevalence of PCOS varies between 5% and 10% of all women (1). Polycystic ovary syndrome is clinically characterized by chronic anovulation, menstrual irregularities, infertility and obesity in combination with some evidence of androgen excess such as hirsutism, acne and increased serum androgen concentrations (2).

The current Rotterdam consensus defines PCOS as the presence of at least two out of the three criteria: chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (PCO), when other disorders of the pituitary, adrenals, or ovary have been excluded (3). Its clinical manifestations are oligomenorrhea or amenorrhea paired with infertility, hirsutism, obesity, acne and alopecia. Insulin resistance accompanied by compensatory hyperinsulinemia constitutes another major biochemical feature of PCOS. .Obesity and insulin resistance however not a constant features of all PCOS patients; It constitutes an often found criterion in consensus of diagnosis (4).

The fundamental pathophysiologic defect still remains unknown. PCOS appears to be a heterogeneous disorder in which ovarian, and possibly adrenal androgen excess is present

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Running title: Metformin in obese and non obese PCOS patients

along with varying degrees of gonadotropic and metabolic abnormalities (5). Additionally insulin resistance, hyperinsulinism, type II Diabetes Mellitus, endometrial carcinoma, dyslipidemia and psychosocial dysfunction are presented as other clinical consequences associated with PCOS (6).

Clomiphene citrate (CC) therapy has variable success rates in anovulatory women; however, it is the lowest in women with PCOS, particularly those with insulin resistance. Currently there is increasing evidence that insulin sensitizers are particularly effective in inducing ovulation in patients with PCOS (7). A magic bullet therapy for PCOS would result in weight loss, improve insulin resistance, restore normal ovulatory cycles, increase fertility, decrease hyperandrogenism, decrease the rate of spontaneous abortions and decrease the risk of GDM. The current front-runner for this magic bullet is the biguanide (metformin) (8).

Metformin, a biguanide, is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to inhibit hepatic glucose production, but it also increases the sensitivity of peripheral tissues to insulin. The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in nondiabetic women with the polycystic ovary syndrome (9). Nevertheless, the mechanisms underlying the beneficial effects of metformin in the treatment of PCOS remain incompletely understood. Improvement of IR by metformine may not only result from the well-known reduction of hepatic glucose production and increase of peripheral glucose utilization but also from a direct effect on ovarian steroidogenesis, as demonstrated by in vitro studies (10).

Metformin enhances insulin sensitivity. Furthermore, this compound displays the unique characteristic of promoting weight loss and reducing appetite. It is a safe and effective drug that is used for the treatment of PCOS patients (11). Since not all PCOS patients are obese or insulin resistant, it is not clear whether PCOS patients without IR and or obesity also benefit from a therapy with insulin sensitizers.Several smaller studies have suggested positive effects of metformin irrespective of weight and/or presence of IR. For example, Goldenberg et al demonstrated an equal improvement of menstrual irregularities both in insulin-resistant and insulin-sensitive PCOS patients (12). Many trials were set up to test insulin sensitizers (mainly metformin) for ovulation induction in women with PCOS. These studies have been summarized in several reviews and meta-analyses (13,14,15) however little evidence was produced on the effect of insulin sensitizers (mainly metformin) on the nonobese women without insulin resistance.
The aim of this study was to compare the efficacy of metformin montherapy in improvement of the clinical and biochemical parameters, ovulation and pregnancy rates in obese and non obese patients with polycystic ovary syndrome.

Patients & Methods

The present study was preformed in the infertility clinic in Minia University Hospital. All PCOS patients attending the infertility clinic with diagnosis as CC resistance had been counseled to participate in the study during the period from November 2009 to Augest 2010.
One hundred tweenty patient counseled to participate in the study, only 100 patient had completed the follow up and were equally allocated into two groups: Group (O) (obese patients with BMI ≥ 30 kg/m2), and Group (N) (non obese patients with BMI<30 kg/m2).

Institutional Review Board (IRB) approval was obtained for the study and informed consent was taken from all included patients.

Inclusion criteria:

- Women with subfertilty aged 18 - 40 years of age, diagnosed according to Rotterdam Criteria (3) diagnosis when two of the following criteria were present; oligomenorrhea or amenorrhea , clinical or biochemical signs of hyperandrogenism and PCO (at least one ovary with at least 12 follicles of a diameter of 2–9 mm or a volume >10 ml), and other pituitary, adrenal, or ovarian diseases were excluded .
- Resistance to CC which defined as failure to ovulate after at least 3 consecutive courses of CC in a dosage of 150mg/d from 2nd – 6th day of the cycle.

Exclusion criteria were patient refusal, presence of other causes of infertility, medical disease affecting patient fertility, drug hypersensitivity, other infertility medications for at least 3 months and patient non compliance for more than 7 days of treatment.
All participant patients were subjected to history talking, general examination ,day 3 vaginal ultrasonography and day 3 hormonal assay (serum FSH, LH, and prolactin). These hormones were assessed by ELISA technique using quomum diagnostic kits. Fasting serum glucose level by one touch method was measuerd.

Both groups received metformin 850 mg tablets twice daily for 12 weeks. Data were collected during the follow up visits with the same physician after 4, 8, 12 weeks respectively. The primary outcomes were; first the ovulation rate, second was the degree of menstrual regularity (28±7).Third was the change of the patients' clinical and biochemical profile before and after inclusion in the study, and after the three months metformin treatment; including the changes in LH/FSH ratio.The secondary outcome was the pregnancy rate. Timed intercourse was encouraged at the expected time of ovulation. The couples were advised to have sexual intercourse every other day. They were asked to contact the infertility clinic as soon as they have missed period (1 week).

Statistical analysis
SPSS for windows; standard version 10.0.7(SPSS Co., Chicago, IL, USA) was used for the statistical analysis. The results were reported as mean ± SD. The groups were compared by using unpaired t-test and the results obtained before and after metformin therapy were compared by using paired t-test. A P-value < 0.05 was regarded as statistically significant.

Results

One hundred CC resistant PCOS patient were equally allocated into two groups; Group (O) (obese patients with BMI ≥ 30 kg/m2), and Group (N) (non obese patients with BMI<30 kg/m2). Both groups received metformin 850 mg tablets twice daily for 12 weeks.

The demographic parameters of the patients before starting of treatment were shown in table (1). There was a statistically significant improvement as regards pre-and post-treatment concerning regularity of the cycle (p<0.0001) , acne (p<0.001) and LH:FSH ratio (p= 0.015) and no statistically significant improvement as regard hirustism(p = 0.88) between both groups as shown in table (2).

There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle (p=0.0001 & 0.0002) , acne (p=0,028 & 0.033) and LH:FSH ratio(p=0.038 & 0.495) and no statistically significant decrease as regard hirustism(p= 0.99 & 0.98) in both groups as shown in tables (3&4). However, there were no statistically significant differences between the two groups concerning the ovulation (p=0.425) and pregnancy rates (p=0.75) after treatment as shown in table (5).

Table (1): The demographic parameters of the patients before starting of treatment.

General characteristics	Patients group No = 100
Age in years Range (Min-Max): Mean ± SD:	 18-37 24.7±4.3
Duration of infertility in years Range (Min-Max): Mean ± SD	 2-15 3.1±2
Type of infertility Primary: No (%) Secondary: No (%)	 70 (70%) 30 (30%)
Weight in Kg Range (Min-Max): Mean ± SD:	 58-100 84.5±6.4
Height in Cm Range (Min-Max): Mean ± SD:	 152-169 161.3±4.1
Body mass index Kg/m^2 Range (Min-Max): Mean ± SD:	 22-35 31.2±3
Random blood glucose level (mg/dl) Range (Min-Max): Mean ± SD:	 74-120 85±14.3

Table (2): Comparison between patient groups as regarding the gynecological characteristics before and after treatment.

Gynecological characteristics	Patients group No = 100		p
	Before treatment	After treatment	
Menstrual cycle Regular: No (%) Irregular: No (%)	 37 (37%) 63(63%)	 72 (72%) 28 (28%)	 <0.0001*
Acne Present: No (%) Absent: No (%)	 42 (42%) 58 (58%)	 20 (20%) 80 (80%)	 <0.001*
Hirustism Present: No (%) Absent: No (%)	 30(30%) 70(70%)	 28(28%) 72(72%)	 0.88
LH/FSH ratio 1: No (%) 2: No (%)	 77(77%) 23(23%)	 60 (60%) 40 (40%)	 0.015*

1: LH/FSH ratio >2 2: LH/FSH ratio <2

Table (2) shows the difference between pre- and post-treatment. There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH: FSH ratio and no statistically significant improvement as regard hirustism.

