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Acknowledgments

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

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2- Books:

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

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

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Contents :

Letter from the Editor:

Dear esteemed colleagues,

Warm greetings
Very interesting subjects are included in this issue. Association of asymptomatic bacteriuria and pre-eclampsia. Asymptomatic bacteruria was more common in preeclamptic group (37%) than control group (22%) but with no significant difference. A simple triaging model based on sonographic criteria for four pregnancy situations where the gestational sac appears eccenterically in the early 1st trimester is described. Coasting Versus GNRH antagonist administration in patients at high risk of ovarian hyper stimulation syndrome and its impact on the ICSI Outcome. Vitamin C supplementation has significantly improved the outcome of In-vitro fertilization techniques with reduced incidence of spotting and miscarriages along with improved term pregnancy. Both placental thickness and transcerebellar diameter are useful fetal biometric parameters that can be used for assessment of gestational age. Intra-umbilical methyl ergometrine should be considered as an effective safe ecobolic in the third stage of labor.

Best regards.
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ASSOCIATION OF ASYMPTOMATIC BACTERIURIA AND PRE ECLAMPSIA IN EL SHATBY UNIVERSITY HOSPITAL

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Abstract

Background: Asymptomatic bacteriuria is defined as the presence of significant bacteriuria>10^5 colony forming units (cfu)/mL without the symptoms of an acute urinary tract infection. Pre-eclampsia is defined by blood pressure of greater than 140/90 mmHg after the 20th week of pregnancy and proteinuria of equal to or higher than 300 mg per 24 hours.

Objective: Detecting the incidence of asymptomatic bacteriuria among study group at El shatby antenatal care clinic and investigate the association between development of PE and presence of ASB.

Subjective: The study included 80 pregnant women. Quantitative culture remains the gold standard for diagnosis of urinary tract infection in pregnancy,Microscopic examination of a wet film of uncentrifuged urine was carried out to detect the presence of pyuria, which is considered when pus cells are >5 pus cells / HPF. Amount of urine (1 µl) is inoculated on MacConkey agar,blood agar and sabouraud dextrose agar plates. The plates are incubated for 24-48 hours at 37°C. After incubation, the colony count of a pure single organism is performed a significant bacteriuria is considered when the colony count is >10^5 (cfu/ml).

Results: The net result of our study showed that the patients were screened for asymptomatic bacteriuria and the incidence was 30%. Asymptomatic bacteruria was more common in preeclamptic group (37%) than control group (22%) but with no significant difference.

Conclusion: Asymptomatic bacteriuria was a common finding among pregnant women in our study (30% of whole cases).

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INTRODUCTION

Urinary tract infections (UTI) are a common occurrence in pregnancy. The physiological and anatomical changes associated with pregnancy predispose to UTIs.(1)

They are of two types: symptomatic and asymptomatic.

Asymptomatic bacteriuria (ASB) is a microbiological

diagnosis where actively multiplying bacteria are isolated in a number greater than 105 CFU/ml from the urine of a person suffering from no symptoms of UTI.[1] Risk of ASB increases with low socioeconomic status, multiparity, increasing maternal age and previous history of UTI.[1]

Patients may often seek treatment for symptomatic UTIs but asymptomatic bacteriuria has a high probability of being left untreated and is associated with diverse maternal and fetal complications.[2]

Fetal complications include low birth weight and associated perinatal morbidity and mortality. Several studies suggest association between asymptomatic bacteriuria and increased prevalence of symptomatic UTI and pyelonephritis which in turn can lead to preterm labour. It has also been indirectly linked to preeclampsia and anemia.[2]

Hence, it is recommended to regularly screen and treat asymptomatic bacteriuria, with increasing antibiotic resistance, consideration of local resistance pattern is necessary when choosing the therapy.[2] In fact, urine analysis of such patients demonstrated considerable bacteriuria without pyuria. Urine culture also was positive.[3]

Escherichia coli is associated with up to 80% of isolates; other pathogens include Klebsiella species, Proteus mirabilis and group B streptococcus. Methods for diagnosing ASB include midstream urine culture (the gold standard), Gram stain and urine dipstick tests.[4]

