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*EDITOR : ABOUBAKR EL NASHAR*

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(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 I, Hamberger L. Interaction between prostaglandins and catecholamines on cervical collagen. In: Toppozada M., Bygdeman ‘.

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## Letter from the Editor:

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*Dear colleagues,*

Very interesting subjects are included in this issue. There was a strong link between gestational sac diameter, yolk sac shape and diameter, CRL, and fetal heart rate in pregnancies that ended in a normal first trimester. Maternal serum creatine kinase is not a reliable tool in predicting or diagnosing placenta accreta. Early oral feeding after uncomplicated CS was safer, more convenient and reduces hospital stay costs and it's strongly recommended for all women after uncomplicated CS. Prenatal ultrasound is the best screening tool for placenta accrete spectrum and presence of abnormal lacunae and loss of retro-placental clear zone are accurate predictors for the operative findings and histopathological diagnosis. The proper use of electrosurgery for abdominal wall incision could be a good alternative for scalpel.

Best regards.

***Aboubakr Elnashar***

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# Acupuncture for infertility: a case report

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## Running title: Acupuncture for infertility

**Keywords:** infertility, anti-mullerian hormone (AMH),  
acupuncture

## Introduction

Infertility is the inability of a sexually active couple trying to conceive for a year. Worldwide, 8-12% of couples face infertility problems, while the percentage keeps increasing. 20% of cases are due to both male and female factors (1,2).

Problems that are likely to occur in men are abnormal sperm, low sperm motility or low sperm count. Causes can be genetic factors, long-term steroid use, age, obesity, stress, testicular inflammation, cystic fibrosis, diabetes and other diseases. In women the most common factors are polycystic ovary syndrome, hyperprolactinemia, thyroid problems, hormonal imbalance, poor quality, cancer, AIDS, etc. Age, obesity and eating disorders also increase the risk of infertility issues (1,2).

## Case report

We present a case of a 30-year-old woman, who presented to the acupuncture clinic with inability to conceive for two years. She had been offered IVF, but wanted to try acupuncture. Her medical history did not reveal any particular pathology except for intense stress and insomnia. Her menstrual cycle, as well as gynecological examination and ultrasound were normal. Laboratory hormonal testing was normal, with the exception of the anti-Mullerian hormone which showed a downward trend, with final values of 0.9 and high levels of androstenedione (4618 ng / mL).

The husband was healthy with blood tests, sperm volume and pH, sperm viscosity and motility, as well as sperm count within normal limits.

The couple did not report any use of drugs or smoke, any alcohol abuse and did not have infections.

After informed consent, acupuncture was performed, with 25mmx25mm needles, at the acupuncture points: Liv3, Sp6, Sp9, S36, LI4, EX-Hin 1, S25, S28, CV10, CV, CV4, CV3, GB20, GV14, GB30, B25, B132.

Simultaneously, infrared rays were applied to the abdomen for 20 minutes. A total of 10 acupuncture sessions were performed as often as once a week.

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The patient then reported a positive pregnancy test and 9 months later she delivered a healthy baby boy.

## **Discussion**

In our case, acupuncture was effective in treating infertility in a woman with low anti-Mullerian hormone (AMH).

AMH is produced in the follicles and its serum levels indicate the reserve of the woman's ovaries. Its levels decrease with age and decrease of the ovarian reserves, while the number of developing follicles visible on the ultrasound decreases. For women of productive age, hormone levels are categorized into four groups: Normal (1.0-3.0 ng / mL), normal low (0.7-0.9 ng / mL), low (0.3-0.6 ng/mL), and very low (less than 0.3 ng/mL). (1,2)

A review of randomized trials by Jang S et al found that acupuncture could improve clinical pregnancy rates, anti-Mullerian hormone (AMH) and antral follicle count (AFC) rates and the number of recovered eggs in women with poor ovarian response.

However, it is difficult to conclude that acupuncture is more effective than conventional therapy, as more clinical trials are needed (3).

Acupuncture has been used to treat infertility issues, both in males and females, in all steps of IVF. (4)

Three possible mechanisms for the effects of acupuncture on infertility have been documented.

1. Acupuncture may mediate the release of neurotransmitters, (3) which in turn may stimulate the secretion of gonadotropin-releasing hormone, thereby affecting the menstrual cycle, ovulation, and fertility. (4)
2. Acupuncture can augment uterine blood flow by suppressing sympathetic uterus activity. (5)

3. Acupuncture can stimulate the production of endogenous opioids, which can inhibit central nervous system outflow and the biological response to stress. (6)

In a randomized controlled trial by Guven et al, three acupuncture sessions before and after IVF significantly increased pregnancy rates. Acupuncture was also found to significantly reduce stress levels that occurred before ET embryo transfer (7)

A systematic review by Liu Yun et al found that the pregnancy rate improved significantly with acupuncture treatment compared to control group. Subgroup analysis, such as polycystic ovary syndrome, fallopian tube infertility, ovulation disorder, and other factors, also showed significant improvement. In addition, ovulation rate and endometrial thickness increased significantly. The combination of acupuncture and western medicine also showed significant improvement, while the side effects of acupuncture were significantly less. (8)

In the study of Amina Zakaria et al, acupuncture, in the follicular phase of the menstrual cycle in patients with polycystic ovary syndrome who underwent in vitro fertilization, was found to have a positive effect. The number of embryos transferred, and pregnancy rates were significantly higher compared to the control group, but had no effect on antimullerian hormone concentrations. (9)

However, in a multicenter study by Xiao-Ke Wu et al in Chinese women with polycystic ovary syndrome, acupuncture alone or add-on to clomiphene failed to increase births as compared to control acupuncture and placebo. (10)

The number of sessions required varies considerably. In the case we described, acupuncture was effective with 10 sessions, once a week in the treatment of infertility in a woman with low antimullerian hormone (AMH) and mild hypothyroidism that gave birth to a healthy baby. In the case of Zhu



et al, a 34-year-old patient with primary infertility for 3 years and low antimüllerian hormone (0.94 ng / mL) required 32 cycles of treatment, one treatment weekly for a period of 1 year, extending the cycle by 1 day at 4, normally developing follicles up to 20 mm with good quality and normal hormone levels. However, the final outcome of the conception is not mentioned. (11)

In another report by Zhu J et al, acupuncture in a young couple with infertility improved the quality of a man's sperm and ovarian function, balancing the endocrine system and hormones and leading to pregnancy. The same acupuncture points were used in both patients. (12)

Despite the positive results of the case described, the quality of the evidence from the literature is poor not only because final results are missing by a proportion of the research projects, but also because the results are contradictory. There is a need for more research to determine the effectiveness of acupuncture in fertility treatment. (13)

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# Evaluation of Gestational Sac Diameter, Crown Rump Length, Yolk Sac Diameter and Fetal Heart Rate in Early Detection of Congenital Fetal Malformation

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## Abstract

Congenital abnormalities impact 3% to 5% of all pregnancies, and they are the leading cause of newborn death. The majority are caused by unknown factors, with pregnancy being the sole risk factor. However, in both affluent and developing nations, they are responsible for rising newborn fatalities.

**Aim of the study:** The purpose of this study was to see whether there was a link between Gestational sac diameter, crown rump length, yolk sac diameter and fetal heart rate in detection of early congenital fetal malformation.

**Patients and methods:** our research included 100 pregnant women who were scanned using 2d ultrasonography beginning in the first trimester, with the first scan taking place between 6 and 8 weeks. at 18-22 weeks, a follow-up scan was performed. the first trimester's outcome was documented.

**Results:** Among cases, 77 (77%) had a normal pregnancy, 20 (20%) had an early miscarriage, 3 (3%) had congenital fetal malformation. a statistically highly significant difference between a normal, early miscarriage and congenital fetal malformation results of scan regarding yolk sac shape ( $p < 0.001$ ). in our research, a small, irregular, calcified, or big yolk sac was a significant predictive factor in pregnancy outcome.

**Conclusion:** there was a strong link between gestational sac diameter, yolk sac shape and diameter, CRL, and fetal heart rate in pregnancies that ended in a normal first trimester.

**Keywords:** Gestational sac, crown-rump, yolk sac, fetal heart rate, scan, congenital fetal malformation

## Introduction

Pregnancy is one of the marvelous events which a woman experiences in her life and the reality of her whole life. The first trimester is a vital time as the pregnancy gets established. It was concluded that ultrasonography (US) plays an important role in differentiating normal from abnormal pregnancies and, therefore, accurately predicting it is normal or not(1).

Antenatal care must include screening for fetal structural and chromosomal abnormalities(2). Congenital fetal abnormalities, uteroplacental circulation insufficiency, and preterm delivery are the most important causes of perinatal death. Therefore, the significance of ultrasound examination during pregnancy cannot be overstated because fetal abnormalities and placental insufficiency may be detected early in pregnancy(3).

Sonographically, the intrauterine gestational sac is the first to show up, followed by the yolk sac, then the fetal pole with heart activity. The yolk sac is the earliest visible embryonic structure inside the gestational sac(4). Various authors have described numerous sonographic signs to predict pregnancy outcomes. For example, an abnormally big, tiny, or irregularly shaped gestational sac, a low implantation site, a large or irregular yolk sac, a poor decidual response, and a sluggish embryonic heart rate were among the symptoms identified by him (5).

A fetal ultrasound scan is performed between 18 and 22 weeks of pregnancy to establish a baseline against which subsequent scans may be compared to assess development and health. This time frame strikes a balance between accurately timing the pregnancy (which would be more accurate if done earlier) and detecting severe congenital abnormalities on time (2).

**Aim of the study:** The purpose of this study was to see whether there was a link between Gestational sac diameter ,crown rump length, yolk sac diameter and fetal heart rate in detection of early congenital fetal malformation.

## **Patients and methods**

### ***Study design:***

A prospective cohort study.

### ***Study population:***

**Sample Size** (number of participants included): 100 patients

### ***Inclusion criteria:***

All pregnant women are in their first trimester of pregnancy at 6-8 weeks of pregnancy.

### ***Exclusion criteria:***

- Pregnant women below 18 and above 35 years old.
- Pregnant women with multifetal gestation.
- Structural anomalies of uterus and cervix.
- Chronic diseases as (SLE, hypertension, diabetes, renal diseases, bronchial asthma, anemia, hyperthyroidism, and cardiac disease).
- Previous child with structural or chromosomal anomalies
- Exposure to irradiation or teratogen.-
- Recurrent fetal loss.

## **All patients were assessed as follows**

**1. Informed consent:** It was written taken from the antenatal women to share in the study.

### **2. Full history taking, particularly for:**

- Menstrual history.
- Obstetric history.
- Presence of medical disorder that affects pregnancy.
- Vaginal bleeding.

### **3. Screening technique:**

The first-trimester ultrasound examination was performed at 6+0 to 7+6 gestational weeks in the prenatal units of Fayoum University Hospitals between November 2020 and July 2021. The rationale for choosing these patients was inclusion/exclusion criteria after verbal and written consent using (Philips Medical Systems) ultrasound machine with the 2D endovaginal probe with frequency 7 MHz.

- The modified Naegle's formula was used to determine gestational age from the known start of the previous

menstrual cycle, verified by sonographic measurement of the crown-rump length.

- The gestational sac was measured using a three-dimensional average (longitudinal, anteroposterior, and transverse). From the interior of the sac to the inside of the decidual reaction, the sac was measured.
- The size of the yolk sac was measured using calipers on the inner boundaries of the larger diameter and the shape, echogenicity, and presence of calcification. Normal YS were those with a 3-6 mm diameter, a rounded form, no degenerative alterations, an echogenic rim, and a hypoechoic center. After two weeks, all pregnancies with an aberrant yolk sac were re-evaluated by sonography.
- CRL was calculated in the embryo's sagittal plane, avoiding the inclusion of YS.
- The embryonic heart rate was calculated using M-mode sonography to average, at least three waves in beats per minute.

### **Clinical Follow Up**

If a subsequent first-trimester scan revealed no heartbeat, the pregnancy was classed as early miscarriage, and if a subsequent second-trimester scan revealed a live baby, it was labeled as living.

Between the 18th and 22nd week of pregnancy, all chosen patients were scheduled for a fetal structural abnormality scan. Following the guidelines established by the Clinical Standards Committee of the International Society of Ultrasound in

Obstetrics and Gynecology (ISUOG), a second-trimester scan was conducted using the same equipment as the first-trimester scan 2D transabdominal probe with frequency 5 MHz:

### **Statistical Analysis**

At the 0.05, 0.01, and 0.001 levels of probability, all statistical computations were performed using Microsoft Excel version 16 and the SPSS (statistical package for the social sciences version 26.00) statistical software. The Chi-squared test was used to compare categorical variables that were given as a number ( percent ). The Kolmogorov-Smirnov test was used to determine if continuous variables had a normal distribution. Regular or non-normally distributed continuous parameters were given as mean (standard deviation) or median (interquartile range, IQR).

### **Results**

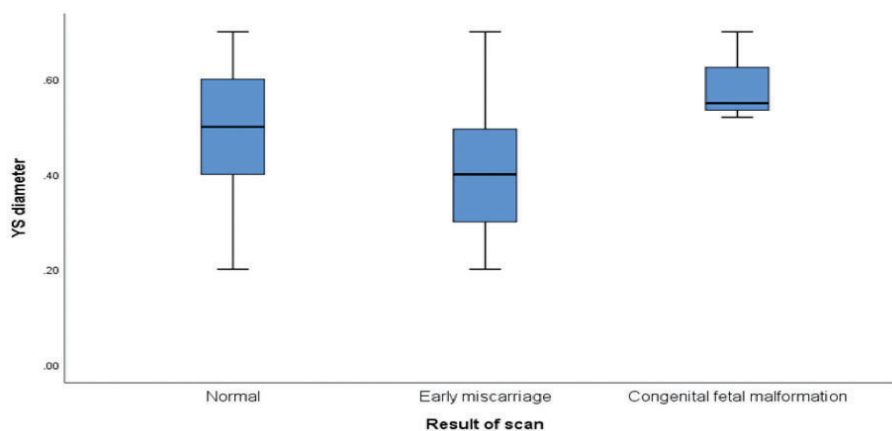
In our study, 100 first trimester pregnant cases attended in the prenatal units of Fayoum University Hospitals were included as per criteria and data collected. The first-trimester pregnancy outcome was evaluated by the normal continuation of pregnancy, early miscarriage, or congenital fetal malformation. Among cases, 77 (77%) had a normal pregnancy, 20 (20%) had an early miscarriage, 3 (3%) had Congenital fetal malformation.

**Table (1): Comparison between normal, early miscarriage, and congenital fetal malformation result of the scan regarding YS diameter and GS diameter.**

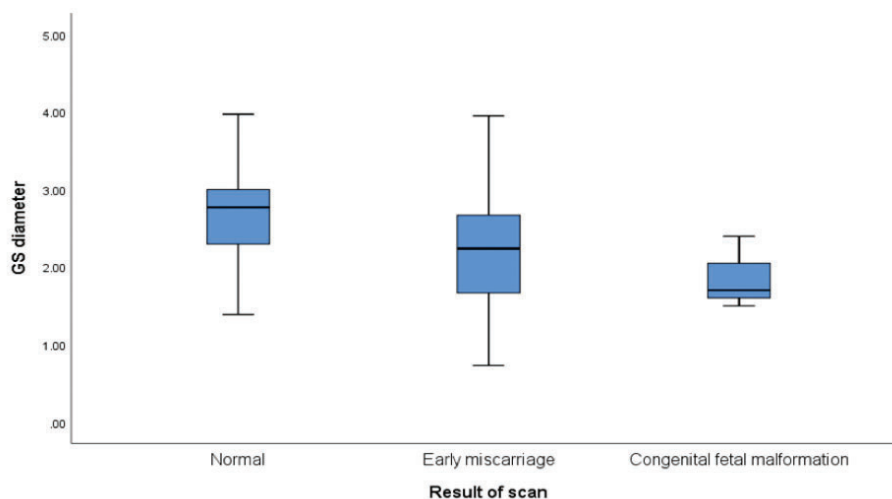
		Result of scan		Congenital fetal malformation (N = 3)	Kruskal-Wallis	P-value
		Normal (N=77)	Early miscarriage (N = 20)			
YS diameter	Median (IQR)	0.50 (0.40-0.60)	0.40 (0.30-0.50)	0.55 (0.52-0.70)	9.024	0.011 S
GS diameter	Median (IQR)	2.77 (2.26-3.0)	2.24 (1.65 -2.67)	1.70 (1.50 -2.40)	8.273	0.016 S

S; significant at p value < 0.05

It reveals a statistically significant difference between normal, early miscarriage, and congenital fetal malformation results of scan regarding YS diameter and GS diameter ( $p < 0.05$ ) as shown in table (1) and figure (1) & (2).



**Figure (1):** Boxplot compares normal, early miscarriage, and congenital fetal malformation results of scan regarding YS diameter.