Table (3): Comparison between the gynecological characteristics before and after treatment among the nonobese group.

Gynecological characteristics	Nonobese group No = 50		p
	Before treatment	After treatment	
Menstrual cycle Regular: No (%) Irregular: No (%)	 20 (40%) 30 (60%)	 38 (76%) 12 (24%)	 0.0001*
Acne Present: No (%) Absent: No (%)	 20 (40%) 30(60%)	 9(18 %) 4 1 (8 2%)	 0,028*
Hirsutism Present: No (%) Absent: No (%)	 14(28%) 36(72%)	 13(26%) 37(72%)	 0.99
LH/ FSH ratio 1: No (%) 2: No (%)	 37(74%) 13(26%)	 26(52%) 24(48%)	 0.038*

1: LH/FSH ratio >2 2: LH/FSH ratio <2

Table (3) shows the difference between pre- and post-treatment among nonobese group .There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH:FSH ratio and no statistically significant decrease as regard hirustism.

Table (4): Comparison between the gynecological characteristics before and after treatment among the obese group.

Gynecological characteristics	Nonobese group No = 50		p
	Before treatment	After treatment	
Menstrual cycle Regular: No(%) Irregular: No (%)	 17 (34%) 33 (66%)	 34 (68%) 16 (32%)	 0.0002*
Acne Present: No (%) Absent: No (%)	 22 (44%) 28 (56%	 11 (22%) 39 (78%)	 0.033*
Hirsutism Present: No (%) Absent: No (%)	 16(32%) 34(68%)	 15(30%) 35(70%)	 0.98
LH/ FSH ratio 1: No (%) 2: No (%)	 40(80%) 10(20%)	 30(60%) 20(40%)	 0.495*

1: LH/FSH ratio >2 2: LH/FSH ratio <2

Table (4) shows the difference between pre- and post-treatment among obese group. There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH:FSH ratio and no statistically significant decrease as regard hirustism .

Table (5): Comparison between obese and non-obese groups as regarding ovulation and pregnancy rates after treatment.

Ovulation& pregnancy	Obese	Non-obese	P
Ovulation Non-ovulation	20 (40%) 30(60%)	24(48%) 26(52%)	0.425
Pregnancy Non-pregnancy	4)8%) 46(92%)	6)12%) 44(88%)	0.75

Table (5) shows that there were no statistically significant differences between the two groups concerning the ovulation and Pregnancy rates after treatment.

Discussion

Since the role of IR in the pathogenesis of PCOS has been established, many interventional studies have demonstrated a positive effect of insulin-sensitizing agents in the treatment of PCOS. For example, Hahn et al (16) pointed out a positive effect of metformin on hyperandrogenism, chronic anovulation and IR . In accordance with these studies, our results showed that PCOS patients benefit from metformin treatment with regard to hyperandrogenism, menstrual disturbances ,ovulation and pregnancy rate.

In this study, both groups of obese and nonobese PCOS patients clearly showed statistically significant improvements as regarding to acne, menstrual irregularities and LH:FSH ratio and statistically non significant improvements as regarding to hirsutism and improvement in ovulation and pregnancy rates. Non obese group responded better but statistically non significant than obese group as regarding to acne, menstrual irregularities, LH: FSH ratio, ovulation and pregnancy rates.

In agreement with our study Costello et al., (17) demonstrated the same findings in a double-blind, placebo-controlled study that performed on twenty-three Caucasian women with PCOS, aged between 18–35 yr , with normal glucose tolerance. Women were randomly assigned to double-blind oral metformin or placebo for 6 months. The dose of metformin was increased stepwise, from 500 mg once daily for the first week to 500 mg twice daily for the next week and to 500 mg tid for a further 24 weeks. They concluded that metformin was effective in many women with PCOS, independently of changes in body weight, in attenuating insulin resistance and hyperandrogenemia and in reversing menstrual abnormalities and chronic anovulation.

These findings were in agreement with our study and several previous studies, For example, Nestler et al., (18) demonstrated in a study included one hundred women who received 850 metformin twice daily that insulin-sensitizing drugs increase ovulation rate and ameliorate hyperandrogenemia, even in nonobese women with PCOS. In addition, Hahn et al., (16) in agreement with our study have demonstrated a positive effect of insulin-sensitizing agents in the treatment of PCOS and pointed out a positive effect of metformin on hyperandrogenism, chronic anovulation, and IR. Michael (19) demonstrated that hyperandrogenemia was reduced by metformin treatment (500 mg three times daily) for 6 months. In addition, non obese PCOS patients benefited better than obese PCOS.

Palomba et al., (20) reported a significant improvement of pregnancy and ovulation rate in comparison with clomiphene and ovarian drilling. Accumulating evidence has shown that the rationale for metformin use makes sense as 2 meta-analyses of randomized controlled trials (RCTs) have shown that the use of metformin alone improves ovulation and pregnancy rates in women with PCOS.

Michael et al., (21) compared metformin cloridrate (850 mg twice daily) plus placebo (group A) versus placebo plus CC (150 mg for 5 d from the third day of a progesterone withdrawal bleeding) (group B).The study included one hundred nonobese anovulatory women with PCOS who received treatment for 6 months. The main outcome measures were ovulation, pregnancy, abortion and live-birth rates. The cumulative pregnancy rate was significantly higher in group A than group B. They concluded that six-month metformin administration was significantly more effective than six-cycle CC treatment in improving fertility in anovulatory nonobese PCOS women.

Kumari et al., (22) demonstrated in a study included 17 lean and 17 obese PCOS patients treated with 1500 mg metformin daily that ovulation and pregnancy rates were higher in the lean PCOS group. These studies were in agreement with our study data, showing a positive effect of metformin therapy on endocrine and metabolic variables even in lean and insulin-sensitive women. Also in agreement with our study, a study was done by Michael (19) to determine the clinical, hormonal, and biochemical effects of metformin therapy in obese and nonobese patients with PCOS. Twenty-nine patients with PCOS were treated with 500 mg metformin t.i.d. for 6 months. This study suggested that non obese patients responded better than obese patients to a 1.5 g/day metformin regimen.

In accordance with our study the effect of 6 months of metformin treatment was prospectively assessed by Tan et al., (23) in 188 PCOS patients, divided into three groups according to body mass index (BMI; lean: BMI<25 kg/m2, overweight: BMI 25–29 kg/m2, and obese: BMI≥30 kg/m2). PCOS patients were evaluated at baseline and following treatment with metformin in a weight-adapted dose for 6 months (body weight <60 kg: 500 mg metformin twice a day (BID), 60–100 kg: 850 mg BID, and ≥100 kg or BMI≥30 kg/m2: 1000 mg BID). This study suggested that metformin improves parameters of IR, hyperandrogenemia, anovulation, and acne in PCOS irrespective of pre-treatment IR or obesity.

On the other hand, other studies that assessed metformin effects in hyperandrogenic subjects did not confirm these findings .The reasons for the striking discrepancies among these studies were not readily explained. Interestingly, where insulin levels were reduced by treatment, serum androgens were lowered as well (24). In this regard, Crave et al., (25) did not observe any additional benefit of metformin over the effects of diet alone as regarding clinical and biochemical feature of PCOS, in a double-blind study comparing the effects of a 4-month low calorie diet vs. diet plus metformin in obese hirsute women. Unfortunately, this study was not specifically designed to recruit women with PCOS and actually the large majority of patients had regular menses. This weakened any conclusion, as hyperinsulinemia likely plays a major role in the pathogenesis of hyperandrogenism only in PCOS subjects

Furthermore, Tan et al., (23) in a randomized, controlled, double-blinded study recruited 56 women aged 18–45 with PCOS. They were treated with either metformin 850 mg or placebo twice daily for 6 months. The conclusion of this study was, in obese PCOS women, metformin treatment for 6 months lowers body weight, biochemical parameters, while there seems to be little effect on these parameters in non-obese PCOS women.However these findings must be interpreted with caution because of the small number of non-obese patients. It must also be taken into account that obese and non-obese women differed at baseline.

In conclusion, metformin alone is an effective drug for restoration of menstrual irregularities, LH: FSH ratio, treatment of acne, inducing ovulation and increase pregnancy rates in clomiphene citrate -resistant polycystic ovary syndrome. However metformin had a very little effect in treatment of hirsutism in obese and non obese patients with polycystic ovary syndrome.

Non obese patients responded better but statistically non significant than obese patients. Further randomized controlled studies on large number of patients are required to compare efficacy of metformin in obese and non obese PCOS patients.