Pre-eclampsia complicates about 3% of all pregnancies and remains a major cause of maternal and perinatal mortality and morbidity, and is particularly devastating in developing countries.[5,6]

Pre-eclampsia can adversely affect all body systems and is defined by blood pressure of greater than 140/90 mmHg after the 20th week of pregnancy and proteinuria of equal to or higher than 300 mg per 24 hours.[7]

Pre-eclampsia predisposes the mother to high-risk pregnancy by affecting all maternal body systems, and can result in hazardous outcomes for both the mother and her fetus.[8]

Despite recent progress towards understanding the cause of preeclampsia and/or its phenotypes, the etiology of this serious disorder remains elusive.[9]

Current theories include abnormal placentation, cardiovascular immune mechanisms, an enhanced systemic inflammatory response, and nutritional, hormonal, and angiogenic factors, It seems probable, however, that multiple factors are involved.[10,11]

Normal pregnancy evokes a mild increase in the systemic inflammatory response that becomes considerably greater in preeclampsia.[10] Based on this concept, some authors have hypothesized that infection pathogenesis of preeclampsia, both in terms of its initiation (by increasing the risk of acute uteroplacental atherosis) and/or its potentiation (by amplifying the maternal systemic inflammatory response).[12,13]

Studies performed in recent years in identifying factors responsible for pre-eclampsia showed that primary infections during pregnancy increase the chance of pre-eclampsia.[14]

It is likely that subclinical infections result in increased maternal cytokines and subsequently cause pre-eclampsia via affecting the vascular endothelium.[14]

Since asymptomatic bacteriuria is one of the most common conditions during pregnancy and can have adverse effects on pregnancy, this study will be performed to investigate the relationship between asymptomatic bacteriuria and development of pre-eclampsia.

AIM OF THE WORK

The aim of this study is to determine the relationship between asymptomatic bacteriuria and pre-eclampsia and if asymptomatic bacteriuria is a predisposing factor for development of preeclampsia.

PATIENTS

The study included 80 pregnant women who was present to El shatby University Hospital antenatal care clinic.
Forty pregnant women who presented with preeclampsia after 20 weeks of gestational age was selected as case group and 40 healthy pregnant women at the same gestational age as control group.
All participants was informed about the nature of the study and informed consent was taken from all of them.

Inclusion criteria:

1. All women at 20 weeks of gestation or later.
2. All primigravida.
3. Age from 20:35.
4. All of them have singleton pregnancy.

Exclusion criteria:

1. Systemic or infectious diseases e.g. DM.
2. Intake of antibiotics in the last three months.
3. Having any renal problems.
4. Having any urinary complaints.

METHODS

Patient's evaluation:

- Detailed history including (age, marital status, occupation, Menstrual and obstetric history).
- The pregnant women was trained how to accurately collect clean catch mid-stream urine samples.
- The samples were immediately delivered to the microbiology lab of Alexandria main university hospital.
- A wet film was performed to detect white blood cells in the urine samples as well as bacteria. Pyuria is defined as ≥ 5 white blood cells per high power field (HPF) in uncentrifuged urine sample.
- Urine culture, bacterial identification and antimicrobial susceptibility was performed using the standard microbiological techniques.
- A significant colony count of one type of bacteria (≥ 105 CFU /ml) growing on culture plates in a patient having no urinary symptoms was interpreted as asymptomatic bacteriuria.

RESULTS

Regarding demographic data the pre eclamptic cases mean age is 24.8 while mean age of control cases is 25.3 with no significant differences were found between the two groups, while the mean gestational age of pre eclamptic cases is 29.1 while mean gestational age of control cases is 29.6 with no significant differences between the two groups as shown in table (1).

The asymptomatic bacteria was higher in preeclampsia group more than no preeclampsia but this increase was insignificant, the incidence of organism identified in the two groups was matched without significant difference, the most frequent organism was E. coli in the two groups (Table 2).