**Figure (2):** Boxplot compares normal, early miscarriage, and congenital fetal malformation scan results regarding GS diameter

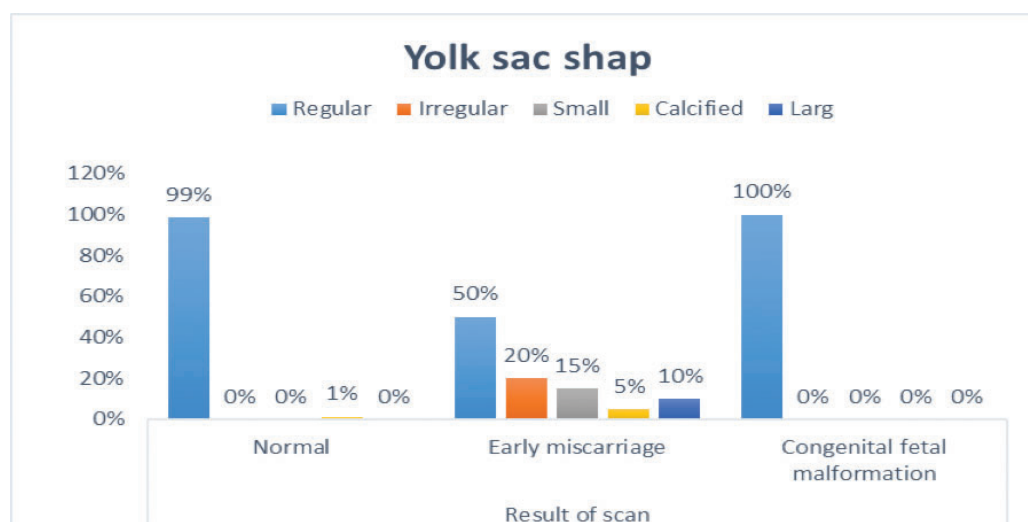


**Table (2): Comparison between normal, early miscarriage, and congenital fetal malformation result of the scan regarding YS diameter and GS diameter.**

Yolk sac shape	Result of scan						Chi	-square P-value
	Normal		Early miscarriage		Congenital fetal malformation			
	N	%	N	%	N	%	41.422	<0.001 HS
Regular	76	98.7%	10	50.0%	3	100.0%		
Irregular	0	0.0%	4	20.0%	0	0.0%		
Small	0	0.0%	3	15.0%	0	0.0%		
Calcified	1	1.3%	1	5.0%	0	0.0%		
Large	0	0.0%	2	10.0%	0	0.0%		

HS; highly significant at p value < 0.001

It reveals a statistically highly significant difference between a normal, early miscarriage and congenital fetal malformation results of scan regarding Yolk sac shape (p < 0.001).

**Figure (3):** Comparing normal, early miscarriage and congenital fetal malformation results of scan regarding Yolk sac shape.**Table (3): Comparison between normal, early miscarriage and congenital fetal malformation result of the scan regarding FHR and CRL.**

		Result of scan			Kruskal-Wallis	P-value
		Normal (N=77)	Early miscarriage (N = 20)	Congenital fetal malformation (N = 3)		
<b>FHR</b>	Median (IQR)	160.00 (140 -170)	88.50 (80.00-99.0)	170.00 (166.0-173.0)	30.30	0.001 HS
<b>CRL</b>	Median (IQR)	1.37 (0.89 -1.66)	0.29 (0-1.10)	1.62 (1.56 -1.85)	19.63	0.001 HS

HS; highly significant at p-value < 0.001

It reveals a highly statistically significant difference between a normal, early miscarriage and congenital fetal malformation results of scan regarding FHR and CRL (p < 0.001).



## **Discussion**

Congenital abnormalities influence 3% to 5% of all pregnancies, and they are the leading cause of newborn death. The majority are caused by unknown factors, with pregnancy being the sole risk factor. However, in both affluent and developing nations, they are responsible for rising newborn fatalities (6).

Sonographically, the intrauterine gestational sac is the first to show up, followed by the yolk sac, then the fetal pole with heart activity. The yolk sac is the earliest visible embryonic structure inside the gestational sac. It manifests as a circular anechoic region between the fifth and twelve weeks of pregnancy, after which it degenerates (7).

Prior studies of early detection of congenital fetal malformation focused mainly on screening at late first trimester between 11-13 weeks gestation. To the best of our knowledge, the present study focused on early first-trimester screening. It was undertaken to describe the relationship between gestational sac (GS), yolk sac (YS) diameter, crown-rump length (CRL), and embryonic heart rate (HR) between 6 and 8 weeks of pregnancy and early detection of major structural fetal malformation.

The significant difference between a normal, early miscarriage and congenital fetal malformation results of scan regarding YS diameter and GS diameter ( $p < 0.05$ ). There is a highly significant difference between a normal, early miscarriage and congenital fetal malformation results of scan regarding Yolk sac shape, FHR, and CRL ( $p < 0.001$ ).

Three cases showed congenital fetal malformation, including 2 cases of anencephaly and 1 case of Cystic hygroma. An early scan of these cases showed a normal gestational sac with smooth normal shape and size yolk sac average CRL with average heart rate. Twenty cases of 100 cases ended by early miscarriage. The highly significant difference between a normal,

early miscarriage and congenital fetal malformation results of scan regarding Yolk sac shape.

In our study, embryonic heart rate influences the pregnancy outcome. Average heart rate between 140-175 beat/ min, resulting in normal pregnancy outcome only 3 cases result in congenital fetal malformation. Fetal bradycardia with average heart rates between 80-100 beats/ min results in early miscarriage.

A further research found that a CRL below the 50th centile on the 28th day of pregnancy was linked to a 19.4% early pregnancy loss rate, compared to just 3.3% when the CRL was above the 50th centile (8)

A very tiny yolk sac has been suggested as a typical feature during the early stages of normal embryologic development. On the other hand, much older research, which has some limitations, indicates that a yolk sac diameter of 2 mm or smaller is linked with a poor result in pregnancies of 8 to 12 weeks gestation. The size of the yolk sac starts to shrink in the late weeks of the first trimester, as is widely known. This is why, while determining the size of the yolk sac, gestational age should be considered. When a smaller-than-expected yolk sac is seen, it is advisable to conduct serial sonographic exams within a short time (9).

A tiny yolk sac with a diameter of less than 3mm between 6-10 weeks or more than 7 mm before 9 weeks suggests an abnormal pregnancy and needs a follow-up ultrasound scan to determine pregnancy viability (10).

Despite the lack of a clear agreement, most writers consider 5 or 6 mm as the maximum limit for the size of a typical yolk sac in pregnancies between the 5th and 10th weeks of pregnancy. According to recent research, a yolk sac diameter of more than 5 mm is linked to a higher chance of spontaneous abortion. However, a few writers have reported a big yolk sac in a normal live pregnancy, such as 8.1 mm (9).

In 2014, Tan et al., reported that an enlarged yolk sac was noted in eight pregnancies (2.6%). Nearly 40% of these pregnancies resulted in a the first trimester miscarriage. These findings indicate that the existence of an enlarged yolk sac (with a diameter of  $> 5$  mm) is of evident clinical significance when it is specified before the 7th week of gestation (9)

In 2015, Shetty et al., also reported that a yolk sac greater than 5 mm (large yolk sac) between 6- 7.5 weeks gestation was a good indicator and that it would end in abortions (11).

In 2016, Ashoush et al., a large yolk sac was most commonly detected (in 36.8%) with isolated congenital anomalies (representing 63.6% of all cases with too-large yolk sac) (12).

In 2016, Srivastava et al., also reported that an enlarged yolk sac was responsible for 77.78% of abortions (13).

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# Creatine Kinase as a diagnostic biochemical Marker in Placenta Accreta, Mansoura experience

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## Abstract

**Background:** placenta accreta is a life-threatening pregnancy complication which usually accompanied with placenta previa. It is important to make the diagnosis before delivery therefore a preoperative planning will decrease complications. The aim of this study was to evaluate the possibility of using creatine kinase as a diagnostic and prognostic marker in placenta accreta.

**Methods:** two groups were recruited; forty-five patients diagnosed by ultrasound with placenta accreta as patient group (group A) and another forty-five as controls (group B). Maternal Creatine kinase level was measured using CK-NAC FS\* IFCC Technical bulletin and compared between patients group and controls group.

**Results:** Our results indicated the presence of significant difference between the patient group and the control group regarding age (P-value= 0.01), gravidity (P-value= 0.01) and parity (P-value= 0.006). While non-significant difference regarding medical history (P-value= 0.59), surgical history (P-value= 0.51), and D & C (P-value= 0.82). Our results indicated no significant difference between both groups regarding serum creatine kinase level (P-value= 0.29). We have identified surgical complications and intraoperative findings which occurred significantly higher in the patient group in compare with the control group (P value <0.001). Our finding also revealed the presence of significant difference between the patient and control group regarding secondary outcomes including the required blood units transfusion (P-value <0.001).

**Conclusion:** We conclude that maternal serum creatine kinase is not a reliable tool in predicting or diagnosing placenta accreta.

**Keywords:** Creatine kinase, placenta accreta, previa, ultrasonography, surgical outcome.

## Introduction

Abnormal invasive placentation is a potential life-threatening pregnancy complication that may cause serious adverse maternal and fetal outcomes <sup>(1)</sup>.



There are three variants of invasive placentation which include placenta accreta where the placental villi occupy the surface of myometrium with a partial or complete absence of decidua basalis layer <sup>(2)</sup> and placenta increta which is characterized by the penetration of the placental villi into the myometrium and placenta percreta where the villi penetrate through the myometrium reaching the uterine serosa and could invade adjacent organs, such as the urinary bladder <sup>(3)</sup>.

high cesarean section (CS) rates in the latest decades have increased placenta accreta cases and as a result, pregnancy and delivery complications are occurring increasingly <sup>(4)</sup>.

It is critical to make the diagnosis before delivery because preoperative planning can significantly decrease intra-operative bleeding and avoid morbidity associated with placenta accreta <sup>(5)</sup>.

Creatine kinase (CPK) (Adenosine-5-triphosphate) is an enzyme found in the heart, brain, and skeletal muscle, it is also found in non-muscle cells such as pancreas, myometrium, endometrium and placenta <sup>(6)</sup>.

In literature, there are controversial results regarding the efficacy of using creatine kinase as a biochemical marker in predicting and diagnosing placenta accreta. One of those studies indicated elevated levels of creatine kinase in pregnant women diagnosed with placenta increta and percreta <sup>(7)</sup>. On the other hand, a second study failed to detect any elevations of creatine kinase levels in pregnant women diagnosed with placenta accreta <sup>(8)</sup>.

Ultrasonography is the main tool in diagnosing placenta accreta, however, many cases with placenta accreta undiagnosed or misdiagnosed by ultrasound leading to poor maternal outcome and complications.

Therefore, the aim of our study was to indicate the possibility of using serum creatine kinase as a diagnostic and prognostic marker in placenta accreta.

## **Patients and methods**

This was a prospective cohort study, patient group (Group A) which included 45 cases in their 2<sup>nd</sup> or 3<sup>rd</sup> semester who were diagnosed by ultrasound with placenta accreta and control group (Group B) which included 45 cases with normal placenta. Patients were examined and evaluated at the antenatal clinic and Inpatient department at Mansoura University hospitals from April 2019 till April 2020. Written informed patient consent was obtained from each case before the study.

Inclusion criteria included maternal age between 19-40 years old. Pregnant women with placenta accreta diagnosed with documented ultrasound and Doppler or MRI. Being at second or third trimester pregnancy and patient with previous hysterotomy or any uterine scar. Exclusion criteria included patient diagnosed with myocardial infarction (heart attack), autoimmune myositis, rhabdomyolysis or acute kidney injury.

Full History taking and examination including general examination, screening for risk factors of placenta increta and percreta, and past history of previous operations myomectomy or previous caesarian section.

Ultrasound examination was performed to ensure the presence of placenta accreta in the patient group. The ultrasound diagnostic criteria of placental accreta include disappearance of the hypoechoic retro-placental zone, disruption of the hyperechoic uterine serosa-bladder interface, increase intra-placental lacunae, and hyper-vascularity at the interface between the uterine serosa and the urinary bladder wall by color Doppler (irregularity of the bladder wall with positive flow on Doppler evaluation). Sagittal imaging was used to assess the depth of placental tissue, its vascularity and its relationship to the bladder wall, while coronal imaging was used to assess the extent of invasion. The presence of vascular structures on the bladder wall on Doppler ultrasound was classified as bladder invasion and the presence of other

sonographic findings on grayscale imaging with negative Doppler was classified as probable bladder invasion.

Measuring creatine kinase level, Blood samples were obtained after an overnight fasting by venipuncture and processed within 1 h after withdrawal by centrifugation at 5000 revolutions/min for 10 min, and analyzed at that time. Serum total creatine kinase was assayed by photometric systems using CK-NAC FS\* IFCC Technical bulletin supplied along with the kit was followed.

### **Ethical consideration**

Study protocol was submitted for approval by Institutional Research Board (IRB) faculty of medicine, Mansoura University. Approval of the managers of the health care facilities in which the study was conducted.

### **Results**

Table (1) represents the demographic characteristics of the studied cases.

**Table 1: Demographic characteristics of the patient and control groups:**

Parameters		Patient group(A)	Control group(B)	X <sup>2</sup>	P value
Age (years)		30.36±5.16	27.7±5.21	2.41	0.01*
Gravidity		3.95±1.49	3.21±1.29	2.52	0.01*
Parity		2.45±0.99	1.79±1.19	2.81	0.006*
Gestational age (weeks)		35.7±2.41	35.7±2.41	1.63	0.11
No. of fetuses	Single	43 (95.6%)	41 (91.1%)	1.05	0.59
	Twins	1 (2.2%)	3 (6.7%)		
	Triplet	1 (2.2%)	1 (2.2%)		

P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Table 1 showed the demographic characteristics of the patient and control cases. There was significant difference between the patient group and control group regarding age (30.36±5.16 years old vs 27.7±5.21 years old respectively), gravidity (3.95±1.49 vs 3.21±1.29 respectively), and parity (2.45±0.99 vs 1.79±1.19 respectively). However, there was no significant difference between the patient group and control group regarding gestational age at the time of the study (35.7±2.41 weeks vs 35.7±2.41 weeks respectively).

Informed verbal consent was obtained from each participant sharing in the study. Confidentiality and personal privacy were respected in all levels of the study.

### **Statistical Analysis of Data**

Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann-Whitney test (non-parametric data).



**Table 2: Comparison between studied cases regarding medical history:**

Parameters	Patient group(A)	Control group(B)	X <sup>2</sup>	P value
Negative	36 (80.0%)	36 (80.0%)	2.7	0.59
Type I DM	2 (4.5%)	0 (0.0%)		
GDM	1 (2.2%)	1 (2.2%)		
HTN	3 (6.7%)	1 (2.2%)		
GHTN	1 (2.2%)	3 (6.7%)		
PE	1 (2.2%)	3 (6.7%)		
PE+DM	1 (2.2%)	1 (2.2%)		

DM: diabetes mellitus. GDM: Gestational diabetes mellitus. HTN: Hypertension. GHTN: Gestational hypertension. PET: pre-eclampsia toxemia. P-value <0.05: significant, P-value >0.05: non-significant.

Table 2 showed that regarding the medical history, including gestational diabetes mellitus (GDM), gestational hypertension (GHTN), pre-eclampsia (PE), pre-eclampsia plus diabetes mellitus (PE+DM), hypertension (HTN) and type 1 DM, there were non-statistic significant difference between the patient group and control (P-value=0.59).

**Table 3: Comparison between studied cases regarding surgical history:**

Parameters	Patient group(A)	Control group(B)	X <sup>2</sup>	P value
Negative	28 (62.2%)	21 (46.7%)	3.28	0.51
Appendectomy	7 (15.6%)	11 (24.4%)		
Cholecystectomy	3 (6.7%)	2 (4.5%)		
Ovarian Cystectomy	1 (2.2%)	1 (2.2%)		
Exploration	3 (6.7%)	0 (0.0%)		
Incisional hernia	2 (4.5%)	0 (0.0%)		
Placenta previa	1 (2.2%)	0 (0.0%)		

P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Regarding surgical history. Table 3 indicated non-significant difference between the patient group and control (P-value=0.51).

**Table 4: Comparison between studied cases regarding CPK at the time of the study:**

Parameters	Patient group(A)	Control group(B)	T test	P value
CPK (IU/L)	70.38±62.81	58.73±37.67	1.05	0.29

CPK: creatinine phospho-kinase. P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Table 4 indicated the measured creatinine phospho-kinase was not significantly different between patient group and control group (P-value = 0.29).

**Table 5: Comparison between studied cases regarding placental site:**

Parameters	Patient group(A)	Control group(B)
FA	0 (0.0%)	19 (42.2%)
FP	0 (0.0%)	24 (53.3%)
Fundal	0 (0.0%)	2 (4.5%)
Anterior type 1	4 (8.9%)	0 (0.0%)
Anterior type 2	11 (24.4%)	0 (0.0%)
PPCC	22 (48.9%)	0 (0.0%)
Posterior type 2	8 (17.7%)	0 (0.0%)

FA: fundal anterior. FP: fundal posterior. PPCC: placenta praevia complete centralis.