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Letrozole in poor responders undergoing ICSI: an egyptian experience

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Abstract

Objective: to compare gonadotropine /antagonist protocol with and without Letrozole for controlled ovarian hyperstimulation for poor responder cases undergoing ICSI.
Materials & Methods: A prospective randomized case control study performed in Mansoura Fertility Care unit, Mansoura University hospital. Controlled ovarian hyperstimulation using gonadotropins/antagonist protocol with (group A) and without Letrozole (group B). The primary outcome is to measure duration of stimulation, total dose of gonadotropins, serum E2 level and endometrial thickness on day of HCG administration. The number and degree of maturation of retrieved oocytes, fertilization rate and number and grade of the developed embryos were evaluated. Secondary outcome includes ongoing pregnancy and take home baby rates.

Results: Duration of stimulation was shorter in group A (10.2± 1.5 days) compared to (11.5± 1.9days) in group B, total dose of gonadotropins was lower in group A (2602±433) in contrast to (2752±515IU) in group B, endometrial thickness was thicker in group B (9±2.2mm) compared to (7.8±2.2 mm) in group A, but no significant difference was detected between the two groups apart from mean duration of stimulation.

Conclusions: Letrozole as an adjuvant to gonadotropins seems to reduce stimulation period and total gonadotropins units used.
Key wards: Letrozole, poor responders, controlled ovarian hyperstimulation, ICSI cycles.

Introduction

The response to controlled ovarian stimulation (COS) regimens differs from woman to another, it could be normal leading to growth of reasonable number of follicles, poor leading to growth of reduced number of follicles or over response referred to as ovarian hyper stimulation syndrome(OHSS) (1).The success of intracytoplasmic sperm injection (ICSI) depends on a properly selected protocol of controlled ovarian stimulation and adequate oocyte recruitment. (2).

It is important to predict poor ovarian response in order to determine the most suitable stimulation protocol. Several ovarian reserve tests have been studied to predict outcome of (ICSI) in terms of response to ovulation induction and likelihood of pregnancy. Some of these tests have become part of the routine diagnostic procedure for infertility patients that will undergo (ICSI). Female age, for instance, is the basic factor that is related to both quantity and quality of oocytes. Basal Follicle stimulating hormone (FSH) gives a more thorough indication of quality aspects. By choosing the right thresholds these tests may eventually correctly predict oocyte quality (3).

The incidence of poor responders varies in the literature between 9 and 24%. Till now, there is no agreement upon its definition; failure to respond adequately to standard protocols and to recruit adequate follicles could be used as a definition (4). At ICSI, a patient is considered a poor responder when three or fewer follicles are recruited and serum estradiol concentrations are lower than 300 pg/ml (if one follicle) or 500 pg/ml (if two or three follicles) at the time of human chorionic gonadotropin (hCG) administration (5). Reduced ovarian reserve represents the most frequent etiological factor (4).which could be due to advanced patient age. Furthermore, a young patient with advanced endometriosis, previous ovarian surgery or pelvic adhesions may present with diminished ovarian reserve. Two other situations that can lead to poor response are the elevated basal serum FSH levels and the reduced inhibin production by granulosa cells (6).

Aromatase is an enzyme that catalyzes the rate-limiting step in the production of estrogens. It is a good target for selective inhibition because estrogen production is a terminal step in the biosynthetic sequence. (7) An aromatase inhibitor (e.g. Letrozole) could be used for ovulation induction, its mechanisms of action could be explained by blocking estrogen-negative feedback, without depletion of estrogen receptors (ERs), A second hypothesis involves an increased follicular sensitivity to FSH, resulting from temporary accumulation of intraovarian androgens because conversion of androgen substrate to estrogen is blocked. Data support a stimulatory role for androgens in early follicular growth in primates (8). Peripherally, it is possible that Letrozole, with suppression of estrogen concentrations in the circulation and peripheral target tissues, results in up-regulation of ERs in the endometrium, leading to rapid endometrial growth once estrogen secretion is restored. (9). In this study, the role of Letrozole as an adjuvant to gonadotropins was evaluated in a subgroup of poor responders undergoing ICSI cycles.

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Materials and Methods

This study was conducted at the Fertility Care Unit, Mansoura University Hospital, Mansoura , Egypt. A group of 60 women were recruited during the period from January, 2010 till December, 2011. Women were diagnosed as poor responders for ICSI cycles. They were recruited if they have one or more of the following criteria:

1. Poor ovarian response with <3 mature follicles on a long GnRH agonist protocol in their previous IVF/ICSI cycles.
2. Repeated high basal levels of FSH >10 IU/l.
3. Older than 40 years.

Participants were asked to sign a written consent to study and were randomized into two groups:

- ***Group A:*** 30 participants received Letrozole 2.5mg/12h (Femara® , Novartis, Egypt) from day 2 of the cycle for 5 days plus gonadotropines 375 IU/day (Merional®, IBSA, Switzerland) followed by gonadotropines given according to response to stimulation detected by follow-up until day of hCG.
- ***Group B:*** 30 participants received gonadotropins 375 IU / day (Merional®, IBSA, Switzerland) from day 2 of the cycle for 5 days then gonadotropins given according to response to stimulation detected by follow-up until day of hCG.

Participants were followed up by the same observer using 7 MHz vaginal probe mounted to an ultrasound machine (Sonoace 3200, Medison, South Korea) for folliculometry after the first 5 days of stimulation then every other day thereafter. Doses of gondotropins were modulated according to the response. Cancellation of cycles were based on low E2 level during follow up (<300 pg/ml) correlated with less than three ovarian follicles detected at the follow up visits after counseling the couple regarding success rate.
Both groups had pituitary suppression by flexible multidose GnRH antagonist protocol (Citrotide®,EMD Serono, Switzerland) 0.25 mg per day SC when the largest follicle reaches 14mm. Citrotide was continued by daily injection until day of hCG administration. All cases received 10000 IU hCG (Choriomon®, IBSA, Switzerland) when the mature follicle reached 18 mm. Serum E2 concentration and endometrial thickness were measured on the day of hCG administration.

Oocytes were collected ultrasound-guided under general anesthesia 34-36 h after hCG administration and categorized as regards number and degree of maturation into metaphase I (MI) and metaphase II (MII). Oocytes were manipulated in the laboratory by ICSI and incubated for 48-72 hours until dividing embryos were formed which were also categorized into grades A, B and C.

Endometrial preparation for embryo transfer was started the day of oocyte collection by giving cases progesterone (Prontogest®, IBSA, AMSA, Italy) 100 mg ampoules IM once per day. Normally cleaving embryos were transferred into the uterine cavity 48-72h after oocyte retrieval using soft embryo transfer catheter under ultrasound guidance. Luteal phase support was continued by the same regimen started on the day of oocytes collection until two weeks after embryo transfer when serum pregnancy test was done. Cases with positive pregnancy tests were examined by ultrasound two weeks later to document intrauterine clinical pregnancy. Pregnant participant were followed up and ongoing pregnancy rate and take home baby rate were determined.

Results

A total of 60 cycles were recruited to the study and the participants were randomized into two groups (A and B). The demographic criteria of the participants regarding age, basal FSH and previous poor response in ICSI cycle were plotted in table (1).
The results of the studied groups were shown in Table (2). Fertilization rate (developed embryos per injected oocytes) was slightly lower in group A (52%) compared with (53%) in group B with no significant difference (P = 0.9). The mean number of embryos transferred was (1.4± 0.9) in group A compared to (1.3±0.9) in group B. Yet, no statistically significant difference could be detected (P = 0.8).

As regards implantation rate, it was equal in both groups (22.2%). Clinical pregnancy rate was equal in both groups (4 cases in each group) which represent (13.3%) of initiated cycle.Also, pregnancy rate per embryos transferred the rate was equal in both groups (14.81%).

There were three cases (two in group A and one in group B) reached full term and were delivered by cesarean section while, there were five cases(two in group A and three in group B)were miscarriaged in the first trimester. The delivered babies in both groups revealed no congenital anomalies.

Table (1): Demographic criteria of the studied groups

Variables	Group A*	Group B **	P
	Mean ±SD	Mean ±SD	
Age	36.4 ± 4.9	35.6 ± 4.8	0.523
Basal FSH	10.1 ± 2.8	10.3 ± 2	0.730
Previous ICSI	11	10	0.061

Table (2): Results of the studied groups

Variables		Group A* (Mean ±SD)	Group B** (Mean ±SD)	P
Stimulation period(days)		10.2 ± 1.5	11.5 ± 1.9	0.008
HMG units used		2602 ± 433	2752 ± 515	0.227
Oocyte quality	MI	1.6± 1.2	0.6± 0.5	0.044
	MII	1.6 ± 0.8	1.8 ± 1	0.445
Embryos Transferred		1.4 ± 0.9	1.3 ± 0.9	0.773
Serum. E2		475.5± 182.7	517.3 ± 276.9	0.533
endometrial thickness		7.8 ± 2.2	9± 2.2	0.068
Cancellation rate		7	8	0.338

Discussion

Letrozole is an aromatase inhibitor. It was introduced as an ovulation induction agent either alone or as an adjuvant with gonadotropins. It acts through transient inhibition of aromatase activity in early follicular phase with subsequent induction of ovulation. Its role in poor responder was evaluated in many studies with varying results regarding its advantages (10- 15).