Pre eclamptic cases with detected pyuria are 3 (7.5%) while in control cases 6 (15%) had pyuria, there were no statistically significant differences, the blood pressure show a significant increase in preeclampsia more than the non eclamptic cases. Table (3).

Cases who had ASB with pyuria was 4 cases(16.7%) while cases without ASB who had pyuria was 5 (8.9%) with no significant differences. Mean age of Cases with asymptomatic bacteruria , was 22 years while mean age of cases without ASB was 26 years with significant difference between the two groups ($P < 0.001$). Mean gestational age of cases with ASB was 27.9 weeks while mean gestational age of casas without ASB was 29.9 weeks with significant difference (p value = 0.049) (Table 4).

Six preeclamptic cases with ASB developed

complication while 5 preeclamptic cases without ASB develop complication. There were no significant difference as regard development of complication between preeclamptic cases with ASB and preeclamptic cases without ASB (Table 5).

Table (1): Comparison between the two studied groups as regard to age and gestational age

	Total (n = 80)	Preeclampsia		T	p
		Yes (n = 40)	No (n = 40)		
Age (years)	25.06 ± 4.31	24.82 ± 4.21	25.30 ± 4.44	0.491	0.625
Gestational age	29.36 ± 4.25	29.10 ± 4.51	29.63 ± 4.01	0.550	0.584

Table (2): Comparison between the two studied groups as regard presence of asymptomatic bacteriuria and the organism identified.

	Total (n = 80)		Preeclampsia				χ^2	p
			Yes (n = 40)		No (n = 40)			
	No.	%	No.	%	No.	%		
Asymptomatic bacteriuria								
No	56	70.0	25	62.5	31	77.5	2.143	0.143
Yes	24	30.0	15	37.5	9	22.5		
Organism identified								
Staphylococcus saprophyticus	4	16.7	1	6.7	3	33.3	1.053	^{FE}p=0.615
E-coli	10	41.7	7	46.7	3	33.3	1.829	0.176
Acinetobacter spp	1	4.2	1	6.7	0	0.0	1.013	^{FE}p=1.000
Enterococcus fecalis	3	12.5	1	6.7	2	22.2	0.346	^{FE}p=1.000
Klebsiella	5	20.8	4	26.7	1	11.1	1.920	^{FE}p=0.359
Staphylococcus aureus	1	4.2	1	6.7	0	0.0	1.013	^{FE}p=1.000

Table (3): Comparison between the two studied groups as regard to the presence of pyuria. and blood pressure of the patients.

Pyuria	Total (n = 80)		Preeclampsia				χ^2	^{FE}p
			Yes (n = 40)		No (n = 40)			
	No.	%	No.	%	No.	%		
No	71	88.8	37	92.5	34	85.0	1.127	0.481
Yes	9	11.3	3	7.5	6	15.0		
Blood pressure (mmHg) Systolic								
Min. – Max.	90.0 – 160.0		120.0 – 160.0		90.0 – 130.0		10.157*	<0.001*
Mean ± SD.	123.62 ± 19.50		138.25 ± 12.38		109.0 ± 13.36			
Diastolic								
Min. – Max.	50.0 – 100.0		70.0 – 100.0		50.0 – 90.0		10.167*	<0.001*
Mean ± SD.	78.75 ± 14.0		89.25 ± 7.64		68.25 ± 10.59			

Table (4): Comparison between cases with ASB and cases without ASB as regard to prescence of Pyuria, age and gestational age. (n = 80)

	Asymptomatic bacteriuria				Test	P value
	No (n = 56)		Yes (n = 24)			
	No.	%	No.	%		
Pyuria						
No	51	91.1	20	83.3	χ^2=1.008	0.441
Yes	5	8.9	4	16.7		
Age (years)	26.21 ± 4.25		22.37 ± 3.12		T=4.501*	<0.001*
Gestational age	29.96 ± 4.23		27.96 ± 4.03		T=2.011*	0.049*

Table (5): Comparison between preeclampsia cases with ASB and preeclampsia cases without ASB as regard to development of Preeclampsia complication (n = 34)