Table 5 indicated the site of placenta in the patient group was anterior type 1, anterior type 2, PPCC and posterior type 2 (8.9%, 11%, 22% and 8% respectively) which indicating placenta previa in most of the studied cases of the patient group. On the other hand, the placental locations in control group were fundal anterior, fundal posterior and fundal (42.2%, 73.3% and 4.5% respectively).

**Table 6: Comparison between studied cases regarding surgical outcome intraoperative findings:**

Parameters	Patient group(A)	Control group(B)	P-value
Negative	5 (11.1)	45 (100.0%)	<0.001*
Focal accretion	20 (44.4%)	0 (0.0%)	
CS Hysterectomy	9 (20.0%)	0 (0.0%)	
Diffuse accretion	4 (8.9%)	0 (0.0%)	
CS Hysterectomy+ bladder injury	2 (4.5%)	0 (0.0%)	
Diffuse accretion+ PPH	1 (2.2%)	0 (0.0%)	
Diffuse accretion+ bladder injury	1 (2.2%)	0 (0.0%)	
Bladder injury	2 (4.5%)	0 (0.0%)	
Focal accretion+ bladder injury	1 (2.2%)	0 (0.0%)	

CS: cesarean section. PPH: post-partum hemorrhage. P-value< 0.001: highly significant, P-value <0.05: significant, P-value >0.05: non-significant.

Regarding the primary outcomes, table 6 indicated there was significant difference between patient group and control group (P <0.001).

**Table 7: Comparison between studied cases regarding secondary outcome:**

Parameters	Patient group(A)	Control group(B)	X <sup>2</sup>	P value
Negative	12 (26.7%)	39 (86.7%)	5.13	<0.001*
Blood transfusion units	2	8 (17.8%)	4 (8.8%)	
	3	3 (6.7%)	2 (4.4%)	
	4	8 (17.8%)	0 (0.0%)	
	5	2 (4.5%)	0 (0.0%)	
	6	6 (13.3%)	0 (0.0%)	
	7	6 (13.3%)	0 (0.0%)	

P-value< 0.001: highly significant, P value <0.05: significant, P-value >0.05: non-significant.

Regarding secondary outcome, Table 7 indicated highly significant difference between patient group and control group (P <0.001).

## Discussion

Placenta accrete is a potential life-threatening pregnancy complication. There are three variants of abnormal invasive placentation including placenta accrete, placenta increta and placenta percreta <sup>(3)</sup>.

Early diagnosis of placenta accreta may reduce the possible adverse outcomes. Despite the improvements in the imaging techniques and attempts to find a reliable marker to predict the abnormal invasion of the placenta, there is still debate for the accurate diagnosis <sup>(9,10)</sup>.

In our study, there were significant difference between the patient group and control group regarding age (P value <0.05), gravidity (P value <0.05), and parity (P value <0.001). However, there was no significant difference between the patient group and control group regarding gestational age at the time of the study (P value= 0.11).

Such results were in agreement with Iacovelli et al <sup>(11)</sup> study which reported that maternal age older than 32 years old is one of the risk factors of placenta accreta. The same findings were confirmed by Saito et al <sup>(12)</sup> and Singh and Kumari <sup>(13)</sup> studies that revealed that both multiparity and advanced maternal age to be predisposing factors to the occurrence of placenta accrete without prior history of cesarean section delivery.

In our study, the measured creatinine phosphokinase was not significantly different between patient group and control group (P-value = 0.29) indicating that creatine kinase does not represent an accurate tool as a diagnostic and prognostic marker of placenta accrete.

Such finding was in agreement with Ersoy et al <sup>(8)</sup> study that measured total creatine kinase and CK-MB levels in fifty-four pregnant women with diagnosed placenta previa and failed to predict the risk of placental accreta.

However, our results were in disagreement with Ophir et al <sup>(7)</sup> study that indicated an

elevation in maternal serum creatine kinase in patients with adherent placenta (increta or percreta).

In our study, the patient group placental location was anterior type 1, anterior type 2, PPCC and posterior type 2 (8.9%, 11%, 22% and 8% respectively) which indicating placenta previa in most of the studied cases of the patient group. On the other hand, the placental locations in control group were fundal anterior, fundal posterior and fundal (42.2%, 73.3% and 4.5% respectively).

Previous studies indicated that anterior location of the placenta in placenta previa increases the risk of postpartum hemorrhage, massive transfusions, and hysterectomy especially if complicated with placenta accreta <sup>(14,15)</sup>.

In the present study, we have identified eight surgical outcomes and intraoperative findings which occurred significantly in the patient group in compare with the control group (P value <0.001) including the presence of focal accretion, diffuse accretion, the incidences of bladder injury, CS hysterectomy alone, CS hysterectomy+ bladder injury, diffuse accretion+ PPH, diffuse accretion+ bladder injury and focal accretion+ bladder injury (P value<0.001).

Our results were in accordance with Clausen et al <sup>16</sup> study which revealed that 17% of placenta accreta patients are under the risk of cystotomy either unintentionally due to impaired visualization and poor dissection planes, or intentional injury to facilitate visualization.

Moreover, Hoffman et al <sup>17</sup> indicated that 10-15% of patients are under the risk of urethral injury during the surgical management of placenta accreta.

Regarding secondary outcome including number of units of blood transfused, our results revealed a significant difference between patient group and control group (P <0.001).

Our results were in agreement with AbdElfatah et al (18) study which indicated that 79.6% of placenta accreta patients required blood transfusion. Additionally, a study performed by Wright et al <sup>(19)</sup> revealed that the most common complication of placenta accreta is hemorrhage. Moreover, blood transfusion was required in more than 80% of cases; at least one half required 4 or more units of packed red blood cells.

In conclusion, maternal creatine kinase is not a reliable tool in predicting or diagnosing placenta accreta.

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# Early versus delayed oral feeding after cesarean section: A Randomized controlled trial

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**Keywords:** early feeding; delayed feeding; elective CS; intestinal recovery; postoperative pain.

## Synopsis

Early oral feeding is superior to delayed oral feeding in gastrointestinal recovery and bowel opening after cesarean section

## Abstract

**Objective:** to compare the effects of early versus delayed oral feeding after Cesarean section (CD).

**Study design:** A Randomized controlled trial included 200 pregnant women who underwent elective CD under regional anaesthesia. They were randomized into two feeding groups. Group I [early feeding] in which women started oral feeding 6 hours after surgery . Group II [delayed feeding] in which women started oral feeding only after return of bowel sounds. The primary outcome parameter was women satisfaction.

**Results:** Women in the early feeding group have earlier bowel sounds ( $6.71 \pm 1.612$  vs.  $8.32 \pm 3.156$ ,  $P = 0.01$ ) , bowel opening ( $8.53 \pm 1.55$  vs.  $10.96 \pm 2.156$ ,  $P < 0.001$ ) and discharge from hospital ( $21.2 \pm 4.6$  vs.  $29.2 \pm 6.1$ ,  $P < 0.001$ ) when compared to those in the delayed feeding group. No difference between women in the 2 groups regarding Pain score at 2,6 and 12 hours after surgery or GIT symptoms named nausea, vomiting or distension ( $P > 0.05$ ). Women in the early feeding group were significantly more satisfied after the operation than women in the delayed feeding group ( $P < 0.001$ ).

**Conclusion:** Early oral feeding after uncomplicated CD was safer, more convenient and reduces hospital stay costs and it's strongly recommended for all women after uncomplicated CD.

**Keywords:** early oral feeding; elective caesarean section; gastrointestinal symptoms.



## **Introduction**

Caesarean delivery [CD] is the most common surgical procedure in modern obstetric practice that excessively performed in the last few decades [1]. CD has an essential role in decreasing perinatal mortality and morbidity [1,2]. After general abdominal surgery, it is customary for the patient to take no fluid or food by mouth for a specific period of time, or until the return of bowel function as evidenced by propulsive bowel sounds or the passing of flatus or stool [2,3]. After CD, practices vary considerably between institutions and individual practitioners, ranging from early oral fluids or food to delayed introduction of oral fluids and food, which may be after 24 hours or more [4]. These discrepancies raise concern as to the bases of the different practices. 'Standing orders' may become accepted as part of everyday practice without their validity being questioned. The practice of allowing early oral fluids or food after CD is often based on the assumption that the bowels are not usually exposed or handled during CD [5,6]. There is no specific time for early oral feeding after CD, it depends on practical custom. Oral feeding is considered after 2-24 hours in different trials. There are controversies about the optimum time of feeding after CD. Some studies provide evidence that early oral feeding after surgery enhances the return of bowel function and does not increase the risk of postoperative complications [7] and advised that early feeding should be initiated without fear of any side effects [8]. while others could not provide such information. Our prospective randomized controlled trial aim to compare the effects of early oral feeding versus delayed oral feeding on gastrointestinal function and women satisfaction after CD.

## **Materials and methods**

This prospective, two-arm, single blind, randomized controlled trial was conducted at

KASR ALAINY maternity hospital between September 2018 and October 2019. The study was prospectively registered at clinicaltrials.gov [registration ID NCT03680391] after approval of the local ethical committee of Cairo university.

A total of 200 women who underwent elective CD participated in this work. Their age ranged between 20 and 40 years old, carry a singleton full term fetus and they were candidate of elective lower segment CD under spinal anaesthesia. Exclusion criteria included women with medical disorders as anemia, heart, liver or kidney diseases, those who had a known GIT disease or GIT symptoms presented before pregnancy and women with psychological or neurological complains that may affect the GIT symptoms or subjective assessment of pain and satisfaction scores. Women with intraoperative complications as organ or major vessel injury, women with previous GIT surgery and those who had postpartum hemorrhage were also excluded. All participants have signed an informed written consent.

Before assignment, all participants were evaluated through complete history and examination to ensure stickiness to the inclusion and exclusion criteria. Transabdominal obstetric ultrasonography was done to confirm the gestational age and evaluate the fetal condition and routine laboratory investigations were done to evaluate fitness for surgery and anaesthesia.

Randomization was done on the same day of the operation using computer-generated random numbers to either early or delayed feeding group. The surgeon and the outcome assessor were blinded for randomization process.

All CD were done by an obstetrician with at least 5 years of experience using the same technique. All used The Munro-Kerr technique through a pfannenstiell incision, uterine incision was transverse located at the lower segment which was closed in 2 layers

followed by closure of both visceral and parietal peritoneum. Neither towel packing of the gutters nor peritoneal irrigation was done.

transverse lower uterine segment incision, immediate cord clamping after delivery of baby, closure of uterus by 2 layers, closure of abdomen in layers. After the operation, women in group 1 (103 women) started oral fluids after 6 hours of surgery irrespective to intestinal sounds, flatus or stool while women in group 2 (97 women) started oral fluids after audible intestinal sounds and semisolid food after passage of flatus or stool.

The primary outcome parameter was maternal satisfaction measured using VAS scale where 0 indicated complete dissatisfaction and 10 indicates the maximum satisfaction. Secondary outcomes included the time of bowel opening, occurrence of nausea, vomiting or abdominal distension, postoperative pain score and the time of discharge from the hospital

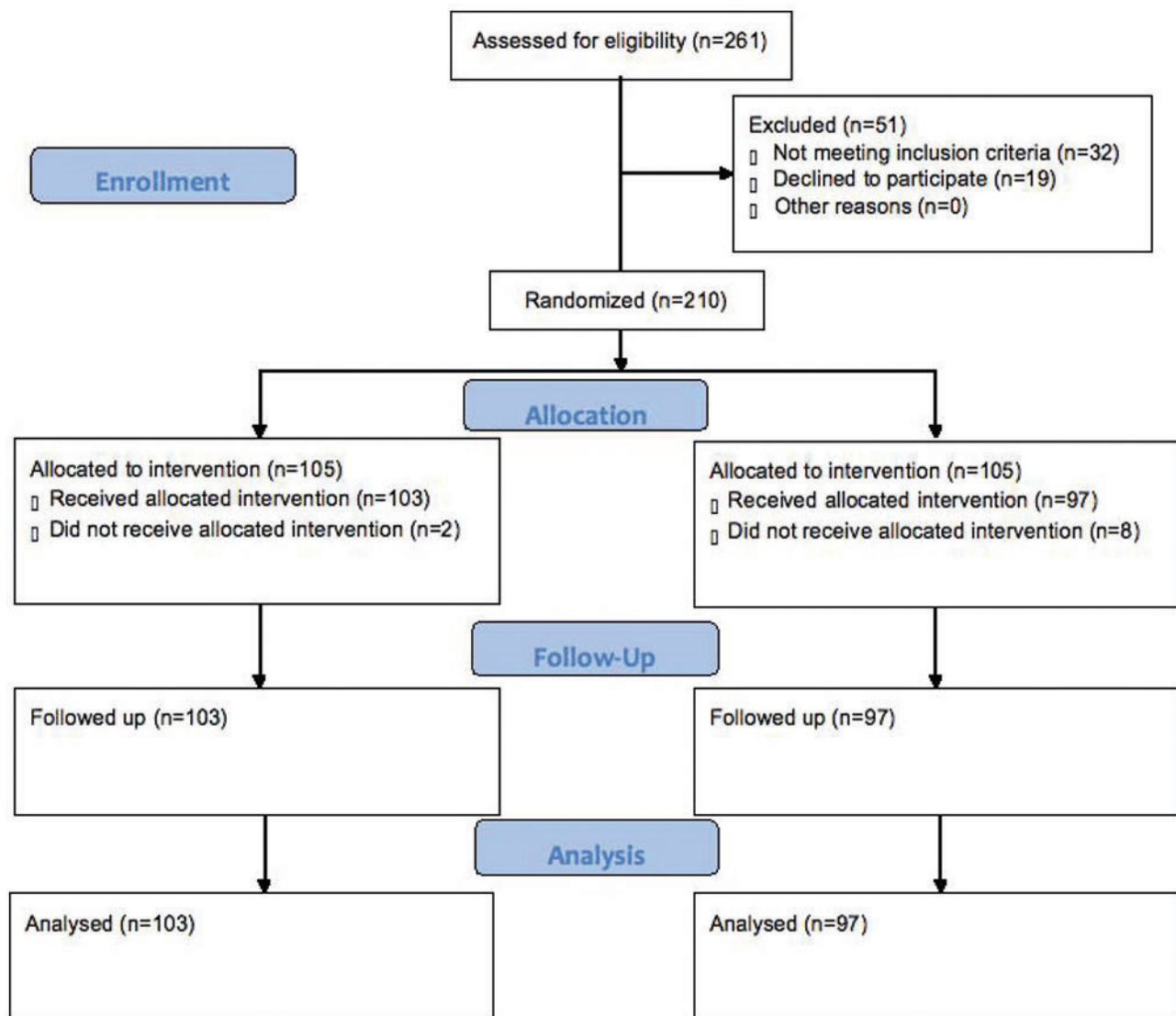
Sample size calculation was done using the comparison of patient satisfaction between early and conventional late feeding after CD. Calculation was done based on comparing two proportions from independent samples in a prospective study using Chi test. The  $\alpha$ -error level was fixed at 0.05. The power was set at 90% and the intervention groups' ratio was set at 1:1. As previously published, the incidence of patient satisfaction among mother with early feeding was 73% while it was 39% in conventional feeding mothers' group [9]. Accordingly, the minimum optimum sample size should be 94 participants in each arm. We recruited 105 women in each group to compensate for any drop out cases. Sample size calculation was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows.

## **Statistical analysis**

Data were collected and then were analyzed using the software package for the social sciences [SPSS], version 25.0 [Armonk, NY]. Demographics and menstrual data were summarized with descriptive statistics such as frequencies, percentages, and means. Categorical variables will be described as numbers and percentage and analyzed using the chi-square test. Continuous variables will be presented as a mean and standard deviation and compared with Student's t-test [The independent sample t-test for intergroup analysis of continuous variables, and dependent sample t-test for intragroup analysis between the discrete time points in the same group]. Besides, a two-sided  $P < 0.05$  was considered as statistically significant.

## **Result**

A total of 261 women were assessed for eligibility. Fifty-one women were excluded from the study (32 don't meet the inclusion criteria and 19 refused to participate). Randomized allocation of 210 women equally to groups. In the early feeding group 2 women didn't receive the intervention as intraoperative complications were encountered during the operation while in the delayed feeding group 8 women didn't receive the intervention as 3 had intraoperative complications and 5 refused to complete the study (figure 1).

**Figure 1: consort flow chart**

There was no significant difference between the early feeding and the delayed feeding groups regarding maternal age, body mass index, gestational age, neonatal birth weight, number and indications of CD. Similarly, no significant difference was found between women in the 2 groups regarding intraoperative blood loss, operative time, or the time of ambulation after surgery (table 1).