In the current study the mean duration of stimulation was shorter in group A compared to group B (10.2±1.5 vs. 11.5±1.9). These results support the results of Yarali et al. (10) who found shorter duration of stimulation in cases received Letrozole. However another study (11) showed no difference regarding days of stimulation on addition of letrozole but this study compared different stimulation protocols, namely, microdose GnRH agonist flare with GnRH antagonist /Letrozole protocol.

Regarding the total gonadotropins units used, in the current study were lower in group A in contrast to group B (2602±433 vs. 2752±515) this could support the results obtained by some authors (10,12). Letrozole used in combination with gonadotropins reduced the cost of infertility treatment by decreasing the gonadotropins dose required for optimum ovarian stimulation. This could make assisted reproductive technology available to a larger group of infertile couples. If this was the case, this could have a reflection on the total cost of the cycle which is an important factor in low income societies like Egypt.

Serum estradiol at day of hCG administration was found lower in group A compared to group B (475.5±182.7vs517.3±276.9) which is comparable to results of Goswami et al (12), Who found significant reduction in serum estradiol level. Other authors (10, 13) found similar results. The current study evaluated endometrial thickness on day of hCG administration and found that endometrium was thinner in group A this is in contrary to the results of Verpoest et al. (13) which showed increased endometrial thickness with Letrozole co-treatment. Although the addition of Letrozole to gonadotropins in the current study reduced the mean serum E2 level and endometrial thickness, there was no negative impact on implantation and pregnancy rates. Although Cancellation rate was slightly lower in group A (23.3% vs. 26.7%), it was not statistically significant difference could be detected. This could reflect the impact of low income of the population studied, as some cases refused cancellation of their cycles despite cancellation criteria. They could not afford another cycle, so they decided to continue. Regarding the oocytes number and quality, no statistically significant difference was found between the studied groups. These findings support the results of some authors (11, 12, 14). In contrast, other authors (13, 15) found Increase in the number of oocytes retrieved this could be explained by the effect of Letrozole which improves ovarian response to gonadotropins.

Fertilization rate in the current study was lower in group A compared to group B(52% vs. 53%) which is comparable to the results of some authors(10). Furthermore the current present study could not demonstrate a statistically significant difference in number and quality of resulting embryos which supports the findings of some authors (11, 12). Ozmen et al (14) showed increased number of embryos but no difference in quality. No difference was found in the current study regarding implantation and pregnancy rates in contrary to the results found by some authors (10, 13, 15).

This study has some limitations and some points remain to be evaluated. First, it has low statistical power regarding the number of the studied ICSI cycles of poor-responders. Second, concerning the issue of Letrozole and congenital anomalies the limited number of delivered babies limited the ability to comment on possible congenital malformation developed in Letrozole group.

There were no congenital anomalies detected in the current study which could add to the finding of Tulandi T. et al, who stated that the use of letrozole for ovulation induction was not associated with congenital malformations (16). The current study could be used as a base for planning a larger multicentric study for better evaluation of the role of Letrozole in the management of poor responders undergoing ICSI cycles.

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The influence of high responders on the outcome of intracytoplasmic sperm injection

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Abstract

Objective: Evaluate the impact of high number of retrieved oocytes on the outcome of ICSI cycles.

Material and methods: A retrospective study performed in Mansoura integrated fertility center. We reviewed 1566 ICSI cycles and compared the patient, cycle features and cycle outcome of ICSI for high responders (> 15 retrieved oocytes corresponding to > 75th percentile) and normal responders (5- 15 oocytes between 25th and 75th percentile). Results: High responders were significantly younger and thinner than the normal responders. The oocyte maturation was significantly lower in high responders. Fertilization rate, Implantation rate and the clinical pregnancy rate revealed significant differences being lower in high responders.

Conclusion: High oocyte yield is detrimental to ICSI outcome. It does not only affect the maturation of oocyte but also affects the fertilization, the implantation and the clinical pregnancy rate.

Key word: High responders, ICSI, implantation, pregnancy rate.

Introduction

The relationship between the number of oocytes retrieved and pregnancy rate following IVF/ICSI cyles has shown conflicting results. Meniru et al 1997 (1), proved that pregnancy rates increased with an increasing number of oocytes. Kably et al 2008 (2), concluded that the best pregnancy rates being obtained with number of oocytes of 10–15. Molina et al 2008 (3) found that 7–16 is the optimal number of oocyte to achieve pregnancy. Hamoda et al 2010 (4) suggested that the numbers of embyos frozen after a fresh IVF cycle are not enhanced by retrieving > 18 eggs.

Bosch and coworkers (2011) (5), concluded that a maximum of 8-9 retrieved mature oocytes is enough to achieve the highest cumulative pregnancy rates and that any protocol of stimulation that results in an increased number of good quality oocytes per cycle will not lead to higher chance for a patient to become pregnant. Sunkara and associates (2011) (6), found that an egg number of around 15 eggs gave the best chance of live birth and there was a decline with 20 or more eggs. Many investigators (7- 9) found that 15 eggs is the optimal number to maximize treatment success while minimizing the risk of OHSS with high number of oocytes > 18. This is a retrospective study to evaluate the impact of high number of retrieved oocytes on the outcome of ICSI cycles; implantation rate and clinical pregnancy rate.

Materials and Methods

A retrospective analysis of patient characteristics, measures of ovarian response, and rates of implantation and pregnancy for first cycles in patients < 35 years of age who underwent ICSI, between October 2006 and October 2011. We compared the outcome of ICSI for high responders (> 15 retrieved oocytes corresponding to > 75th percentile) and normal responders (5- 15 oocytes between 25th and 75th percentile) as defined by Simon et al [10]. All patients underwent ovarian downregulation using leuprolide acetate. Once down regulation was confirmed, leuprolide acetate was decreased and gonadotropin (follicle stimulating hormone or human menopausal gonadotropin) was started at a dose of three to four ampoules per day (75 IU each). The ovarian response was assessed by ultrasound and serum E2 level on the 5th day of gonadotropin administration, and serially thereafter. HCG (10,000 IU) was administered intramuscularly when lead follicles reached 18 mm in diameter. A serum E2 (peak E2) level was obtained on the day of HCG administration. Ultrasound-guided transvaginal oocyte retrieval was performed 34–36 hours later under intravenous sedation. Intracytoplasmic sperm injection was carried out. Cleavage stage embryos were transferred 72 hours or blastocysts after 5 days of follicular aspiration. Pa-

tients undergoing IVF-ET received transvaginal progesterone (400 mg/day) for luteal support starting on the day of oocyte retrieval. Pregnancies were documented by measuring serum hCG 14 days after embryo transfer. At 7 weeks after embryo transfer an ultrasound was performed and the presence of an intrauterine sac confirmed clinical pregnancy.

Statistical analysis

This was performed by using the statistical package for social science program (SPSS) version "16". The qualitative data were presented as frequency and percentages. The quantitative data were examined by using Kalmogrov-Smirnov test to test for normal distribution of the data and when parametric, expressed as mean and standard deviation. Student t test was used, to test for difference in normally distributed quantative data between the two groups. Mann-Whitney-µ test was used for comparison between two groups when data are not normally distributed. Significance was considered when P value less than 0.05.

Results

Table (1) and (2) compare ICSI outcome of normal responder and high responder groups. The high responders were significantly younger (26.45±4.24 vs 28.84±4.49) with significant lower BMI (30.5 ±5.09 vs 32.16±5.66). While causes of infertility, the basal FSH and the total doses of gonadotropins were insignificant in both groups. Inspite of the significant higher number of the retrieved oocytes and the available embryos in the high responders group, they show significant lower mature oocyte yeild (80.69699 ±15.2 vs 84.34809 ±16.5), significant lower fertilization rate (77.70 ±21.8 vs83.21027±20.1) and significant lower implantation rate (10.6 vs13.8). Also the clinical pregnancy rate was significant lower in the high responders when compared to normal responders (31.4 vs. 40.6). Table 3 summarized the ovarian responses, the number of oocytes retrieved and the percentage of blastocyst transfer between pregnant and non-pregnant women. The number of retrieved oocytes were significantly lower when comparing pregnant and non-pregnant groups. Blastocyst transfer was significantly higher in the pregnant group (29.98% vs 9.58%).