	Asymptomatic bacteriuria				χ^2	^{FE}p
	No (n = 22)		Yes (n = 12)			
	No.	%	No.	%		
Eclampsia						
Negative	21	95.5	11	91.7	0.201	1.000
Positive	1	4.5	1	8.3		
HELLP syndrome						
Negative	21	95.5	9	75.0	3.130	0.115
Positive	1	4.5	3	25.0		
Abruptio placenta						
Negative	19	86.4	10	83.3	0.057	1.000
Positive	3	13.6	2	16.7		
Uncomplicated						
Negative	6	27.3	6	50.0	1.756	0.27
Positive	16	72.7	6	50.0		

There were six cases failed to be traced

DISCUSSION

In our study, the prevalence of asymptomatic bacteriuria among antenatal population at El shatby hospital was common (30% of all subjects). The reported asymptomatic bacteriuria in pregnant women has been noted as 10.1% in Tehran, Iran ,14.2% in Saudi Arabia, 28.5% in Pakistan, 23.9% in Nigeria, 12.3% in brazil ,8.5% in turkey ,4% in Australia, and 2.2% in London. [15-18]

These figures reflect variable rates of asymptomatic bacteriuria in different geographic regions. It seem that various factors such as age, sexual activity, socioeconomic status, history of urinary tract infection before pregnancy, anatomic malformations of the urinary system, and gestational age all have influential role in asymptomatic bacteriuria rate.

The high rate of asymptomatic bacteriuria observed in the current study can be the result of the method of sampling, cultural, and social status of the study population. These statistics indicate that, although the incidence of ASB in pregnancy varies in different countries and geographic regions, ASB

could overall be considered to affect a significant number of pregnant women worldwide.

For the first time in 1936, Peters et al. suggested association between bacteriuria and pre-eclampsia. [19] Then, Smith and Bullen reported that bacteriuria was more common in pregnant women with pre-eclampsia compared to those without pre-eclampsia. [20] Stuart et al. later noted that pre-eclampsia was 4 times more common in women with bacteriuria than in those without bacteriuria. [21]

In our study The rate of asymptomatic bacteriuria was higher in pre-eclampsia group(37%) than in control group(22%) but with no significant difference , perhaps this due to small number of our cases. In our study, ASB rate was more common in preeclamptic cases than control cases by 1.6 times.

There is partial agreement in our results with other studies by Borghei in Gorgan, Akerele, and Caroline as they showed similar results as ours, but they reported that bacteriuria was significantly more common in pregnant women with pre-eclampsia unlike our study, ASB was more common in pre eclamptic cases but with no significant difference [22-24]

Studies by Shamsi in Pakistan and Rizek from UAE showed similar results as ours, with no significant difference was seen regarding bacteriuria between pre-eclampsia group and control group. [25-26]

Maybe the agreement of our results with those of reported by Shamsi in Pakistan and Rizek from UAE is the adjustment for confounding variables such as gestational age and maternal age with matching.

The discrepancy with the results by Borghei, Akerele, and Caroline may be due to differences in cultural and socioeconomic status and the fact that the mentioned studies did not adjust confounding variables.

The results of our study showed that there was no significant difference between groups of cases and control as regard to age.

Sheraz et al reported that PE was more common in patients younger than 21 years and above 35 years. [27] Sajith et al reported that the highest prevalence of pregnancy hypertension was observed in the 22–28 age group with 41.3 %. [28]

As can be seen, the results of these studies are consistent with the findings of our study as preeclampsia rate is more common in the age range from 20:25 (57%) so PE is more common in younger age.

In our study, the mean gestational age of the two groups was not significantly different, as mean gestational age of preeclamptic cases was 29.1 while in control cases was 29.6 This finding was consistent with Hazhir and Shamsi's studies. [15] [25]

In our study, the mean age of cases with ASB was 22 years and 79 % of these cases had an age range from 20:25 years so ASB is more common in younger age. This consistent with increased prevalence of ASB with lower maternal age by Hazhir [15] .The exact link between maternal age and ASB is yet to be established.