**Table 1 baseline characteristics of the study population**

		Early feeding (n=103)	Delayed feeding (n=97)	P value
Age (years)		27.96 ± 4.551	28.26 ± 5.261	0.271
BMI (Kg/m <sup>2</sup> )		28.3 ± 5.039	28.11 ± 4.318	0.761
Gestational age (weeks)		38.24 ± 1.033	38.28 ± 0.944	0.812
Neonatal birth weight (gm)		3243 ± 475	3314 ± 525	0.532
Cesarean section (CS)	Number of previous CS	1.23 ± 0.797	1.47 ± 0.812	0.293
	Indication of CS	Repeated CS	31 (30.1%)	0.169
		Malpresentation	28 (27.18%)	
		CPD	21 (20.39%)	
		Failure of progress	17 (16.5%)	
		Others	6 (5.82%)	
	Operative time (min)	49.2 ± 14.2	51.6 ± 16.2	0.152
	Intraoperative blood loss (ml)	623 ± 216	584 ± 278	0.153
Time of ambulation		5.9 ± 0.7	6.1 ± 0.8	0.721
Start of feeding		6	10.65 ± 2.15	<0.001

Data are presented as mean ± SD or Number (percent)

BMI Body mass index; CPD cephalopelvic disproportion

There was no significant difference between women in the early feeding group and those in the delayed feeding one regarding Pain score at 2, 6 and 12 hours after surgery or GIT symptoms named nausea, vomiting or distension (table 2).

Women in the early feeding group have earlier bowel sounds ( $P=0.01$ ), bowel opening ( $P<0.001$ ) and discharge from hospital ( $P<0.001$ ) when compared to those in the delayed feeding group (table 2). Women in the early feeding group were significantly more satisfied after the operation than women in the delayed feeding group (table 2).

**Table 2 Postoperative outcome parameters**

		Early feeding (n=103)	Delayed feeding (n=97)	P value
+ve bowel sounds		6.71 ± 1.612	8.32 ± 3.156	0.01
Bowel opening		8.53 ± 1.55	10.96 ± 2.156	<0.001
Pain score	At 2 hours	0.61 ± 0.31	0.59 ± 0.42	0.612
	At 6 hours	4.13 ± 1.65	4.87 ± 1.81	0.664
	At 12 hours	6.1 ± 2.1	6.3 ± 2.0	0.391
Satisfaction score		8.1 ± 0.8	5.2 ± 1.2	<0.001
GIT symptoms	Nausea	14 (13.59%)	18 (18.56%)	0.259
	Vomiting	3 (2.91%)	5 (5.15%)	0.211
	Distension	3 (2.91%)	4 (4.12%)	0.786
Discharge		21.2 ± 4.6	29.2 ± 6.1	<0.001

Data are presented as mean ± SD or Number (percent)



## **Discussion**

Our prospective randomized controlled trial showed that early oral feeding is superior to delayed oral feeding in gastrointestinal recovery and bowel opening after CD.

Recovery of the normal peristalsis of the small intestine occurs 4 -8 hours after laparotomy and resuming of the gastric emptying occurs in the first day after it [10-12].

Early oral intake enhanced recovery postoperative gastrointestinal movement. This movement have different eating and postprandial forms. It's characterized by alternating periods of forceful contractions and quiescence in between meals and presence of food in the intestine changes that pattern to random bursts of spike potential [13]

Previous studies suggested that oral feeding can started in most cases immediately after surgery as they found no beneficial effects of gastric decompression even after GIT surgery [14].

Three meta-analyses showed that early postoperative feeding is associated with significantly lower complications when compared to the classic delayed feeding and a significantly beneficial effects on bowel recovery and hospital discharge [15-17].

In our study there was no significant difference between early feeding and delayed feeding women regarding GIT complications as nausea , vomiting or distension

Tavasolli and colleagues reported no significant difference between early and delayed feeding groups regarding occurrence of vomiting.[18]. The same findings were reported by Stewart et al [19] and Seenu and Goel [20]

According to our findings, women who started their oral feeding early were significantly more satisfied than those who started it late.

In our study, Women with early feeding were discharged from the hospital earlier than women with delayed feeding.

A meta-analysis that included 2112 adult patients who had upper gastrointestinal surgery included in 15 trials (8 of them were RCTs) proved that early feeding was associated with significantly shorter hospital stay [21].

Recent meta-analysis regarding to our topic made on 11 article indicated that EOF is associated with early back to bowel function recovery and does not increase the risk of postoperative complications. Oral intake within 8 h as a part of standard care for women who undergo CD is recommended. However, this study included some heterogeneity of included studies [7]. Several studies reveals that early oral feeding has better effects on gastrointestinal functions compared to delayed oral feeding after CD [8]. Guo et al made meta-analysis on 20 articles showed that early oral feeding is safe and accelerates recovery after CD. Early oral feeding led to a clinically significant reduction in time to return of gastrointestinal function, lowered the amount of postoperative care needed, reduced hospital stay, and shortened time to first breastfeeding, without increasing rates of postoperative complications[22].

Mehta et al stated early oral intake of food, following uncomplicated CD under regional anesthesia, is safe and well tolerated produces a better outcome, compared to delayed feeding; does not cause significant increase in postoperative paralytic ileus; and results in better patient satisfaction[23]. Aydin at al recommended oral feeding 2 hours after CD under regional anesthesia to achieve rapid postoperative recovery and early hospital discharge [24]. Another study reveals that early-oral intake after an elective CD is well tolerated by patients and promoted gut function without an increase in postoperative nausea and vomiting[25].

Moreover, Izbizky et al stated that early feeding after a CD in low-risk women increased women satisfaction, was as safe as the traditional approach with more beneficial effects on women's perceived pain [26].

Jalilian et al revealed that early oral feeding 2 h post-cesarean section reduced the time required for return of normal bowel function. This is without significant detrimental effects on the incidence of gastrointestinal complications[27].

To the best of our knowledge, our study is the first RCT with properly calculated sample size to evaluate all outcomes of patient satisfaction, GIT complications and hospital stay after CD. We can conclude that early oral feeding after uncomplicated CD is safer, more convenient and reduces hospital stay time and costs compared to delayed feeding and it is strongly recommended for all women after uncomplicated CD.

### ***Compliance with Ethical Standards***

The study was performed in accordance with the Declaration of Helsinki ethical standards. Informed consents were taken from study participants.

### ***Author contributions***

MI Mostafa: Data analysis, Manuscript writing, manuscript revision

BM Elbokl : Data collection, Manuscript writing

M Shalaby: Data analysis, manuscript revision, project development

### ***Disclosure***

The authors report no conflicts of interest in this work

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# The diagnostic accuracy of ultrasound in the prediction of placenta accreta spectrum (PAS)

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## Abstract

**Objective:** To evaluate the ability of each sonographic parameter in the prediction of PAS and to correlate this ultrasound assessment to operative judgement of an experienced accreta team and to histopathology of the specimen in cases who were indicated for hysterectomy.

**Materials and Methods:** A total of 60 patients diagnosed as having placenta previa with high possibility of placenta accreta, PAS was diagnosed by the presence of at least one of the following features in color Doppler scan: diffuse or focal lacunar flow, sonolucent vascular lakes and hypervascularity of the utero-vesical interface with bridging vessels connecting the placenta to the bladder. The sonographic provisional diagnosis of accreta was documented. An experienced accrete team who were blinded for the ultrasound result made an intraoperative judgment and classified the case to either (mostly accreta) or mostly (non accreta). Histopathological examination was done to assess the presence of placental invasion & to confirm the diagnosis of placenta accreta for the specimens who required hysterectomy by a pathologist who were also blinded for the ultrasound diagnosis,

**Results:** Placental invasion was found in 35(58.3%) by ultrasound examination of placenta previa cases. Intraoperatively, 36 (60%) patients were assessed to have morbidly adherent placenta (MAP). By histopathological examination 16 cases (45.7 %) were confirmed as placenta accreta and 19 cases (54.3 %) were confirmed as placenta increta .Out of the different ultrasound parameters abnormal lacunae was found to have the highest sensitivity, specificity, PPV, NPV and accuracy in its relation to both intraoperative assessment and histopathological analysis.

**Conclusion:** prenatal ultrasound is the best screening tool for PAS and presence of abnormal lacunae and loss of retro-placental clear zone are accurate predictors for the operative findings and histopathological diagnosis.

**Keywords:** Placenta accreta, ultrasonography, Diagnosis, operative findings.

## **Introduction**

Over the last decade, abnormal placentation (accreta, increta and percreta) has emerged as one of the obstetric catastrophes (1). Placenta accreta is classified according to the depth of myometrial invasion with the risk of hemorrhage and maternal morbidities directly related to the depth of myometrial invasion (2,3).

Uterine surgical procedures were claimed as the predisposing-factors for placenta accreta, yet repeated cesarean section and placenta previa remains the major contributing risk factor for the development of placenta accreta spectrum (PAS) (3,4).

Early diagnosis of abnormal placentation allows proper counselling of the patients and improves the maternal and fetal outcomes by allowing multidisciplinary management and optimizing the timing and the preparation for cesarean delivery (5, 6).

Ultrasonography remains the primary golden method for diagnosis of PAS while Doppler is the first line tool for diagnosis of myometrial invasion (5,7,8). Multiple ultrasound variables have been used to diagnose abnormal placentation, these markers included myometrial thinning <1 mm, presence of irregular vascular spaces (i.e., placental lacunae), loss of the normal retroplacental hypoechoic area, thinning and irregularity of the uterine-bladder interface together with the vessels bridging between bladder and myometrium detected by color Doppler (9-13).

The current study aimed to evaluate the accuracy of different ultrasound parameters (separately) in the diagnosis of PAS and their correlation with operative judgement and histopathological diagnosis.

## **Material and methods**

The current study was a prospective cohort one conducted in kasr El-ainy hospital

(The obstetrics & Gynecology department - Faculty of medicine - Cairo University) in the duration between December 2017 and January 2021. 60 pregnant women (aged from 20 to 40 years) with singleton living healthy fetus diagnosed as having placenta previa with high possibility of placenta accreta (claimed by level 2 ultrasound), and candidate for repeated elective cesarean section (CS) or elective cesarean hysterectomy (if the diagnosis of placenta accreta is confirmed intra-operatively) were included. Inclusion criteria included: gestational age more than 28 weeks (confirmed by a reliable date for the last menstrual period and/or 1st trimester ultrasound scan) and one or more previous cesarean delivery. Women who had chronic or pregnancy induced diseases or any emergency or unplanned delivery were excluded. Women who became hemodynamically unstable or requested conservative management for accreta (if possible) were also excluded. The study was approved by the hospital ethical committee and was registered at ClinicalTrials.gov (registration No.: NCT03286998).

Informed consents were obtained from all patients after explanation of the aim of the study & discussing the potential hazards. For all participants, full history was obtained followed by complete physical examination & routine obstetric ultrasound (to confirm the presence of placenta previa i.e., placental tissue covers the internal cervical os or within 2 cm from it). Later on, the placentae were reexamined in systematic manner by gray-scale & color Doppler ultrasound via transabdominal and/or transvaginal approach using Voluson Pro-V ultrasonography machine (GE Healthcare Austria GmbH, Seoul, Korea) and the possibility of concomitant placenta accreta was checked. All ultrasound exams were done by an expert single sonographer. The placenta was scanned with adequate bladder volume to visualize the bladder- uterine serosal interface correctly & the angle of insonation was kept

as low as possible. The presence of one or more of the following features in grey scale ultrasound was considered as indicative of PAS: presence of abnormal placental lacunae, complete loss of retroplacental sonolucent zone, myometrial thinning, disruption of the uterine serosa-bladder interface, presence of mass invading the urinary bladder. Similarly, PAS was diagnosed by the presence of at least one of the following features in color Doppler scan: diffuse or focal lacunar flow, sonolucent vascular lakes, hypervascularity of the utero-vesical interface with bridging vessels connecting the placenta to the bladder. The grey scale and Doppler ultrasound finding were defined according to FIGO consensus guidelines on PAS (14). The presence or absence of the studied sonographic parameter (namely; loss of clear zone, abnormal lacunae, myometrial thinning, bladder wall interruption, placental bulge, uterovesical hyper vascularity, bridging vessels and placental lacunae feeder vessels) for each patient were recorded. The sonographic provisional diagnosis of accreta (i.e., focal, total, accreta, increta or percreta) with the concomitant invasion of adjacent structures (e.g., the urinary bladder) was documented (Figure 1).

Routine preoperative labs were obtained 48 hours before the elective termination of pregnancy (whether by elective CS or elective cesarean hysterectomy) which were done multidisciplinary team (accreta team) consisted of senior staff obstetricians, urology team and general surgery team. Intra-operatively, following the bladder downward displacement and exposure of the lower uterine segment just before the uterine incision, a quick evaluation was done by the accreta team (if placenta invade the outer uterine wall, placenta is bulging or bridging vessels were present) to decide whether the placenta was accreta or not (operative judgement) and accordingly they are classified into "MOSTLY ACCRETA" or "MOSTLY NOT ACCRETA". Following

the delivery of the fetus and cord clamping, if placenta was not separated for 5 minutes in spite the use of ecbolics, the accreta team proceeded to caesarean hysterectomy (Figure 2). The operative judgement (Mostly accreta or mostly not accreta), operative procedure, operative findings (as regard the invasion of adjacent structures) and all operative steps were documented. For hysterectomy specimens, histopathological examination was done to assess the presence of placental invasion & to confirm the diagnosis of placenta accreta (Figure 3). According to the pathological examinations, the specimens were classified into accreta & non-accreta. Both the accreta team and the pathologist were blinded to the ultrasound report. Each of the following eight sonographic parameters (Loss of clear zone, abnormal lacunae, myometrial thinning, bladder wall interruption, placental bulge, uterovesical hyper vascularity, bridging vessels, placental lacunae feeder vessels) was correlated to the operative judgement of the accreta team & the histopathological reports.

Primary outcome measured the ability of each sonographic parameter (the above-mentioned) in the prediction of PAS while the secondary outcome measured their correlation to operative judgement of experienced accreta team.

### **Statistical analysis of the collected data**

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic efficacy were calculated as described by Galen (15). Comparisons



between groups were done using unpaired t test (16). For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5 (17). P value less than 0.05 was considered as statistically significant.

A priori sample size calculation using Fisher's exact test predetermining the alpha error to be 0.05 and the power to be 0.95 showed a required sample size to be 56 generated by G\*power 3.1 statistical package.

Assuming a dropout rate of 20% (N=11) we decided to recruit 67 candidates.

## **Results**

Sixty pregnant women diagnosed as having placenta previa with high possibility of being placenta accreta were finally included in this prospective study. 35 patients (58.3%) were diagnosed as having accreta (confirmed by histopathological examination that denotes myometrial invasion) [accreta cases] while 25 cases (41.7%) were diagnosed as placenta previa without invasion (either when the placenta separated after fetal delivery or when pathological examination of the specimen denied any myometrial invasion) [not accreta cases]. Flow of patients were summarized in figure 4 and participants' demographic features and pregnancy characteristics were summarized in table 1.

## **Parameters of ultrasound in correlation to intraoperative judgement:**

Intraoperatively and before uterine incision, the accreta team classified 36 patients as MOSTLY ACCRETA while the remaining 24 were classified as MOSTLY NOT ACCRETA (figure 4). Our results showed a significant correlation between loss of clear zone (n=29, 80.6%), presence of placental lacunae (n=31, 86.1%), myometrial thinning, (n=27, 75%), bladder wall interruption (n=28, 77.8%), uteroplacental hyper vascularity (n=29, 80.6%) and the operative judgement of

accreta team (Table 2). Based on such results, presence of abnormal lacunae in ultrasound had the highest sensitivity and accuracy (86 & 92%, respectively) in predicting the operative judgement followed by the loss of clear zone (81 & 85%, respectively) (Table 3).

## **Parameters of ultrasound in correlation with histopathological findings:**

Following the delivery of the fetus, 42 placentae were not separated for 15 minutes in spite the use of ecbolics, the accreta team proceeded to caesarean hysterectomy. Out of 42 specimens, histopathological examination confirmed placenta invasion in 35 specimens [16 cases (45.7 %) were confirmed as placenta accreta and 19 cases (54.3 %) were confirmed as placenta increta] (figure 4).

Our results showed only statistically significant correlation between loss of and clear zone (n=29, 82.9%), presence of abnormal lacunae (n=32, 91.4%) with the histopathological examination (Table 4). Based on such results, presence of abnormal lacunae in ultrasound had the highest sensitivity and accuracy (91 & 93%, respectively) in predicting the histopathology of accreta followed by the loss of clear zone (83 & 83%, respectively) (Table 5).

According to these data abnormal lacunae was found to have the highest sensitivity, specificity and accuracy in its relation to both intraoperative judgement and histopathological analysis of accreta.

## **Discussion**

Placenta accreta spectrum is multifactorial disorders in which the placental trophoblastic tissue abnormally adheres and invades the myometrium and uterine serosa. It has been associated with severe adverse maternal outcomes including severe life-threatening bleeding, massive blood transfusion, injury to adjacent structures, prolonged ICU admissions and death. The definitive diagnosis



is made by the pathological examination of hysterectomy specimens; however, early prenatal diagnosis of PAS is crucial step that allows the multidisciplinary planned management to be tailored for each case which in turns helps to reduce maternal/fetal morbidity and mortality. Ultrasonography is highly sensitive and specific primary tool in the diagnosis of placenta accreta especially those performed by skilled sonographer. Several ultrasound parameters have been reviewed as regard their diagnostic accuracy to predict PAS in order to obtain a universal definition and to standardize the sonographic evaluation of such conditions.