Table1: clinical and cycle features of normal compared to high responder

	Normal responder (n=1324)	High responder (n=242)	p
Age	28.84±4.494	26.45±4.248	<0.001
BMI	32.16±5.66	30.5 ±5.09	<0.001
Basal FSH	7.44±4.392	8.01± 4.387	0.063
Indications	N %	N %	p
Male Factor **Unexplained** **Tuba Factorl**	728 54.75% 132 9.96% 464 35.04%	164 67.7% 24 9.91. % 54 22.31%	0.6641
Total Stim. Dose(Amp)	31.2±5.5	30.9 ±7.2	0.53
HP-FSH Total Dose(Amp)	14.3±4,4	14.2±5.2	0.77
% Maturity (M±Sd)	84.34809 ±16.5	80.69699 ±15.2	0.0007
Source Of Sperm	N %	N %	p
Ejaculate **Testicular biopsy**	1074 81.11 250 18.88	189 78.09 53 21.9	0.69
Fertilization % ((M±SD)	83.21027±20.1	77.70 ±21.8	0.0002
Embryoes Transferred(n) (M±Sd)	3.30 ±0.803	3.39± 0.679	0.065
Grade A T(n)(M±Sd)	2.43±0.97	2.61 ±0.95	0.006
CES Ceavage Embryo (M±Sd)	69.90 ±37.071	79.31 ± 35.301	. 0.001
Blastocyst T(%)	516 38.97%	121 50%	0.36

Table 2: Cycle outcome in normal compared to high responders

	Normal responder			High responder			P
	All cycles	Clev Et	Blst ET	All cases	Clev ET	Blst ET	
Transfers (n)	1324	1202	122	242	220	22	
Pregnancy (n)	538	468	70	76	68	8	
CPR(%)	40.6[a]	38.3[b]	57.3[c]	31.4[a]	30.9 [b]	36.3 [c]	[a] .008 [b] 0.028 [c] 0.01
IR (%)	13.8[d]	12.4[e]	30.07[f]	10.6[d]	9.09[e]	23.8[f]	[d]0.0009 [e]0.010 [f]0.285

Table 3: pregnant vs. non pregnant clinical and laboratory feature

	Pregnant (n=627)	Non pregnant (939)	P,
Age (years) (m±sd)	27.5±5.78	27.40±4.56	0.715
FSH (mIU/ml)(m±sd)	5.9 ±2.3	6.1±3.1	0.143
Retrieved eggs (m±sd)	14.9322034 ±4.09	17.01389 ±5.32	<0.001
MII eggs (m±sd)	13.15 ±3.7	14.86 ±5.36	<0.001
Total cleavage ET(m±sd))	3.4±0.58	3.4±0.59	<0.001
Cumulative embryo score of Cleavage Embro (m±sd)	92.31 ±30.33	90.20±26.9	0.158
Ratio of Blastocyst transfere (%)	188 (29. 98%)	90 (9.58%)	<0.001

Discussion

Since the first IVF-embryo transfer was carried out in 1978, the treatment of infertility has advanced significantly (11). The subsequent introduction of COS for multiple follicular developments significantly increased pregnancy rate (12). Such stimulation protocols have been refined to obtain an optimal number of oocytes and to maximize pregnancy rates (5). However, many controversies are still excisting.

In the present study the main causes of ICSI were male factor, tubal factor and unexplained infertility, while cases with PCOS and endometriosis were not encountered. The high responders were significantly younger with significant lower BMI when compared with normal responders, this in acordance with Hourvitz et al (2009) (13) and Bellver et al (2010) (14).

The retrieved oocytes in this series were significantly lower in pregnant when compared to non pregnant (14 vs 17 oocytes) (table 3). This is confirmatory to Kably et al (2008) (2) and Sunkara et al (2011) (6), who found that the best chance of live birth was associated with the number of eggs around 15 eggs and showed a decline with > 20 eggs.

In the present study the significant lower clinical pregnancy rate in high responders showed the affection of most steps in ICSI including the reduction of oocyte quality, fertilization rate and implantation rate (table 1- 2). These results are contradictory to some investigators who found that the main step to be influenced is the reduction in implantation rate and endometrial receptivity while the oocyte quality improved (9, 15- 22). Papanikolaou et al. (2009) (23), concluded that the theory of impaired oocyte/embryo quality in high responders is unlikely. On the other hand, Van der Gaast, 2006 (24), suggested that milder ovarian stimulation produce fewer but higher quality oocytes without compromising endometrial receptivity and implantation.

The lower implantation rate and clinical pregnancy rate and the deleterious outcome of high responders in ICSI cycles was the debate of many investigators giving the negative effect of high estradiol (10, 15, 22, 29) and progesterone levels on the day of hCG (30, 31, 32) as an explanation.

Valbuena et al 2001 (26) suggested that increasing levels of E2 are deleterious to embryonic implantation because they directly affect the embryo. Others concluded that the high E2 might be related to asynchronous endometrial development (27, 28). Ma et al 2003(29), found that the window of uterine receptivity remains open for an extended period at lower estrogen levels but rapidly closes at higher levels.

Bourgain and Devroey, 2003(33), found that the increase in progesterone has the potential to advance the endometrium, without influencing the embryo and lead to a state of asynchrony between embryo and endometrial dating. Still there is a great argue on the mechanism by which this negative effect occur. Further researches are ongoing to clarify this point.

The pregnancy rate in the present study significantly improved with blastocyst transfer, being transferred in 29.9% in the pregnant cases versus 9.5% in non pregnant cases (table 3). This is in accordance to Chen et al (2007) (34) and Papanikolaou et al (2009) (23), who suggested that blastocyst transfer on day 5 offer the endometrium time to recover from any negative effects of high peak E2 and progesterone levels.

Conclusion

It was concluded that high responders have negative impact on ICSI outcomes with low pregnancy rate. We recommend the use of mild stimulation protocol. Hoping to maximize the pregnancy rate not to maximize the number of oocytes that proved to be negatively associated with pregnancy beyond a certain levels.

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Combined use of cell phone technology, serum Progesterone and ß-HCG can reduce the extra visits in the management of pregnancy of unknown location in law resource settings

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ABSTRACT

Objectives: The aim of this study was to evaluate efficacy and safety of the combined use of mobile phone and serum progesterone in the management of patients with pregnancy of unknown location.

Material & methods: A prospective interventional study was introduced to the emergency ward for managing all patients attended to emergency gynecological ward in El Minya maternity university hospital between the period of 1st of August 2010 and 31st of October 2011 whereby clinically stable patients with PUL and serum progesterone level less than 10 nmol/l were discharged after initial visit. Patients were advised to contact emergency mobile number to two dedicated persons (author & co-author) who follow a chart of symptoms & reading of serum levels of progesterone and incorporate the human chorionic gonadotropin (β-hCG) /48 h ratio if necessary.
Surgical or medical intervention was offered to all women with persistent or worsening symptoms and non-declining serum β-hCG.

Results: During 15 months of the study period (from the 1st of August 2010 and 31st of October 2011),675 pregnant women had a clinical and ultrasound diagnosis of PUL with serum progesterone level less than 10 nmol/l were attended to our emergency unit. 590 were included in the final data analysis. The final outcomes were four groups, the first one was the normal intrauterine pregnancy group which was diagnosed in 9 (1.5 %) cases .The second group in which 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage. In the third group, the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra –uterine) and they resolved spontaneously without any intervention .The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy .From the above figures it is well evident that, the initial level of progesterone was found to predict the outcome of PUL. There was significant reduction in the number of visits ($P < 0.001$).

Conclusions: The introduced protocol based upon combined use of mobile phone technology, serum progesterone less than 10 nmol/l at law risk of developing complications and if combined with β-hCG 48 h/48 h ratio notification will be effective in reducing the extra visits & costs and help in triaging women with PULs without significant maternity harm especially in law resource settings.

Keywords: Pregnancy of unknown location, β-hCG, serum progesterone, Law resource settings.

INTRODUCTION

The pregnancy of unknown location (PUL) is a term used to describe a situation where there is a positive pregnancy test but no sign(s) of either intra- or extra uterine pregnancy or even evidences of retained products of conception on transvaginal ultrasound [1].The prevalence of PUL depends on the sonographer's experience as well as the quality of the machine used. Although ,the sensitivity of modern ultrasound equipment is very high [2] ,but still in many cases the location of pregnancy cannot be determined on initial scan. The diagnosis of PUL leads to urgent clinical assessment and estimation of serum beta human chorionic gonadotrophin (β-hCG) where A number of different protocols have been recently used in order to differentiate between viable intrauterine pregnancies and pathological ones in PUL patients using serial measurements of serum β-hCG [3].The combined use of ultrasound and serum β-hCG using the dicsrimatory zone has been used extensively [4] with a sensitivity 100% [5] in diagnosing ectopic pregnancy and a positive predictive value 18.2% [6] .