In the current study we tested the diagnostic value of eight sonographic parameters (i.e., loss of clear zone, abnormal lacunae, myometrial thinning, bladder wall interruption, placental bulge, uterovesical hyper vascularity, bridging vessels and placental lacunae feeder vessels) when applied individually as predictor for PAS in correlation to both the intraoperative assessment and histopathological analysis. Our results demonstrated that presence of abnormal lacunae had the highest sensitivity, specificity and accuracy in correlation to both intraoperative judgement (86%, 87.5% and 92%, respectively) and histopathological analysis of accreta (91%, 100% and 93%, respectively) followed by the loss of clear zone.

This agrees with several studies that found a strong relationship between presence of abnormal lacunar spaces and placental invasion and considering it a reliable ultrasound sign (9,10,14,18-21). Comstock and his colleagues (22) reported that presence of placental lacunae in 3rd trimester ultrasound scan is the most reliable diagnostic sign (sensitivity was 93% and PPV was 93%) for the diagnosis of accreta among women with previous caesarean delivery. Similarly, Boroomand and his colleagues (20), reported that the sole presence of abnormal lacunae had a predicting power of 96 to 100% for

PAS. Also, D'Antonio and his colleagues (21) in their review stated that among 13 studies, that tested the diagnostic performance of placental lacunae, a pooled sensitivity and specificity of 77 and 95% respectively were demonstrated in the diagnosis of placenta accreta.

The lack of decidua basalis (loss of the retroplacental clear zone in ultrasound) and trophoblastic invasion into the myometrium are constant and early findings in all variants of PAS. Our results demonstrated a significant correlation between loss of clear zone in ultrasound when corelated with intraoperative judgement (sensitivity, specificity and accuracy were 81%, 87.5% and 85%, respectively) as well as with histopathological examination (sensitivity, specificity and accuracy were 83%, 86 % and 83%, respectively). Our results were in accordance with those demonstrated by Cali and his coworkers (23) who reported that the absence of the retroplacental clear zone was the most effective sonographic measure for detection of PAS with certain limitation as the lower uterine segment appears as a very thin line in late third trimesteric ultrasounds making the evaluation of the interface between the myometrium and the placenta a challenging process. The same was reported by D'Antonio and his colleagues (21) who reported a pooled sensitivity and specificity of 66 and 96% respectively.

The presence of bladder wall abnormality (i.e., focal interruption, uterovesical hypervascularity OR exophytic mass) is a reliable ultrasound finding that rules in the diagnosis of accreta (21). Our study demonstrated significant correlation between bladder wall interruption and uterovesical hyper vascularity with only the intraoperative judgement of placental invasion (no significant correlation with histopathological diagnosis). The sensitivity, specificity and accuracy of bladder interruption in predicting the operative findings were 78%, 71% and 77% respectively, while

the sensitivity, specificity and accuracy of uterovesical hyper vascularity were 81%, 79% and 73% respectively. Our results were in agreement with Cali and his colleagues (23) and D'Antonio and his colleagues (21) who reported a pooled sensitivity of 50% and specificity of 99.7 for abnormalities of uterus–bladder interface in the diagnosis of placenta accreta. The same reported by Boroomand and his coworkers (20) who introduced a highly predictive ultrasound model for PAS included abnormal lacunae, bladder wall interruption and uterovesical vascularity.

Our finding also showed that myometrial thinning (less than 1mm) had sensitivity of 75% and accuracy of 69% in the prediction of PAS. This was in accordance with Twickler and his coworkers (9). On the other hand, our results demonstrated that the presence of placental bulge, bridging vessels or placental lacunae feeder vessels had low predictivity for PAS sensitivity was 57, 57 and 51% respectively and accuracy was 55,

50 and 50%, respectively). This agrees with Comstock (22) who stated that placental bulge wasn't sensitive sign.

To the best of our knowledge, the current study is the 1st one that assessed the relation between different ultrasound markers (solely) in relation to operative findings and judgement. Add to the strengths, the operative team and the pathologist were blinded to the ultrasound findings and all ultrasounds were done by single expert sonographer. Yet, we faced some limitations such as the small sample size and the ultrasound findings are not correlated to the degree of placenta invasion (accreta, increta or percreta) which in turn may classify the severity of the condition and adjust the plan of management.

In conclusion, prenatal ultrasound is the best screening tool for PAS and presence of abnormal lacunae and loss of retroplacental clear zone are accurate predictors for the operative findings and histopathological diagnosis.

**Table 1: Demographic profile, gestational age, estimated blood loss and number of cesarean sections.**

	Accreta Cases (n=35)		Not accreta Cases (n=25)		P value
	Mean	SD	Mean	SD	
Age (in years)	31.20	4.89	32.44	5.22	0.350
Parity	2.91	1.07	3.32	1.18	0.170
BMI (kg/m <sup>2</sup> )	29.59	5.64	25.39	3.15	0.002
GA at termination (in weeks)	35.83	2.33	35.92	2.27	0.880
Estimated blood loss (in ml)	2642.86	824.37	2056.00	1065.79	0.019
No. of CS	2.60	1.01	2.92	1.15	0.258

**BMI: body mass index / GA: gestational age / CS: caesarean section**

**Table 2: Parameters of ultrasound in correlation to operative judgement.**

Ultrasound Parameter	Operative Judgement		P- value
	Mostly Accreta (n=36)	Mostly not Accreta (n=24)	
Loss of clear zone	Yes 29 No 7	Yes 3 No 21	> 0.001
Abnormal lacunae	Yes 31 No 5	Yes 3 No 21	> 0.001
Myometrial thinning	Yes 27 No 8	Yes 9 No 16	0.003
Bladder wall interruption	Yes 28 No 8	Yes 7 No 17	0.001
Placental bulge	Yes 21 No 15	Yes 9 No 15	0.190
Uterovesical hyper vascularity	Yes 29 No 7	Yes 5 No 19	> 0.001
Bridging vessels	Yes 21 No 15	Yes 10 No 14	0.315
Placental lacunae feeder vessels	Yes 19 No 17	Yes 11 No 13	0.793

**Table 3: Sensitivity, specificity, PPV, NPV of different ultrasound parameters in relation to operative judgment**

	Sensitivity	Specificity	PPV	NPV	Accuracy
Loss of clear zone (%)	80.6	87.5	90.6	78.6	85
Abnormal lacunae (%)	86.1	87.5	94.1	88.4	91.7
Myometrial thinning (%)	75	66.7	74.2	64	70
Bladder wall interruption (%)	77.8	70.8	80	72	76.7
Placental bulge (%)	58.3	62.5	66.7	50	58.3
Uterovesical hyper vascularity (%)	80.6	79.2	82.3	30	73
Bridging vessels (%)	58.3	58.3	64.5	48.2	56.7
Placental lacunae feeder vessels (%)	52.8	54.2	60	43.3	51.7

**PPV: positive predictive value / NPV: negative predictive value**

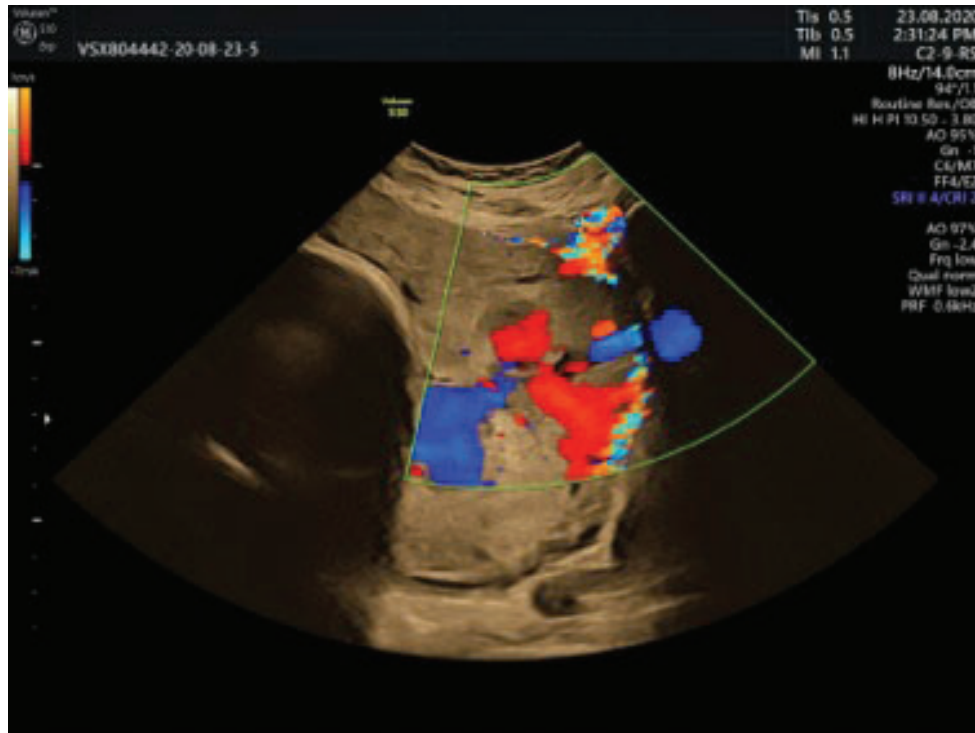
**Table 4: Parameters of ultrasound in correlation to histopathological diagnosis**

Ultrasound parameter	Histopathological diagnosis				P- value
	Accreta specimens (n=35)		Non-accreta specimens (n=7)		
Loss of clear zone	Yes	29	Yes	1	<0.001
	No	6	No	6	
Abnormal lacunae	Yes	32	Yes	0	<0.001
	No	3	No	7	
Myometrial thinning	Yes	26	Yes	4	0.359
	No	9	No	3	
Bladder wall interruption	Yes	28	Yes	4	0.195
	No	7	No	3	
Placental bulge	Yes	20	Yes	4	1.00
	No	15	No	3	
Uterovesical hypervascularity	Yes	28	Yes	4	0.195
	No	7	No	3	
Bridging vessels	Yes	20	Yes	6	0.222
	No	15	No	1	
Placental lacunae feeder vessels	Yes	18	Yes	4	1.00
	No	17	No	3	

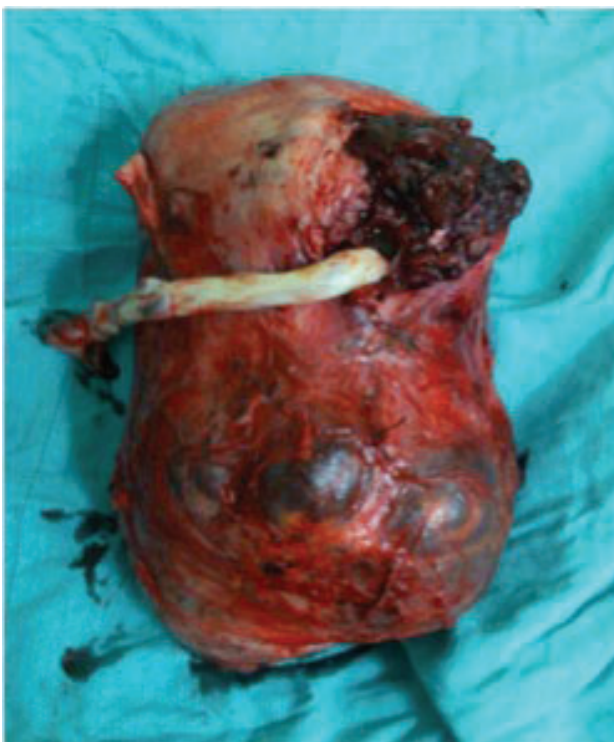
**Table 5: Sensitivity, specificity, PPV, NPV of different ultrasound parameters in relation to histopathological diagnosis.**

	Sensitivity	Specificity	PPV	NPV	Accuracy
Loss of clear zone (%)	82.9	85.7	96.7	50	83.3
Abnormal lacunae (%)	91.4	100	100	70	92.9
Myometrial thinning (%)	74.3	42.9	86.7	25	69
Bladder wall interruption (%)	80	42.9	87.5	30	73.8
Placental bulge (%)	57.1	42.9	83.3	16.7	54.8
Uterovesical hyper vascularity (%)	80	42.9	87.5	30	73.8
Bridging vessels (%)	57.1	14.3	76.9	6.3	50
Placental lacunae feeder vessels (%)	51.4	42.9	81.8	15	50

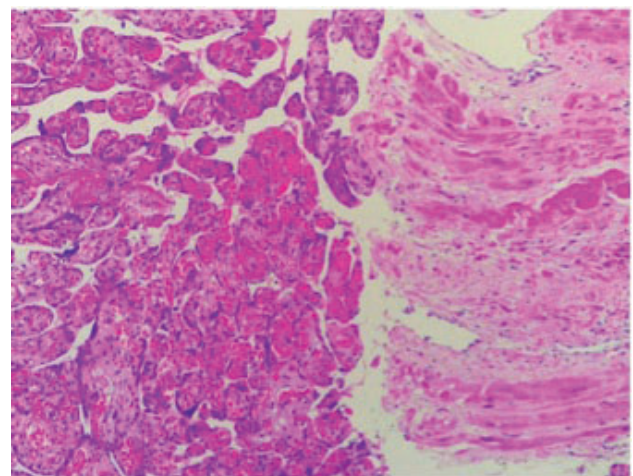
**PPV: positive predictive value / NPV: negative predictive value**



**Figure (1):** Ultrasound a case of placenta accreta with thinned out myometrium and striking vesico-placental vascularity with bridging vessels.



**Figure (2):** CS hysterectomy specimen (The case of placenta accreta with the ultrasound in fig 1).



**Figure (3):** Histopathology of the specimen in Figure 2, showing trans-myometrial invasion by small sized chorionic villi showing increased vascularity, focal fibrin deposition and evident trophoblastic knots (third trimesteric villi) with absent normal decidual plate (original magnification x100.H&E stain).



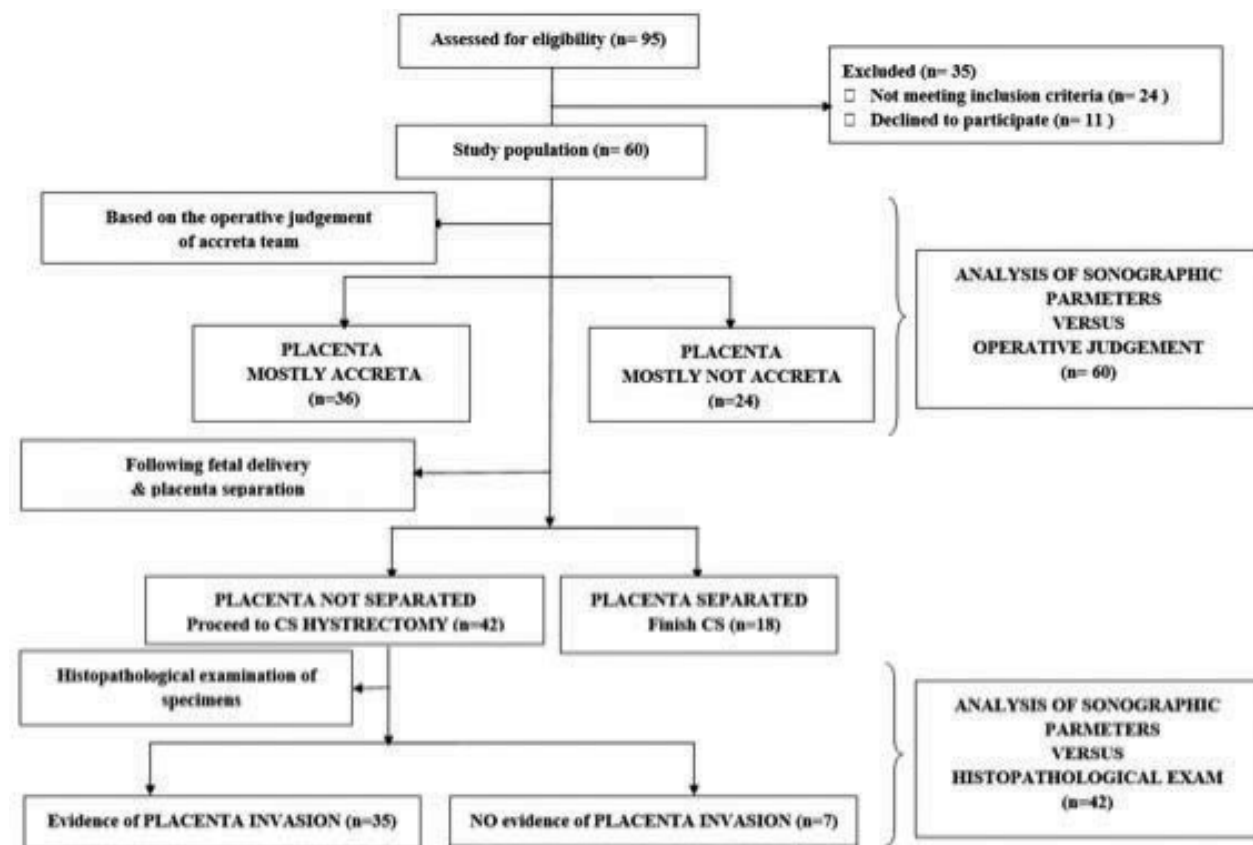


Figure 4: Flow of patients.

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# Cold knife versus monopolar electrosurgery for abdominal incisions (clinical trial)

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- **No funding sources.**
- **Conflict of interest;** Shaimaa I. Borhamy, Nahed E. Mahmoud and Iman I. El Noor declare that they have no conflict of interest.

## **Abstract**

**Background:** Scalpel incisions cause low injury to surrounding tissues. Electrosurgery has been used extensively for hemostasis, but the risk of producing huge scars and poor tissue recovery has kept it from being used in skin incisions for the time being.

**Aim:** In patients with benign gynaecological disorders receiving abdominal incisions, to evaluate early postoperative and late term wound complications among scalpel and electrosurgery.

**Patient and method:** Within a 20-month period, a randomised controlled trial (parallel group study with 1:1 randomization) was undertaken at the gynaecology department of Alzhraa University Hospital in Cairo, Egypt.

We included 120 women in the trial after determining their eligibility. 16 of them were disqualified for failing to satisfy the inclusion criteria and refusing to participate. During follow-up, 14 patients were lost because they did not attend their second appointment or did not provide their incision photo to the first author (Shaimaa Ismail). Analysis was done on 90 participants, 45 in each group. Cases randomly assigned at the operation day into two groups. Group A: scalpel used for anterior abdominal wall incision and simple compression or stitch for hemostasis, Group B: electrosurgery used for same incision and hemostasis (CUT and COAG). Primary outcomes: wound incision time/seconds and wound related blood loss/grams). Secondary outcomes: postoperative pain by VAS score, analgesia needed in first 12 hours postoperative in number of doses, wound infection and ugly scar formation at day 40.

**Results:** the electrosurgery group had a significantly low wound related blood loss ( $7.39 \text{ g} \pm 5.5 \text{ g}$  vs.  $24.72 \text{ g} \pm 9.75 \text{ g}$ ;  $U = 137$ ;  $P < 0.001$ ) and lesser incision time ( $2.16 \pm 0.09$

min vs.  $3.9 \pm 1.58$  min;  $U = 303$ ;  $P < 0.001$ ; Mann-Whitney test) compared to scalpel group. Electrosurgery significantly decrease postoperative pain in both subjective and objective methods. There was no statistical difference found between the groups regard to wound infection ( $P = 0.3$ ; Fisher exact test ).

**Conclusion:** The proper use of electrosurgery for abdominal wall incision could be a good alternative for scalpel.

We registered our study protocol at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) . ClinicalTrials.gov Identifier: NCT04236401

**Keywords:** electrosurgery, scalpel, abdominal incision.

## **Introduction**

The employment of an alternating current via tissue resistance to elevate tissue temperature for vaporization or a combination of desiccation and protein coagulation is known as electrosurgery. <sup>(1,2)</sup> Since Dr Harvey Cushing first introduced electrosurgery on October 1, 1926, it has been frequently employed in surgical operations. <sup>(3)</sup> However, it is mostly utilized for hemostasis and dissection. The use of electrosurgery for skin incision was thought to be problematic. <sup>(4)</sup> There are worries about utilizing electrosurgery in skin incisions because of the possibility of big scars and poor tissue repair <sup>(5)</sup>

## **Aim**

To compare the initial postoperative and late term wound complication degrees among the scalpel and electrosurgery in patients with benign gynecological disorders undergoing abdominal incisions.

## **Patients and methods**

From November 2019 to June 2021, a randomized controlled trial (parallel group study with 1:1 randomization) was undertaken at

Alzhraa University Hospital's gynaecological department.

A total of 90 opaque sealed envelopes comprised 45 pieces of written paper for cold knife and 45 pieces of written paper for electrosurgery, all prepared before recruitment and utilized to conceal allocation.

## **Ethical Approval**

Approval of ethical committee was obtained from quality education assurance unit, Al-Azhar university faculty of medicine, Egypt. Oral informed consent was taken from all cases before participation in this study. The nature and aim of this work were fully discussed to all women who were included in the study.

## **Sampling method**

Consecutive sampling (non-probability sample).

## **Sample size justificationn**

The sample size was obtained using the following formula :

$$n = (Z_{\alpha/2} + Z_{\beta})^2 \cdot 2 \cdot \sigma^2 / d^2,$$

where  $Z_{\alpha/2}$  is the critical value of the Normal distribution at  $\alpha/2$  (e.g. for a confidence level of 95%,  $\alpha$  is 0.05 and the critical value is 1.96),  $Z_{\beta}$  is the critical value of the Normal distribution at  $\beta$  (e.g. for a power of 80percent,  $\beta$  is 0.2 and the critical value is 0.84),  $\sigma^2$  is the SD of wound incision time of electrocautery from previous study (Kadyan, et al, 2014)(6)  $SD = 5.07$  , and  $d$  is the difference in incision time between the two groups that we expect to detect,  $d = (3 \text{ minutes})$ .

$n = (1.96 + 0.84)^2 \cdot 2 \cdot 5.07^2 / 3^2 = 44.78$  so we will recruit 45 patients in each group with total sample 90 patients and we considered potential dropouts, so we recruited a total sample of 120 patients.



## **Participants**

At morning of the operation, after confirming inclusion criteria, the patient was informed about the study's objectives, and oral consent was obtained. One envelop is randomly chosen and opened, red by the surgeon on the morning of the surgery.

## **Setting**

Inpatient & Outpatient

## **Inclusion Criteria**

All individuals wanting to participate in the research who are scheduled for elective gynecological abdominal operations for benign illnesses. As per hospital regulation, the subjects were given 2 gm second generation cephalosporin 1 hour before surgery. All of the surgeries were performed by a surgeon who works at Alzhraa University Hospital as a lecturer or assistant professor of obstetrics and gynecology.

## **Exclusion Criteria**

Antibiotic use in the last seven days, chronic medical conditions such as diabetes, asthma, or TB, anemia, surgically scarred tissues, immune-compromised individuals, pregnant women, patients with pacemakers devices, and patients on anticoagulant treatment.

## **Intervention**

scalpel incision (A) or monopolar electrosurgery incision (B)

The abdominal skin and vagina were prepared as local hospital policy with povidone iodine in the operating room. All operation done through lower transverse incision under spinal anesthesia.

Accordingly, group A, scalpel used to incise abdominal wall including skin, subcutaneous tissue and anterior rectus sheath and

hemostasis was achieved by either simple compression of skin blood vessel or stitch while in group B, abdominal wall including same previous layers opened by electrosurgery unit cutting mode (at settings of 45 watt monopolar current) and hemostasis was achieved by coagulation mode electrosurgery unit. We used the electrosurgical generator: Valley lab ForceEZTM-8C, Monopolar: 300 W/300 Ohm, Bipolar 70 W / 70 Ohm. Only one surgical mop used for the incision and were weighed pre- and post-skin incision in a sterile manner using specialized weighing scales. No suction was used while making the incision. At recovery room, all patients received paracetamol (1gm perfalgan) administered by i.v. infusion and on shifting analgesia given on demand according to the patient's need.

## **Study outcome**

### **Primary outcomes: -**

- Wound incision time/ min. (time consumed between beginning of skin incision and opening of parietal peritoneum.
- Wound-related blood loss. (by weighing towels used only for anterior abdominal wall layers incision before and after abdominal wall incision/ gram).

### **Secondary outcomes**

- Postoperative pain (pain score 2-4 hr postoperative).
- Analgesia needed type, number of doses during first 12 hours postoperative.
- Wound infection (sepsis: pus pouring from incision, ecchymosis, seroma, hematoma or gapping)
- Ugly scar formation. Follow up visit was arranged on the 5th day and 40 days after surgery to evaluate scar condition (good – adequate –bad or Keloid) .



## Statistical analysis of the data

The IBM SPSS software programme version 20.0 was used to examine the data that was supplied into the computer. (IBM Corporation, Armonk, NY) <sup>(7)</sup>

**A- Descriptive statistics:** To determine the central tendency and dispersion of quantitative data, the mean and standard deviation were determined.

**B- Analytic Statistics:** Comparing groups was prepared utilizing **student's t-test** to compare among two quantitative variables while qualitative data were compared by using **Chi-square(X2) test, and fisher's exact test** was used instead when over than 20percent of cells have predictable frequencies<5. For abnormally quantitative variables, to compare between two studied groups **Mann Whitney test** used. Numbers and percentages were used to describe qualitative data. A p-value of less than 0.05 was used to determine the degree of significance. Tables and graphs were used to report the results.

## Results

A total of 120 women were screened for participation in the study. 16 of them were disqualified for failing to satisfy the inclusion criteria and refusing to participate. 14 patients were missed to follow-up in this study because they did not join their second

appointment or did not email their incision photo to the first author (S.I).Analysis was done on 90 participants ,45 in each group.

In the present study we reported that electro-surgery decreases wound incision time and wound related blood loss significantly than in scalpel group.

Both groups were comparable regarding age, BMI, and employment status as shown in table (I), 71.1% and 68.9% of studied groups respectively had TAH, and the rest of sample had the surgery for another cause with no statistical difference shown in table (II).

Table (III) presents how significantly electrosurgery decreases wound incision time/sec and wound related blood loss/grams. Also within the first 12 hours after surgery, the electrosurgery group was also associated with considerably reduced pain levels and the amount of analgesia needed showed in table (IV).

Table (V) shows: Wound infection complicates 6.7%- 2.2% in scalpel and electrosurgery groups respectively with no statistical difference, also in the second visit we observed 2.2%- 0% ugly scar formation in scalpel and electrosurgery groups respectively with no statistical significance.

Regression analysis was done to show which factor greatly affect wound infection. Table (VI) shows: the most significant factor was increasing Body Mass Index ( BMI ) which increases wound infection. Figure (1): histogram shows significant effect of BMI on wound infection rate in our study.

**Table (I) Socio-demographic data among the studied sample**

Groups	Scalpel group (45)	Electrosurgery group (45)	Significance test	P value
<b>Socio-demographic data</b>				
<b>Age /years: mean± SD</b>	43.24±8.291	46.42±12.938	Mann-Whitney test U =814.5	0.11
<b>BMI</b>	29.35± 3.785	30.59±5.954	U=972.00	0.62
<b>Employment:</b>				
- House wife	45(100%)	43(95.6%)	Chi-Square test X <sup>2</sup> =2.045	0.494
- Employed	0(0.0%)	2(4.4%)		

**Table (II): surgical indication among the studied sample**

Groups	Scalpel group (45)	Electrosurgery group (45)	X <sup>2</sup>	P value
Surgical indication				
• <b>TAH</b>	32 (71.1%)	31 (68.9 %)	1.236	0.872
• <b>Myomectomy</b>	6 (13.3%)	7 (15.6%)		
• <b>Sacropexy</b>	3 (6.7%)	4 (8.9%)		
• <b>Ovarian cyst</b>	3 (6.7%)	3 (6.7%)		
• <b>Others</b>	1 (2.2%)	0 (0%)		

**Table (III): Intraoperative data among the studied sample**

Groups	Scalpel group (45)	Electrosurgery group (45)	Test of significance Mann-Whitney test	P value
Intraoperative data				
<b>Wound incision time / sec</b> <b>Mean ±S.D</b>	236.71±94.875	129.62±35.985	U= 303.00	<0.001
<b>Wound related blood loss (grams)</b> <b>Mean±S.D</b>	24.72±9.758	7.39±5.506	U=137.00	<0.001

**Table (IV): Effect on post-operative pain among the studied sample**

Groups	Scalpel group (45)	Electrosurgery group (45)	Mann-Whitney test	P value
Post-operative pain				
<b>VAS score (Mean±S.D)</b>				
• <b>2 hrs.</b>	9.58±0.78	8.44±1.324	U=536.00	<0.001
• <b>4 hrs.</b>	7.69±0.763	7.04±1.021	U=685.00	0.002
Analgesia needed during 1st 12 hrs. postop in number of doses ( <b>Mean±S.D</b> )	3.02±0.0452	2.16±0.367	U=230.00	<0.001

**Table (V): Wound complications among the studied sample**

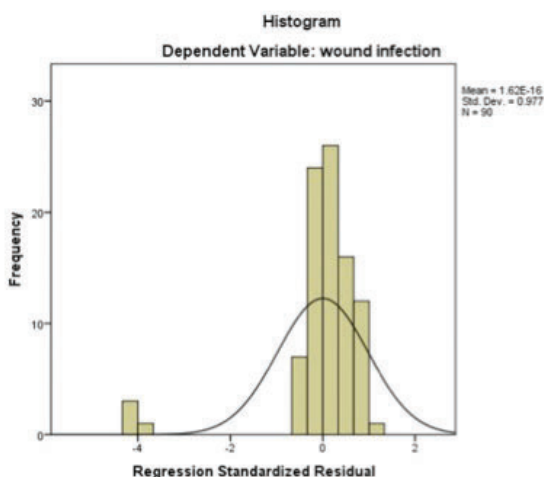
Groups	Scalpel group (45)	Electrosurgery group (45)	P value
Wound complications			
Wound infection Yes/No	3	1	0.3063
<b>Ecchymosis</b>	1	0	
<b>Hematoma</b>	1	0	
<b>Seroma</b>	0	1	
<b>Dehiscence</b>	1	0	
Wound healing postop			
<b>Ugly scar at day 7</b>	1	0	1.00
<b>Ugly scar at day 40</b>	1	0	1.000

P was calculated by using *Fisher exact test*

**Table (VI): Regression analysis of different risk factors which affected the indices of wound infection.**

Model	Unstandardized Coefficients		Standardized t Coefficients		Sig.
	B	Std. Error	Beta	t	
(Constant)	2.406	.142		16.934	0.0001*
Age (yrs)	.001	.002	.028	0.269	0.788
BMI	-.005	.002	-.362	-3.476	0.001*
wound related blood loss in grams	-.003	.002	-.151	-1.265	0.209
wound incision time (sec.)	1.420E-005	.000	.006	0.051	0.959

a. Dependent Variable: wound infection



**Figure (1): histogram show significant effect of BMI on wound infection rate**

## Discussion

Given the fact that scalpel utilization is well-known to pose a serious and well-known risk to the surgeon and other team staff, a survey conducted by Assiotis et al. in 2009 showed that only 24 percent of higher surgical trainees in the Great Britain used diathermy for laparotomy skin incisions, while 76 percent used a scalpel.<sup>(8)</sup>

The belief that electrosurgical instruments augment devitalized tissue within the wound,

leading to rising wound infection, scar production, and wound repair delays, has led to aversion to incising skin with electrosurgery.<sup>(5)</sup> Recent skin incision investigations have found no evidence to support these fears.<sup>(9)</sup> Electrosurgery units nowadays is becoming more advanced, intelligent and popular since it is effective, precise, easy to obtain, causes minimum post-operative bleeding, and reduces the risk of surface infections.<sup>(10)</sup>

Recent Cochrane systematic reviews observed low confidence evidence of a distinction in wound infection among scalpel and electrosurgery and advised additional studies to discover the relative effectiveness of scalpel compared with electrosurgery for major abdominal incisions.<sup>(11)</sup> That is why the present study is conducted to compare the early postoperative and short term wound complication rates among use of scalpel and electrosurgery in transverse abdominal wall incision in elective benign gynecological operations. All participants received 2 gm 2<sup>nd</sup> generation cephalosporines within 1 hour preoperative per hospital policy.

Our study results demonstrate that use of electrosurgery decreases wound related blood loss and wound incision time signifi-

cantly than in scalpel group. And within the first 24 hours after surgery, the electrosurgery group was also associated with considerably reduced pain levels and the amount of analgesia required. As scalpels are primarily used to produce surgical incisions, its use typically results in skin bleeding, which obscures the operating field and wastes time.

In accordance with our study, several studies (Elbohoty et al., 2015, Pandey et al., 2019, Abdel Aal et al., 2017 & Yadav et al., 2021) compared diathermy versus scalpel in transverse in women undergoing repeated cesarean section, midline abdominal incision and herniorrhaphy in randomized controlled trials, they proved that electrosurgery was superior in terms of wound incision time and wound related blood loss.<sup>(10, 12-14)</sup>

Telfer et al., (1993) studied two groups of 101 patients who were performed on using diathermy and scalpel for gastrointestinal resection; the authors observed no significant variation in wound incision time among electrocautery and scalpel. On the opposite, they found a statistically significant difference in blood loss during incision, with the electrosurgery group losing less blood. This variation might be related to the varied types of incisions used (in their study, patients received full-length midline laparotomy incisions).<sup>(15)</sup> Also They observed no significant variation in wound incision time per wound area among electrosurgery and scalpel in Kearns 2001; Prakash 2015; Siraj 2011.<sup>(16-18)</sup>

The present study demonstrate that postoperative pain score and doses of analgesia required within first 12-hour post-operative was less in electrosurgery group, that is attributed to good haemostasis less hematoma formation and less bacterial colonization in electrosurgery group.