Recently ,a useful tool in the management of PUL is the assessment of serum proges-

terone [7] .Elevated serum progesterone levels indicating the viability of the corpus luteum while its decrease indicating failing of the pregnancy. in a meta-analysis study done by Mol BW et al has Shown serum progesterone levels <25 nmol/l to be associated with nonviable pregnancy, although viable pregnancies (0.3%) have been reported with initial levels <15.9 nmol/l [8]. The same study showed that Levels >25 nmol/l is likely to indicate intrauterine pregnancy while levels >60 nmol/l are strongly associated with pregnancies subsequently shown to be intrauterine, although a small proportion of ectopic pregnancies (2.6%) have been reported with a serum progesterone concentration of >60 nmol/l. If the diagnosis of PUL is established in asymptomatic patient, the guidelines of early pregnancy association recommends conservative management in the form of estimation of serum β-hCG at 48 Hours to detect the pattern of the hormone .and follow up accordingly [9] .

As it was demonstrated from previous many studies [10] , the fast majority of PUL is law risk and a small proportion being ectopic in which 15% will be resolved spontaneously .So, there is emerging consensus to offer the expectant management protocol to all clinically stable patients [11] . This should help to avoid unnecessary operative interventions ,but this is on the expense of multiple visits to an early pregnancy assessment unit before a diagnosis can be made. The reported number of visits is 3 visits (with range from 2-6) within 5 days (with range from 2-25).

Nowadays, Mobile phones used widely by staff in different issues concerning patients .Interference with medical equipment inside hospitals appears to be not a serious problem as users are keen to not use cell phones near the equipment [12] .It plays a really important role in the developing countries in different aspects of medicine . it is much easier to reach doctors in case of an emergency. Also we all have cell phones and there is a wide range of area for mobile phone coverage. At a more complex level, mobile phones are being used to improve and increase compliance with taking medications.

The prevalence of PUL varies from 7-31% in women attending early pregnancy units [13] & [14] ,so it does represent a major burden to the health service facilities despite its benign course. It is therefore essential to develop protocols to reduce the number of extra-visits and subsequently the extra-costs without of course endangering the safety of the women.

A single visit strategy [15] proposed to reduce the number of visits was shown to be unsafe as 67% of women with ectopic pregnancy were discharged without adequate follow-up. Introducing a protocol to reduce these extra visits in such low risk cases appears to reduce the burden to the health service providers as well as on the patients.

The aim of this study was to assess the use of cell phone technology between the clinicians and the patients to triage women with PUL through assessment of symptoms and serum levels of β-hCG and progesterone that could reduce the extra visits in law resource settings.

MATERIAL & METHODS

A prospective interventional study was introduced to the emergency ward for managing all patients attended to emergency ward in El Minya maternity university hospital between the period of 1st of August 2010 and 31st of October 2011 whereby All clinically stable patients with the diagnosis of PUL (positive serum pregnancy test ,no detected either intrauterine or extra uterine pregnancy by transvaginal ultrasound with no evidence of retained products of conception) and serum progesterone level less than 10 nmol/l were discharged after initial visit. All cases were invited to the research project after full explanation of the idea of the project, possibility to withdrew without prior notice without affection of her care. A written consent in Arabic language was taken from each participant with 3 copies (one for authors, the second will be kept in the hospital file and the third one for the participant) .In all cases a full medical history is taken and clinical assessment is performed by the clinician in charge .All demographic, clinical, ultrasound and laboratory findings are recorded in a clinical file. The main collected data are the women's age, menstrual history ,past obstetric history ,transvaginal findings (endometrial thickness ,any adnexal findings), serum β-hCG and progesterone measurements. Exclusion criteria were: an early pregnancy sac-like structure within the uterine cavity that required ultrasound follow-up for confirmation of viability, an adnexal mass suspicious of ectopic pregnancy, clinically unstable women, indirect signs of a specific pregnancy location (e.g. hematoperitoneum) and the presence of products of conception that could be visualized either by transvaginal ultrasound or on speculum examination.

Patients were advised to contact emergency mobile number(s) to one of the two dedicated persons (author & co-author) who follow a agreed chart (Figure 1) of symptoms & reading of serum levels of progesterone and incorporate the human chorionic gonadotropin (β-hCG) /48 h ratio if necessary. The group of participants who were free of symptoms (pain & bleeding) with declining of both serum β-hCG (below 25 IU/L) & progesterone offered no further visits .The group who developed worsening of symptoms are advised to attend to the emergency ward immediately irrespective of the serum readings. When the location of pregnancy had been determined on the follow-up scan, the women were managed according to the protocol described below. Surgical or medical intervention was offered to all women with persistent or worsening symptoms and /or abnormal levels of serum β-hCG.

The final outcomes were normal intrauterine pregnancy, miscarriage, ectopic pregnancy , failing pregnancy (whether intra or extra uterine) and persistent PUL. Spontaneously resolving pregnancies are applied to all abnormal pregnancies that did not require any form of intervention (medical or surgical) . They included all failing pregnancies as well as all miscarriages and ectopic that were eventually detected on ultrasound scan during follow-up, but then resolved spontaneously on expectant management.

Normal pregnancy was diagnosed by the presence of a live embryo with an intrauterine gestational sac on follow-up scans, while early embryonic demise was diagnosed in women with an empty intrauterine gestational sac >25 mm or a sac with an embryonic pole with crown–rump length >10 mm with no visible heart action on follow-up scans [16]. Miscarriage was diagnosed if there was no evidence of progressive pregnancy growth on two scans at least 2 weeks apart or measurements below the mentioned figures. Incomplete miscarriage was diagnosed in women with evidence of well-defined hyperechoic tissue within the uterine cavity with typical ultrasound features of retained trophoblastic tissue. An ectopic pregnancy was diagnosed when a pelvic swelling with morphological features typical of an ectopic pregnancy was eventually detected on follow-up scans.

All statistical analyses were carried out using SPSS version 16 (SPSS, Chicago, IL, USA). The outcomes were dichotomized into intervention and no intervention categories. Comparison of the means of continuous variables was performed using the Mann–Whitney U-test or Student's t-test depending on data distribution. Proportions were compared using Yates corrected Chi-square test, and $P < 0.05$ was considered statistically significant.

RESULTS

During 15 months of the study period (from the 1st of August 2010 and 31st of October 2011),675 pregnant women had a clinical and ultrasound diagnosis of PUL with serum progesterone level less than 10 nmol/l were attended to our emergency ward in El Minya university maternity hospital which is a tertiary centre located at the upper Egypt serving about 5 million population. Follow-up was incomplete in 65 cases due to failure to contact them in the follow-up period by the given contact details (phone numbers & home address).20 cases preferred to go for private care outside the university hospital and they withdrawn from the study after being consented. The remaining 590 were included in the final data analysis.

The final outcomes were four groups ,the first one was the normal intrauterine pregnancy group which was diagnosed in 9 (1.5 %) cases on follow-up scan after doubling ratio of the β-hCG titer and serum progesterone level more than 60 nmol/l. They offered the 2nd visit after raising of the β-hCG titer more than 1500 unit where definite viable intrauterine pregnancy was confirmed .In this group no extra visits were needed and they continued their usual antenatal care as planned. The second group in which 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage. In the third group ,the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra –uterine) and they resolved spontaneously without any intervention .In this group the mean number of visits was 3±1 till β-hCG titer below 25 unit. The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy .

The second group (those who had miscarriage), 9 cases (1.5%) required intervention (surgical evacuation of retained products of conception due to persistent clinical symptoms and/or medical therapy by using PGs), and the remaining 21 (3.6 %) women were managed expectantly until the products of conception were spontaneously expelled from the uterine cavity.

In the group in which the final diagnosis was ectopic , five cases (0.8 %) had intervention (three cases of them had surgical intervention e.g. salpingosotomy & salpingectomy and ,two cases managed by methotrexte) .Eight cases managed conservatively . This group showed suboptimal rise or decline of the β-hCG titer by cell phone follow-up and progesterone level between 10-20 less nmol/l .The mean visits were 3±1 .They asked to attend for extra unusual visits for the worsening pain or continues spotting. From the above figures it is well evident that , the initial level of progesterone was found to predict the outcome of PUL.

The overall intervention rate in our study group was 2.3 % (14 cases) cases .Comparing the 2 groups (who had intervention and who had not) showed significant differences in maternal age, gestational age, history of previous abnormal early pregnancy and initial serum β-hCG levels among women who did and did not require medical intervention (Table 1).