The findings of Patil et al., 2017 and Nandurkar VS et al., 2018 are consistent with our findings. They investigated the use of a scalpel versus electrocautery for subcutaneous incisions in elective gynaecological sur-

geries and discovered that postoperative pain was significantly higher in the scalpel group.<sup>(19,20)</sup> In addition, in agreement with our findings, Chrysos et al., 2005 reported that the electrosurgery group required just half the dose of parenteral analgesics in the postoperative phase, which is consistent with our findings.<sup>(21)</sup>

In contrast, Parkash et al. (2015) conducted a study in which they compared the electrocautery incision with the scalpel incision in midline abdominal surgery in a double blind randomized controlled trial and found that there was no substantial change in postoperative pain among the two techniques.<sup>(17)</sup> Their sample included midline incision which characterized by less vascularity, more lengthy extensible wound and expected to more painful than transverse incision also authors included muscle cutting in their incision.

Surgical site infection (SSI) is the most frequent infection acquired while in the hospital among all postoperative consequences. About two-thirds of these infections involve superficial wounds. SSI can develop up to 30 days after surgery, according to the Centers for Disease Control and Prevention (CDC).<sup>(22)</sup>

We monitored our patients for 40 days post-operative and looked for ecchymosis, seroma, dehiscence, hematoma, or spilling contaminated fluid as signs of wound infection and complications. In our study, scalpel group showed (6.7%) of wound infection versus (2.2%) in electrosurgery group, it was statistically insignificant. We did regression analysis of different risk factors which affected the indices of wound infection, while the significant item was only the increasing of body mass index causing post-operative wound infection, while the age, wound related blood loss and wound incision time show insignificant effect on post-operative wound infection.

In line with our results, a cross-sectional study, participants undergoing midline ab-



dominal incision for uterine malignancies compared to electrosurgery in coagulation mode (433 participants) against cold scalpel (531 participants) for serious wound sequelae (Franchi 2001). In the scalpel group, they reported a higher rate of severe wound complications. However, after adjusting for confounding variables, there were no important change among groups.<sup>(23)</sup>

Several recent clinical trials and systematic reviews in accordance with our result (Charoenkwan K et al., 2017, Patil et al., 2017, Nandurkar et al., 2018, Talpur et al., 2015 & Eren et al., 2010) reported no significant difference in surgical site infection between the scalpel and electrosurgery skin incision.<sup>(11, 19, 20, 24, 25)</sup>

In first post-operative visit at 5th day we checked for wound infection and completeness of the process of healing, however, on the second visit, we wanted to double-check the cosmetic appearance of the wound incision, therefore we collected data directly from patients or photographs submitted by participants after 40 days. We could not find any difference between both groups as regard the shape and patient satisfaction of wound.

One of the few studies that looked at cosmetic outcomes as the major endpoint In a double-blind randomized clinical trial, Aird L. N. F. et al. (2015) evaluated the cosmetic outcomes of utilizing the cutting mode of electrosurgery and scalpel for incising abdominal layers at six months after surgery, and they indicated that the obtained results encourage the assumption that diathermy generates a scar with a cosmetic results comparable to scars produced by scalpel.<sup>(3)</sup>

In accordance with the findings of our study, Kaban et al., 2019 and Douglas A et al., 2013 studies conducted to compare cutting diathermy and scalpel undergoing elective open abdominal general surgical procedures, they use both approaches in the same patient (half of incision done by scalpel and other half by electrosurgery) When comparing

Pfannenstiel or midline incisions to scalpel usage in regards of wound repair and scar appearances, they discovered that they were equal in terms of wound repair and cosmetic appearance.<sup>(5,26)</sup>

We tried to apply blinding as much as possible, blinding of surgeon was not feasible, but allocation concealment was applied and patient were also blind to the type of intervention. One of the limitations in our study is non-blinding of outcome assessor, limited time for follow up, in addition smaller sample size, all these due to limited resources and due to COVID outbreak. The inter-variability between surgeons regarding preferences of skin incision approach was also considered one of our limitations.

In order to improve the method's reliability, further robust trials in this area are required. Adjustment of electrosurgery unit use in abdominal wall incision (cutting or coagulation mode, watt adjustment) should be assessed in such a trial.

## **Conclusion and recommendation**

Nowadays in both laparotomy and minimally invasive laparoscopy, electrosurgery is the most often used type of surgical energy. Proper use of electrosurgery for abdominal wall incision could be practical alternative for scalpel, it saves time ,less painful, reduces wound related blood loss and wound incision time without increase in wound related infection or complications .

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# Dual triggering for final oocyte maturation compared to single triggering in GnRH antagonist (IVF-ICSI) protocols (Randomized Controlled Trial)

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## **Abstract**

**Background:** Infertility is one of the major medical problems in the world which has led to continuous research and advances in the field of assisted reproductive technology (ART),

**Aim of the work:** to investigate whether co-administration of GnRH-a and hCG for final oocyte maturation (dual trigger) would improve number of oocytes retrieved & its quality and eventually IVF/ICSI clinical outcomes compared to single triggers in women with normal ovarian response undergoing (IVF/ICSI) technique using GnRH antagonist protocol of stimulation.

**Patients and Methods:** A total 120 patients were included in this study, randomized and divided into two groups: Group (1): The study group; included 60 patients who received the dual trigger. Group (2): The control group; who included 60 patients, age matched, who received the hCG trigger alone. All participants were subjected to proper history taking, complete general, abdominal and pelvic examination, and full investigations to confirm criteria of the study. All participants were subjected to controlled ovarian hyper stimulation protocol according to GnRH antagonist protocol starting on day 2-3 of the menstrual cycle with a starting daily administration of FSH, human menopausal gonadotropin hMG, or highly purified hMG, or highly purified FSH or with recombinant FSH (r.FSH) intramuscularly for 4–5 days, and continued until the day of final oocyte maturation injection.

**Results:** the current study showed statistically significant difference with p-value <0.05 between study groups as regards to the number of retrieved oocytes (cases:  $11.42 \pm 4.2$  vs. control:  $9.8 \pm 4.9$ ), number of MII oocyte retrieved (dual trigger:  $6.2 \pm 2.7$  vs. single trigger:  $4.6 \pm 3.1$ ), and number of fertilized oocyte (dual trigger:  $4.03 \pm 2.2$  vs. single trigger:  $3.05 \pm 2.5$ ) with higher mean among dual trigger group. In the current study also the dual-trigger group demonstrated a significantly higher percentage as regards to biochemical pregnancy rate (cases: 68.3% vs. 33.3% among controls), clinical pregnancy rate (cas-

es: 58.3% vs. 31.7% among controls) and implantation rate (cases: 41.3% vs. 21.4% among controls) with a statistically significant difference with p-value <0.05 between study groups. Both groups showed no statistically significant difference as regards to the mean number of embryos transferred ( $1.9 \pm 1.01$  in cases vs.  $1.7 \pm 1.2$  in control) and number of frozen embryos ( $1.33 \pm 1.08$  in cases vs.  $1.1 \pm 1.4$  in control), or as regards to complications; whether ET cancellation or incidence of sever OHSS.

**Conclusion:** In conclusion, in terms of the number of mature retrieved oocytes, implantation rate and clinical pregnancy rate in normal responders undergoing IVF/ICSI using antagonist protocols, a dual-trigger approach with a GnRH agonist and the standard dosage of hCG was found to be significantly superior to an hCG trigger alone.

**Key words:** Dual triggering, oocyte maturation, single triggering, GnRH antagonist.

## **Introduction**

Infertility is one of the major medical problems in the world which has led to continuous research and advances in the field of assisted reproductive technology (ART) <sup>(1)</sup>.

Controlled ovarian hyperstimulation (COH) is a fundamental step of in vitro fertilization (IVF) that has been in practice since the 1970s <sup>(2)</sup>.

Over the past two decades, gonadotropin-releasing hormone (GnRH) antagonist protocols have been proposed as a safer and efficacious way for ovarian stimulation <sup>(3)</sup>.

GnRH antagonist protocols have several advantages over the long agonist, including the rapid decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels without flare-up effect, decreased number of days of stimulation and the amount of gonadotropin administered, (4) and statistically significant reduction of ovarian hyperstimulation syndrome (OHSS) <sup>(5,6)</sup>.

Since the pioneering days of in vitro fertilization (IVF), human chorionic gonadotropin (hCG) has been used as a surrogate for the natural mid-cycle luteinizing hormone (LH) surge <sup>(7)</sup>.

The administration of hCG results in sustained luteotrophic effect and supraphysiological levels of estradiol and progesterone; the sustained luteotrophic effect may contribute to the development of ovarian hyperstimulation syndrome (OHSS) <sup>(8)</sup>.

More than 30 years ago, Nakano et al., described that it was possible to trigger an endogenous LH surge sufficient for induction of ovulation with a single injection of a gonadotropin-releasing hormone agonist (GnRH-a). Unfortunately, this finding was soon underestimated, as GnRH-a rapidly became the first line treatment to prevent premature luteinization, which precluded the use of GnRH-a to induce final follicular maturation <sup>(9)</sup>.

When the third generation GnRH antagonist was introduced into the market for the use in ovarian stimulation protocols during the 1990's, it became possible to trigger final oocyte maturation and ovulation with a single bolus of a GnRH-a as an alternative to hCG <sup>(10)</sup>.

Though some studies have suggested an increase in the percentage of mature oocytes retrieved when triggered with GnRH-a compared with hCG (11), it has been found that triggering ovulation with GnRH agonist leads to a suboptimal luteal phase <sup>(12)</sup>.

"Dual trigger" was first defined as the concept of a combination of GnRH agonist and a low-dose hCG in GnRH antagonist cycles for triggering final oocyte maturation and prevention of Ovarian Hyperstimulation syndrome (OHSS), <sup>(13)</sup>.

Lin et al. conducted a retrospective study, consisted of normal responders undergoing IVF with GnRH antagonist protocol and showed significant improvement in total number of retrieved oocytes and number of



mature (**MII**) oocytes, also rates of embryo implantation, clinical pregnancy, ongoing pregnancy and live birth when dual trigger regimen was used <sup>(14)</sup>.

Lu et al. also presented a retrospective data analysis of medical records where final oocyte maturation was triggered using a GnRH-a alone (**Decapeptyl 0.1–0.2 mg**) or in combination with hCG (**1,000, 2,000, or 5,000 IU**), and concluded that using a dual trigger with a low dose of hCG (**1,000 IU**) as an adjuvant to GnRH-a to induce final oocyte maturation significantly improved the oocytes retrieval rate of suboptimal responders <sup>(15)</sup>.

## **Aim of the Work**

The objective of the present study is to compare between single trigger with standard dose of hCG alone and dual triggering with the combination of GnRH agonist and hCG in **IVF/ICSI** cycles in improving the number of oocytes retrieved and oocyte quality.

## **Patients and methods**

The current study was designed as a prospective, case-control, randomized study, from February 2020 to April 2021, conducted at ART unit of Ain Shams University, maternity hospital. One hundred and twenty participants (**120**) were assigned into the study and prepared to undergo IVF/ICSI trial using GnRH antagonist protocol of controlled ovarian hyper-stimulation.

After getting approval of Research Ethics Committee (**REC**), Ob/Gyn department, Faculty of Medicine, Ain Shams University and written consent obtained from all participants with restrict confidentiality of the data after explanation of the purpose of the study, the participants were divided by random allocation computer program into two groups: **Group (A)**: The study group; who included **60** patients who received the dual trigger and **Group (B)**: The control group; who included

**60** patients, age matched, who received the hCG trigger alone.

The study aimed to compare between single trigger with standard dose of hCG alone and dual triggering with the combination of GnRH agonist and hCG in IVF/ICSI cycles in improving the number of oocytes retrieved and oocyte quality.

## **Study Participants**

The study was conducted on infertile women attending Ain Shams University assisted reproductive technology unit; fulfilling the inclusion criteria and investigations eligible for IVF/ICSI and to confirm criteria of the study.

Recruitment was done at day of trigger. At our hospital during the COVID-19 pandemic, all patients have obligatory PCR testing for COVID-19 before any operative intervention, and who had +ve results; operative interventions were cancelled.

To be noted, we started our study with 120 patients, **4** of them were dropped out from the study (**2** in the study group; after the day of OPU and **2** in the control group; one before ET and **the other** before the day of OPU) due to their +ve PCR results.

The study included patients with ages between **20** and **35** years old, undergoing **IVF/ICSI** trial using **GnRH** antagonist protocol of controlled ovarian hyper-stimulation, with expected normal ovarian response, which is defined as: Antral follicle count (**AFC**) between **3-8** for each ovary, Serum anti-müllerian hormone (**AMH**) level of **1.0-4.0 ng/mL** on cycle day **3** and Serum estradiol (**E2**) level on the day of triggering between **500-4000 pg/mL**).

While patients with body mass index, **BMI**  $\leq 18$  or  $\geq 35$  kg/m<sup>2</sup>, undergoing **IVF/ICSI** trial using GnRH agonist or minimal stimulation protocols, occult ovarian failure which is defined as day-3 follicle stimulating hormone (**FSH**) concentration of  $\geq 10$  IU/L

or serum anti-mullerian hormone (**AMH**) level of  $\leq 1.0$  ng/mL, either poor response to controlled ovarian hyper-stimulation (**COH**), which is defined as a serum estradiol (**E2**) level less than **500 pg/mL** on the day of triggering or as the number of retrieved oocytes  $\leq 3$ , or high ovarian response, defined as an E2 level greater than **4,000 pg/mL** on the day of triggering or as the number of retrieved oocytes  $\geq 20$ , presence of endocrine disorders as (diabetes mellitus, hyper-prolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, Cushing syndrome, or polycystic ovary syndrome) or presence of uterine anomaly confirmed by either hystero-salpingography or hysteroscopy were excluded from the study.

### **Ovarian Stimulation Protocol**

All patients began controlled ovarian hyper-stimulation on day 2-3 of the menstrual cycle with a starting daily administration of human menopausal gonadotropin hMG (**Menogon 75IU, Ferring Pharmaceutical, Ltd, Germany**), or highly purified hMG (**Menopur 75IU, Ferring Pharmaceutical, Ltd, UK, or Merional 150IU, IBSA Pharmaceutical, Switzerland**), or highly purified FSH (**Fostimon 150IU, IBSA Pharmaceutical, Switzerland**) or with recombinant FSH rFSH (**Gonapure 150IU, Mina Pharmaceuticals, Egypt**) intramuscularly for 4–5 days, and continued until the day of final oocyte maturation injection.

The starting dosage was determined according to patient age, **AFC**, **BMI**, serum **FSH** on day 2–3, and previous ovarian response to **COH**. The dose was adjusted on the basis of serum estradiol and follicular growth, and monitored by serial trans-vaginal ultrasound.

After at least one follicle had reached 14 mm in diameter, or on reaching the number of ten follicles, patients also began subcutaneous injection of GnRH antagonist, cetrorelix (**Cetrotide; Merck Serono, S.P.A-Italy**) at a dosage of 0.25 mg per day along with the

HMG/FSH. GnRH antagonist administration was continued until the trigger day for final oocyte maturation.

When at least two leading follicles reached 18 mm in diameter, final oocyte maturation was triggered in (recruitment point): Group A, by single dose of hCG **5,000 IU (Choriomon, IBSA Pharmaceutical, Switzerland)** plus 0.2 mg of triptorelin acetate (**Decapeptyl, Ferring Pharmaceuticals, Germany**). Group B, by standard dose of hCG **10,000 IU (Choriomon, IBSA Pharmaceutical, Switzerland)** alone.

These dose adjustments were planned to achieve the induction of an endogenous LH surge that would coincide with the LH-like effect of the standard hCG administration 34–36 hours before oocyte retrieval.

Serum LH, E2 and progesterone levels were assessed the day after trigger to ensure adequate LH surge response and hCG absorption. Oocyte retrieval was done under general anesthetic using a starting pressure of 180 mmHg. Oocyte retrieval and embryos transfer procedures were performed only by the senior supervisor. All embryo transfers were performed 72 hours after oocyte retrieval. The remaining viable embryos were cultured to the blastocyst stage and were cryopreserved.

### **Luteal Phase Support and Confirmation of Pregnancy**

The luteal phase support included daily vaginal supplementation of progesterone 400mg (**Cyclogest, Actavis pharmaceutical, UK**) starting on the day of oocyte retrieval.

Serum  $\beta$ -hCG was measured 14 days after embryo transfer, and a value above 5 IU/mL considered being a positive pregnancy. The luteal support was continued until the 10th week of gestation after the establishment of luteal-placental shift for all positive pregnancies.



## Outcome Variables

The study's main outcome variable was the Implantation rate, defined as the number of gestational sacs on ultrasound at 6 weeks divided by total number of embryos transferred x 100.

Other analyzed variables included the oocyte number and stage of maturity, the fertilization rate defined as the percentage of transformation of micro injected oocyte into two pronuclei, the clinical pregnancy rate, the incidence of severe OHSS, and embryo transfer cancellation rate.

Clinical pregnancy was defined as viable pregnancy when there is evidence of gestational sac with fetal heart beat by trans-vaginal ultrasound between the 5th to 6th weeks of gestation.

Embryo transfer cancellation, defined as discontinuation of embryo transfer due to fertilization failure or embryonic cleavage arrest.

## Statistical Analysis

Data collected and coded to facilitate data manipulation and double entered into Mic-

rosoft Access and data analysis performed using the Statistical Package of Social Science (SPSS) software version 22 in windows 7 (SPSS Inc., Chicago, IL, USA). Simple descriptive analysis in the form of numbers and percentages of qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion of quantitative parametric data. Quantitative data included in the study first tested for normality by One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests selected.

### - For quantitative parametric data:

- **Independent samples t-test** was used to compare quantitative measures between two independent groups

### - For quantitative non parametric data

**The Mann-Whitney test** used to compare two independent groups.

### - For qualitative data

- **Chi square test** used to compare between two of more than two qualitative groups.
- **The P-value < 0.05** was considered as statistical significant.

## Results

**Table (1):** Comparison of demographic characteristics differences of study groups.

Variables	Cases (N=60)		Control (N=60)		P-value	Sig.
	Mean	SD	Mean	SD		
Age (years)	30.35	4.4	29.6	3.8	0.32	NS
BMI (kg/m <sup>2</sup> )	21.88	2.2	22.58	2.4	0.08	NS

The table illustrates that there is no statistically significant difference with p-value >0.05 between both study groups as regards age and BMI which indicates proper matching between groups.

**Table (2):** Comparison of infertility characters in different study groups:

Variables	Cases (N=60)		Control (N=60)		P-value	Sig.
	No.	%	No.	%		
Type of infertility						
1 ry	25	41.7%	35	58.3%	0.1	NS
2 ry	35	58.3%	25	41.7%		
Cause of infertility						
Male	21	35%	28	46.7%	0.4	NS
Female	17	28.3%	18	30%		
Mixed	4	6.7%	2	3.3%		
Unexplained	18	30%	12	3.3%		
Infertility duration						
Mean ± SD	3.45 ± 1.9		4.26 ± 2.6		0.1	NS

The table illustrates that there is no statistically significant difference with p-value  $>0.05$  between both study groups as regards infertility characters (type, cause, and infertility duration), which indicates proper matching between groups.

**Table (3):** Comparison of hormonal profile and AFC in different study groups:

Variables	Cases (N=60)	Control (N=60)	P-value	Sig.
	mean $\pm$ SD	mean $\pm$ SD		
AFC	10.73 $\pm$ 3.57	10.77 $\pm$ 3.57	0.5	NS
Baseline FSH	6.67 $\pm$ 2.1	6.93 $\pm$ 2.37	0.35	NS
Baseline LH	4.58 $\pm$ 2.03	4.78 $\pm$ 2.3	0.61	NS
Baseline E2	57.4 $\pm$ 13.2	52.6 $\pm$ 17.2	0.08	NS
Baseline TSH	2.18 $\pm$ 0.96	2.09 $\pm$ 0.89	0.54	NS
Baseline Prolactine	12.76 $\pm$ 4.9	12.22 $\pm$ 5.4	0.56	NS
AMH	1.94 $\pm$ 0.63	2.11 $\pm$ 0.85	0.63	NS

The table illustrates that there is no statistically significant difference with p-value  $>0.05$  as regards hormonal profile (FSH, LH, E2, TSH, prolactin, and AMH level) and AFC.

**Table (4):** Comparison of type and dose of Gonadotropins injection in different study groups:

Type of injection	Cases (N=60)		Control (N=60)		P-value	Sig.
	No.	%	No.	%		
HMG	8	13.3%	6	10%	0.68	NS
Highly purified HMG	16	26.7%	15	25%		
Highly purified FSH	17	28.3%	23	38.3%		
Recombinant FSH	19	31.7%	16	26.7%		
Dose of injection						
Mean ± SD	49.7 ± 9.4		49.3 ± 17.9		0.9	NS

The table illustrates that there is no statistically significant difference with p-value  $>0.05$  between study groups as regards type and dose of Gonadotropins injection used.

**Table (5):** Comparison of intervention outcomes in different study groups:

Variables	Cases (N=60)	Control (N=60)	P-value	Sig.
	mean $\pm$ SD	mean $\pm$ SD		
Number of oocyte retrieved	11.42 $\pm$ 4.2	9.8 $\pm$ 4.9	0.01	S
Number of MII oocyte retrieved	6.2 $\pm$ 2.7	4.6 $\pm$ 3.1	0.002	HS
Number of fertilized oocyte	4.03 $\pm$ 2.2	3.05 $\pm$ 2.5	0.01	S
Number of embryos transferred	1.9 $\pm$ 1.01	1.7 $\pm$ 1.2	0.48	NS
Number of cryopreserved embryos	1.33 $\pm$ 1.08	1.1 $\pm$ 1.4	0.08	NS

The table illustrates that there is a statistically significant difference with p-value  $<0.05$  between study groups as regards number oocyte retrieved (dual trigger: 11.42 $\pm$ 4.2 vs. single trigger: 9.8 $\pm$ 4.9), Number of MII oocyte retrieved (dual trigger: 6.2 $\pm$ 2.7 vs. single trigger: 4.6 $\pm$ 3.1) and Number of fertilized oocyte (dual trigger: 4.03 $\pm$ 2.2 vs. single trigger: 3.05 $\pm$ 2.5) with higher mean among dual trigger group.

On the other hand, there is no statistically significant difference with p-value  $>0.05$  as regards other variables (number of embryos transferred and number of cryopreserved embryos) between dual trigger and single trigger groups.

**Table (6):** Comparison of outcomes in different study groups:

Outcomes		Cases (N=60)		Control (N=60)		P-value	Sig.
		No.	%	No.	%		
Biochemical pregnancy							
Positive		41	68.3%	20	33.3%	0.001	HS
Negative		12	20%	27	45%		
Complication		7	11.7%	13	21.7%		
Clinical pregnancy							
Abortion rate (%)		6	14.6% (6/41)	1	5% (1/20)	0.4	NS
Pregnancy	Single	22	58.3% (35/60)	15	31.7% (19/60)	0.003	HS
	Twin	13		4			
Implantation rate							
Implantation rate		41.3% (48/116)		21.4% (23/107)		0.02	S

The table illustrates that there is a statistically significant difference with p-value  $<0.05$  between study groups as regards biochemical pregnancy rate (cases: **68.3%** vs. **33.3%** among controls), clinical pregnancy rate (cases: **58.3%** vs. **31.7%** among controls), and implantation rate (cases: **41.3%** vs. **21.4%** among controls), with higher percentage among the dual trigger group of study.

**Table (7):** Comparison of complications in different study groups:

Variables	Cases (N=60)		Control (N=60)		P-value	Sig.
	No.	%	No.	%		
ET cancellation	7	11.7% (7/60)	12	20% (12/60)	0.2	NS
Sever OHSS	0	0%	1	1.7% (1/60)	0.3	NS

The table illustrates that there is no statistically significant difference with p-value  $>0.05$  between study groups as type of complications.

## Discussion

Numbers of retrospective cohort studies <sup>(16,17,18)</sup>, and few numbers of randomized controlled studies <sup>(19,20)</sup> have investigated whether dual triggering of final oocyte maturation with a gonadotropin-releasing hormone agonist (GnRH-a) and standard dose of human chorionic gonadotropin (hCG) can improve clinical outcomes for normal ovarian, sub-normal and poor responders in GnRH antagonist cycles, however it's still debated between researchers who found significant improvement of the outcomes of IVF/ICSI cycles and those who didn't find a significant improvement <sup>(21,22)</sup>.

A total 120 patients were recruited in the current study, randomized and divided into two groups; each group consisted of 60 patients, where the study group received the dual trigger, and the control group received the standard dose hCG trigger alone for final oocyte maturation, in a trial of improving number of oocytes retrieved & its quality and eventually IVF/ICSI clinical outcomes compared to single triggers in women with normal ovarian response undergoing (IVF/ICSI) technique.

In the current study, the baseline characteristics and demographics (mean age & BMI), infertility characters (type, cause & duration of infertility), hormonal profile, AFC, and type and dose of gonadotropins injection were all incomparable between study groups.

As regards to the interventional main outcome, there was a statistically significant difference with p-value <0.05 between study groups as regards number oocyte retrieved (dual trigger:  $11.42 \pm 4.2$  vs. single trigger:  $9.8 \pm 4.9$ ), number of MII oocyte retrieved (dual trigger:  $6.2 \pm 2.7$  vs. single trigger:  $4.6 \pm 3.1$ ) and number of fertilized oocyte (dual trigger:  $4.03 \pm 2.2$  vs. single trigger:  $3.05 \pm 2.5$ ) with higher mean among dual trigger group.

As regards to the outcomes of biochemical pregnancy, implantation and clinical preg-

nancy rates, there was a statistically significant difference with p-value <0.05 between study groups as regards biochemical pregnancy rate (cases: 68.3% vs. 33.3% among controls), clinical pregnancy rate (cases: 58.3% vs. 31.7% among controls), and implantation rate (cases: 41.3% vs. 21.4% among controls), with higher percentage among the dual trigger group of study.

In the present study, the baseline characteristics and demographics showed no statistically significant difference between the study and control groups (Table 1), with p-value >0.05 regarding mean age (y) ( $30.35 \pm 4.4$  vs.  $29.6 \pm 3.8$  respectively), and body mass index (BMI) ( $\text{kg/m}^2$ ) ( $21.88 \pm 2.2$  vs.  $22.58 \pm 2.4$  respectively); which agreed with all of the studies done before like Lin et al., (2013), where mean age (y) ( $34.81 \pm 3.70$  vs.  $34.68 \pm 3.44$  respectively), and body mass index (BMI) ( $\text{kg/m}^2$ ) ( $22.2 \pm 5.4$  vs.  $22.0 \pm 3.1$  respectively) were comparable between the study and control groups respectively.

Zhou et al. <sup>(18)</sup> conducted a study comparing dual trigger with combination of GnRH agonist and hCG versus hCG alone trigger for oocyte maturation in normal ovarian responders; where there was no statistically significant difference between the study groups as regards infertility characters in terms of the percentage of the cause of infertility whether male factor (cases; 9.8% vs. control; 5.9%), female factor (cases; 63.4% vs. control; 50.5%), mixed (cases; 12.5% vs. control; 25.7%) or unexplained infertility (cases; 5.4% vs. control; 2.0%), or infertility duration; with mean between the study group and control was ( $4.55 \pm 3.23$  vs.  $5.92 \pm 4.34$  respectively).

In the current study, there was no statistically significant difference with p-value >0.05 between both study groups as regards to infertility characters (Table 2) in terms of [type of infertility; where the percentage between the study and control groups was (41.7% vs. 58.3% respectively) in primary type and (58.3% vs. 41.7% respectively) in secondary



type, cause of infertility; with percentage related to male factor (35% in cases vs. 46.7% in controls), female factor (28.3% in cases vs. 30% in controls), mixed (6.7% in cases vs. 3.3% in controls) or unexplained infertility with percentage of (30% in cases vs. 20% in controls), or infertility duration; with mean (cases;  $3.45 \pm 1.9$  vs. control;  $4.26 \pm 2.6$ ), which indicated proper matching between groups.

To exclude any hormonal disturbance factor that may affect the purpose of the study, it was essential to study the hormonal profile of both study groups with special emphasis on FSH, LH, Estradiol, TSH, AMH and Prolactin levels which all showed no statistically significant differences between study groups (Table 3); with p-value  $>0.05$ , where the mean FSH among cases was ( $6.67 \pm 2.1$ ), while in control group was ( $6.93 \pm 2.37$ ). Mean LH among cases was ( $4.58 \pm 2.03$ ), while in control group was ( $4.78 \pm 2.3$ ). Mean TSH among cases was ( $2.18 \pm 0.96$ ), while in control group was ( $2.09 \pm 0.89$ ). Mean Estradiol among cases was ( $57.4 \pm 13.2$ ), while in control group was ( $52.6 \pm 17.2$ ). Mean AMH among cases was ( $1.94 \pm 0.63$ ), while in control group was ( $2.11 \pm 0.85$ ), and mean Prolactin among cases was ( $12.76 \pm 4.9$ ), while it was ( $12.22 \pm 5.4$ ) in control group.

Also, there was no statistically significant difference with p-value  $>0.05$  between study groups as regards mean antral follicle count (AFC) (Table 3) ( $10.73 \pm 3.57$  in study group vs.  $10.77 \pm 3.57$  in control group) or COH variables (Table 4) such as: type of gonadotropins used for injection, where percentage of HMG was (13.3% in cases vs. 10% in control), percentage of Highly purified HMG was (26.7% in cases vs. 25% in control), Highly purified FSH was (28.3% in cases vs. 38.3% in control) and Recombinant FSH was (31.7% in cases vs. 26.7% in control), or mean total dose of gonadotropins used ( $49.7 \pm 9.4$  in study group vs.  $49.3 \pm 17.9$  in control group), which all actually agreed with previous studies of Lin et al., Griffin et al., and Zhou et al.

In a previous prospective randomized study<sup>(19)</sup>, 221 normal responder patients were randomized either to receive hCG or dual trigger for final oocyte maturation. There was no statistical difference between the study and control groups as regards to the number of oocytes retrieved ( $9.9 \pm 7.8$  vs.  $7.9 \pm 11.1$  respectively). However; the results in our present study showed statistically significant difference with p-value  $<0.05$  between study groups (Table 5) as regards to the number of retrieved oocytes (cases:  $11.42 \pm 4.2$  vs. control:  $9.8 \pm 4.9$ ).

In the current study, the number of MII retrieved oocytes (cases:  $6.2 \pm 2.7$  vs. control:  $4.6 \pm 3.1$ ), and number of fertilized oocytes (cases:  $4.03 \pm 2.2$  vs. control:  $3.05 \pm 2.5$ ) showed statistical significant difference with p-value  $<0.05$  with higher mean in the dual group which came in agreement with Hass et al. (2020), who conducted a prospective, randomized, double-blinded clinical trial on 155 normal responder patients either to receive hCG or dual trigger for final oocyte maturation where there was statistical difference between the study and control groups as regards to the number of MII retrieved oocytes (cases: 10.3 vs. controls: 8.6, p-value=0.009), and number of 2 pronuclei (cases: 7.8 vs. control: 6.3, p-value=0.007) with higher significance among the dual trigger group.

On the other hand, there was no statistically significant difference with p-value  $>0.05$  as regards other variables; the mean number of embryos transferred ( $1.9 \pm 1.01$  in cases vs.  $1.7 \pm 1.2$  in control) and number of cryopreserved embryos ( $1.33 \pm 1.08$  in cases vs.  $1.1 \pm 1.4$  in control) between dual trigger and single trigger groups.

In terms of the main present study outcomes, the dual-trigger group demonstrated a significantly higher percentage as regards to biochemical pregnancy rate (cases: 68.3% vs. 33.3% among controls), clinical pregnancy rate (cases: 58.3% vs. 31.7% among controls), and implantation rate (cases: 41.3% vs. 21.4% among controls) with a statistical-



ly significant difference with p-value  $<0.05$  between study groups (Table 6). The difference in abortion rate between the two groups was not statistically significant.

These results actually came in agreement with Hass et al. (2020) study, where their results showed statistically significant improvement in the implantation rate (22.8% vs. 43.7%), and the clinical pregnancy rate (37.3% vs. 56.8%) with significantly higher percentages in the dual trigger group.

Conversely, Şükür et al.,<sup>(22)</sup> conducted a retrospective cohort study in a total 214 normal responders who underwent ICSI trial following a cycle down-regulated by a GnRH antagonist protocol. The biochemical pregnancy rate (33.9 in cases vs. 36.5% in control), and clinical pregnancy rate (33.9% in cases vs. 30.6% in control) were similar among both study groups.

Also Eser et al.,<sup>(21)</sup> conducted a case-control study of a total 109 ICSI cycles “in poor responders” where a dual trigger was used for final oocyte maturation compared with hCG trigger, where they reported no statistically significant difference between ICSI outcomes as regards to biochemical pregnancy rate (in cases 16% vs. 12.1% in control), Clinical pregnancy rate (4% in cases vs. 12.1% in control), and implantation rate (3.2% in cases vs. 9.3% in control).

In our present study, (Table 7) there was no statistically significant difference with p-value  $>0.05$  between study groups as regards to complications. One out of 13 patients of the control group had sever OHSS, but she did not require hospitalization, and none occurred in the dual trigger group. Nine patients of the control group out of the 60 participants had their ET cycle cancelled due to failed fertilization, one had ET cycle cancelled due to oocyte degeneration and 2 had ET cycle cancelled due to +ve. COVID-19 PCR, where 7 patients in the study group out of the 60 had their ET cycle cancelled, 3 out of 7 due to arrest of cleavage, 2 due to failed fertiliza-

tion and 2 had ET cycle cancelled due to +ve. COVID-19 PCR.

One of the weaknesses of the present study is that we did not include a third arm of patients who were triggered with GnRH agonist alone. If we had added the third arm, we would have been able to test whether it was the administration of GnRH agonist or the co-administration of GnRH agonist and hCG that improved the outcome as demonstrated in the study.

## **Conclusion**

In conclusion, in terms of the number of mature retrieved oocytes, implantation rate and clinical pregnancy rate in normal responders undergoing IVF/ICSI using antagonist protocols, a dual-trigger approach with a GnRH agonist and the standard dosage of hCG was found to be significantly superior to an hCG trigger alone.

The results we presented here are another proof-of-concept that suggests a possible paradigm shift in ovulation triggering agents in GnRH antagonist cycles.

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