DISCUSSION

The majority of PUL is of law risk and it does represent a major burden on the resource settings .Many authors accept the philosophy of reducing interventions in patients with PUL but this of course must not be at the expense of maternity safety. Having Saied that ,the use of modern technology e.g. cell phone by expert clinician and the use of prepared flaw chart of symptoms to diagnosis the possible fates of PUL and combined results of serum β-hCG and progesterone may reduce the need to do extra visits and consequently reduce the burden to the health service without endangering the maternity safety.

In our study, normal intrauterine pregnancy group was diagnosed in 9 (1.5 %) cases on follow-up scan after doubling ratio of the β-hCG titer and serum progesterone level more than 60 nmol/l. cases which is similar to study done by Day et. Al [17] .However ,this figure is lower than that mentioned in several studies [18] & [15] ,and this can be explained by the using cut off level of serum progesterone less than 10 nmol/l in our series. They were offered the 2nd visit after raising of the β-hCG titer more than 1500 unit where definite living intrauterine pregnancy was confirmed .In this group no extra visits were needed and they continued their usual antenatal care as planned, so the mean number of visits was one .

The second group in our study , 30 (5.1 %) of the recruited cases, had the diagnosis of miscarriage by ultrasound and , the β-hCG titer neither failed to raise optimally or decline sub optimally and those patients were attended for additional visit after heavy bleeding of severe pain or invited for visit if no further complaint to diagnose missed miscarriage. In such group, 9 cases (1.5%) required intervention (surgical evacuation of retained products of conception due to persistent clinical symptoms, and medical therapy by using PGs), and the remaining 21 (3.6 %) women were managed expectantly until the products of conception were spontaneously expelled from the uterine cavity. The mean number of visits in this group was 2±1 .Some patients from this group attended to the emergency unit with severe bleeding and/or pain and offered surgical evacuation of the uterus after settling the diagnosis of miscarriage.

The third group ,the site of pregnancy was never determined in 538 (91.2 %) cases (neither intra-uterine nor extra –uterine) and they resolved spontaneously without any intervention .In this group the mean number of visits was 3±1 till β-hCG titer below 25 unit and serum progesterone never raised above 10 nmol/l. This category represent the major score in our study and showed difficulty to be counseled by the authors about the fate of their pregnancy .They were advised to attend for re-evaluation & reassurance if they worried .This could explain the higher number of visits in such group rather than the need for further assessment.

Identification of this group and proper diagnosis is essential step for counseling for further pregnancies. While the diagnosis of failed ectopic necessities the future counseling about the possibility of future recurrence, the diagnosis of failed intra-uterine pregnancy necessities the investigation of recurrent early pregnancy loss.

The fourth group which was consisted of 13 cases (2.2%) diagnosed as ectopic pregnancy . In this group, five cases (0.8 %) had intervention (three cases of them had surgical intervention e.g. salpingosotomy & salpingectomy and ,two cases managed by methotrexte) and eight cases managed conservatively . The intervention rate in this group was comparable to previous studies [10] ,[11] ,[3],[19] &[15] .Our intervention rate reflect our recent tendency to manage the stable and asymptomatic ectopic cases

conservatively and this is our target .also in this group we had 2 cases of ruptured ectopic came to us with picture of mild pelvic collection and were subjected to laparoscopic intervention in the form of salpingectomies. The patients who had ruptured ectopic were advised to attend to the emergency ward as they have severe pain with suboptimal rise of serum β-hCG and progesterone level between 10-20 u/ml. In this issue we need to ensure the safety of conservative management for all women so they have to be educated about the symptoms of intra-abdominal bleeding and they should be provided with immediate access to emergency facilities in case of worsening clinical symptoms. In the ectopic group, we had two cases presented with a history of heavy vaginal bleeding .and are found to have suboptimal decline of β-hCG and serum progesterone less than 10 nm/l with picture of trans-vaginal ultrasound showed empty uterus with no adenaxial suspicious of ectopic. Decision to admit those cases was taken as the consultants in charge did not assumed to have had complete miscarriage but rather classified as PUL. Follow-up of the two cases showed picture suggestive of ectopic .One case of them managed conservatively while the other managed by methotrexate.

In a previous study done prospectively to diagnose IUPs and ectopic pregnancies on the basis of three visits within 7 days and failing PULs on the basis of two visits within 2 days. The results showed that 97.5% of women with PULs were given a diagnosis (IUP, failing PUL or ectopic pregnancy) by day 7 and 88.7% of these were confirmed using the planned number of visits [20]

Our main objective of combing the triple use of cell phone technology ,serum β-hCG and progesterone level is to assess the intervention rate in each individual case and to calculate the mean visits required until reaching the final diagnosis and managing the case and so limiting wasting of resources especially in our countries and so focusing these available resources to the high risk cases .Extra benefits of reducing the visits will be reflected on the social and economical burden of the families who pay the whole cost of health service in law resources settings. On the other hand ,repeated visits is associated with poor compliance and disruption of the life in working women .In our study , Follow-up was incomplete in 65 cases due to failure to contact them in the follow-up period by the given contact details (phone numbers & home address) and 20 cases preferred to go for private care outside the university hospital and they withdrawn from the study after being consented. The explanation of this high numbers could be due to non preferring the general sector of health care and preferring the private one which is costing too much and carries a big burden to the economic state of the families .Another explanation is the huge number of attendants to the hospital daily which could be reflected on the service quality as explained by some attendants . The high non- compliance rates which was similar in a study done by Kirk [3] is alarming as this may lead to delayed diagnosis of high risk cases with subsequent morbidities and may mortalities even. So, reducing the number of extra visits could save resources of both the (patients & country), and more importantly divert the efforts of the health professionals to the high risk case to avoid complications provided that probably selected criteria for high and low risk subgroups. The strategy of single visit in managing low risk patients with PUL has already been discussed in many previous publications.

In our study ,when we combining serum progesterone level ≤10 nmol/L and the doubling ration of serum β-hCG notified by cell phone to dedicated expert personnel complying to a flaw chart of symptoms can reduce the extra visits in low risk group without endangering the maternity safety and reassure the client if there is no other warning symptoms and this noticed to be associated with very low risk cases . However, this combination cannot completely eliminate the need for follow-up visits especially in women with abnormal serum readings or complained symptoms.

The rate of subsequent intervention rate in this group was found to less than 3% in ectopic or miscarriage cases. So, it is well evident from our results that such combination strategy (flow chart symptoms, serum β-hCG & serum progesterone level ≤10 nmol/L) can eliminate more than 50% of unnecessary visits without significant increase in the adverse outcomes.

The cornerstone advice from this study is to select the proper patient to be subjected to such new protocol and in case of worries from either the patient ,family or the treating doctor, admission to the inpatient sector under monitoring should be the best option to have.

In conclusion, initial clinical evaluation and serum progesterone level ≤10 nmol/L ,with proper serum β-hCG interpretation ,and the use of cell phone technology can reduce the extra visits and hereby reduce the extra costs and may divert the efforts towards more risky cases without endangering the maternity life. Of course ,this combination needs to be evaluated prospectively in a large study in order to assess its efficacy and safety and before all the community acceptability ,cost-effectiveness and its complications if any.

Figure (1): Flaw chart of the study:

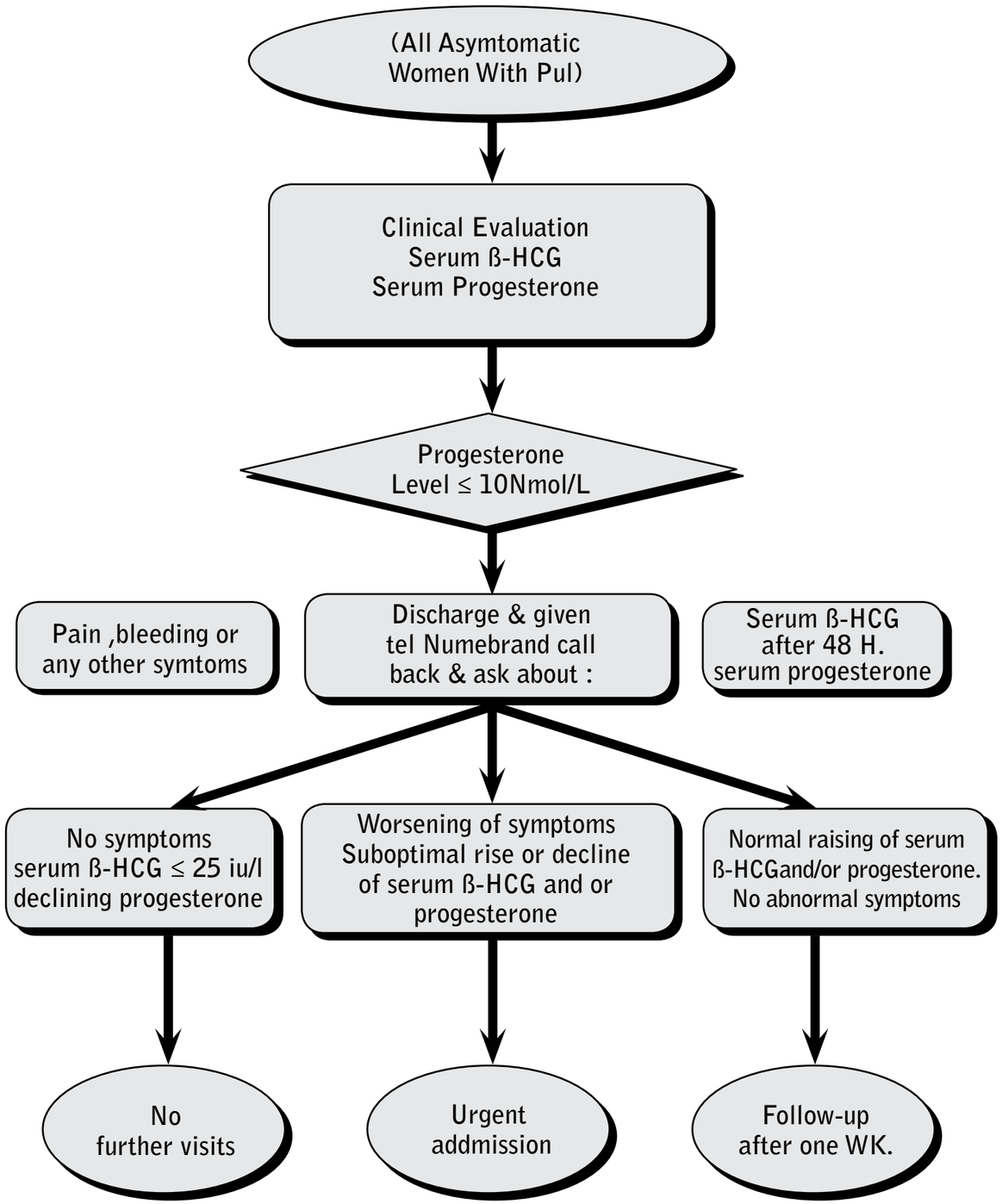

Figure (2):

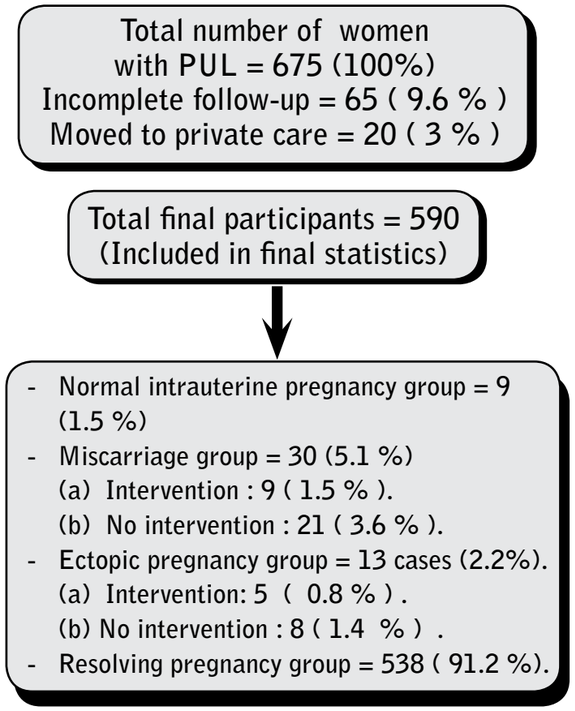

Table (1):
Comparison of demographic, clinical and biochemical findings in women with pregnancies of PUL at the initial visit in respect to the need for intervention.

	Intervention group (14)	Non – interventional group (576)	Significance (P value)
Maternal age	33.6 ± 5.6	28.9 ± 4.6	0.010
Gestational age (days)	43 ± 10.4	48 ± 9.4	0.003
Previous abnormal pregnancy	110	210	0.010
Initial serum B-hcg IU/L	812 ± 410	324 ± 214	0.002

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Men behind most unexplained infertility cases

A study of 239 couples with unexplained fertility, published in the journal Reproductive Biomedicine Online, found high sperm DNA damage in 80 per cent of the couples trying to conceive. Currently, some 50,000 couples require fertility treatment in the UK every year, but up to one third of these are diagnosed with unexplained or idiopathic infertility, as tests are unable to find a cause for the problem. The researchers from Queen's University Belfast said the discovery will lead to better treatment for couples, saving them time, money and heartache.

For almost one third of couples, until now, there has been no obvious cause for infertility and these couples are given the diagnosis of 'unexplained fertility'. In our study we have now had a breakthrough which explains the cause of infertility for many of those couples. The study is also the first to show that the chances of having a baby after IVF is closely related to the amount of DNA damage a man has in each of his sperm. (TheFamilyGP.com)

Exposure to pollution may reduce fertility

Couples with high levels of certain chemicals in their bodies took about 20% longer to conceive compared with those with lower exposures, says the study from the National Institutes of Health. That type of delay is similar to the effects of other factors known to reduce fertility, such as smoking, obesity and older age, according to the findings, published today in Environmental Health Perspectives. PCBs, or polychlorinated biphenyls, were widely manufactured from 1929 to 1979, with hundreds of uses, such as coolants and lubricants in electrical equipment, according to the Environmental Protection Agency. Although they're no longer manufactured, PCBs still may be present in older products, such as caulking, oil-based paint, floor finish and insulation. PCBs persist for years in the environment — in soil, water and the food chain — as well as in body fat, the EPA says. PCBs also are found in breast milk.

Researchers tried to contact more than 424,000 households, in order to find 500 couples who were going to try to conceive a baby within the next two months. The study followed the couples for a year, and followed women through the end of any pregnancies. Only 0.1% of couples contacted were planning to try to conceive in that time. Scientists asked couples to provide blood and urine samples before conceiving, as well as keep daily diaries, undergo frequent interviews and pregnancy tests.

Researchers measured levels of 63 environmental chemicals. Virtually everyone had detectable levels of PCBs and a breakdown product of the banned pesticide DDT, Louis says. The couple's chances of conceiving each month then were calculated and showed that the likelihood of a pregnancy fell by about 20% among men and women with high exposure to certain types of PCBs. Other environmental pollutants also were related to a lower chance of conceiving. Women with high levels of a flame retardant also had a 20% lower chance of conceiving. Men with high levels of a breakdown product of the pesticide DDT also had a 17% lower rate of conception, the study says. DDT has been banned in the USA since 1972, but is still used in other countries. (Liz Szabo, USA TODAY).

Cell phone exposure during pregnancy related to fetal brain development problems in babies

Avoiding cell phone exposure during pregnancy may be a necessity in protecting your unborn child, according to Yale School of Medicine. According to a recent study, cell phone radiation may lead to brain development problems including hyperactivity in children amongst other things. "This is the first experimental evidence that fetal exposure to radiofrequency radiation from cellular telephones does in fact affect adult behavior," said senior author Dr. Hugh S. Taylor, professor and chief of the Division of Reproductive Endocrinology and Infertility in the Department of Obstetrics, Gynecology & Reproductive Sciences.

A control group case study using pregnant mice exposed to an active but muted and silenced cell phone revealed more “hyperactive and had reduced memory capacity” in their offspring. The study measured brain electrical activity in adult mice exposed to the radiation as fetuses against those not exposed. Dr. Taylor’s study reveals that the development of neurons in the fetus prefrontal cortex region is adversely effected, when exposed to cell phone use during pregnancy.

The dangers behind cell phone use are nothing new. Exposure to “radio frequency” (RF) has been a concern for almost 20 years. More concerning is the possible exposure to RF near the fetus. The results of the control study group revealed that even using an active phone around a fetus can be dangerous to the unborn child. Arguments can be made that the subjects used (mice) against the bombardment of frequency’s received (cell phones) was not in proportion, but the concern still exists.

If a muted, silenced cell phone can actively emit RF’s then it can still expose a fetus to the dangers caused through contact. The concern over whether or not this frequency can cause irreversible brain damage should be enough to eliminate the use of or exposure to cell phones during pregnancy. Quick Tips for Wellness: The safest way to protect your unborn child is to avoid cell phone exposure during pregnancy.

(http://medicine.yale.edu/publications/medicineatyale/may2012/news/advance/12479)

*These news in reproductive medicine were compiled and modified from the web site of the American Society for Reproductive Medicine

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