In our study, mean gestational age of cases with ASB was 27 weeks

In our study, most culture positive cases were seen in second trimester (54.2%), which was similar to Girishbabu R J study and Nath et al study. [29-30]

In our study Escherichia coli species was the most prevalent organism isolated in 41% of cases followed by Klebsiella in 20%. Most of the earlier reports showed Escherichia coli to be the predominant organism. [16] [31-33]

Unlike these reports, in a regional study in Ethiopia, the prevalent agents in ASB cases in pregnancy are coagulase-negative Staphylococcus species in 32.6% of cases, followed by E. coli in 26.1% and Staphylococcus aureus in 13%.[34]

Another study, by Akerele et al in Benin found that the most prevalent organism was klebsiella [23]

The possibility of pre-eclampsia is the highest when there is previous history of contact with antigens that affect the body and especially affect the lymphocytes function. [38-40]

In general, ASB are more common in women with pre-eclampsia and this may reflect a background disease in the kidneys.

The results of this study showed that ASB is more common in cases with preeclampsia by 1.6 times than cases without preeclampsia but with no significant difference so to fully understand if there is any link between PE and ASB ,we need a larger number of cases to study.

CONCLUSIONS

- Asymptomatic bacteriuria was a common finding among pregnant women in our study (30% of whole cases).
- Asymptomatic bacteruria was more common in preeclamptic group (37%) than control group (22%).
- The most common organism in asymptomatic bacteriuria in the studied group of pregnant women at El shatby antenatal care clinic is E.coli (41%).
- E.coli was most sensitive to Imipenem (100%) ,nitrofurantoin (100%) and trimethoprim sulphamehoxazole (100%) , while Klebsiella spp to Imipenem (100%) and Cefotriaxone (100%) while Staphylococcus saprophyticus to Vancomycin ,teicoplanin and Linezolid (100%)

RECOMMENDATIONS

We recommend screening for bacteriuria early in pregnancy (1st prenatal care) and follow in 2nd and 3rd trimester of pregnancy to detect cases with asymptomatic bacteruria so we can prevent the main side effect in pregnancy and the safety of mothers.

There is particular need for guidelines defining the basic principles to be followed in antibiotic treatment of ASB in pregnant women.

We recommend doing more clinical research on larger scale of pregnant women with PE and ASB to investigate the association between both of them.

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Triaging of eccentric gestational sac in early pregnancy using two dimensional and three dimensional transvaginal ultrasound

Keywords: interstitial ectopic pregnancy, rudimentary horn, cornual pregnancy, angular pregnancy, 3D transvaginal ultrasound.

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Abstract

Objectives: Interstitial ectopic pregnancy and pregnancy in a rudimentary horn of a unicornuate uterus are rare forms of ectopic pregnancy but carry a high risk for maternal morbidity and mortality. Their diagnosis is challenging and can be misdiagnosed with less dangerous conditions; namely: angular pregnancy or pregnancy in one side of septate or bicornuate uterus. This study aimed to differentiate between these four situations to allow early detection that will enhance the prognosis.

Methods: This is a retrospective study, carried out on 26 patients referred to a private referral center for obstetric and gynecology sonography, in the period from November 2019 till November 2020. All cases were referred due to unusual eccenteric location of the gestational sac. In each case we assessed 3 variables using 2D -TVUS which were: relation to the endometrium , interstitial line sign and condition of the overlying myometrium. We assessed also 2 variables using 3D- TVUS which were: shape of the uterine cavity and the relation of the gestational sac to the uterotubal junction.

Results: It was found that the gestational sac (GS) is within the endometrium in angular pregnancy and pregnancy in septate and bicornuate uterus while GS is outside the endometrial interface in interstitial ectopic pregnancy and pregnancy in rudimentary horn of unicornuate uterus. The interstitial line sign was +ve and the overlying myometrium was thin only in interstitial ectopic pregnancy. Cavity was normal in angular and interstitial ectopic pregnancy but it has a Mullerian fusion anomaly in cases of pregnancy in rudimentary horn of a unicornuate uterus and cases with pregnancy in one side of a septate or bicornuate uterus. GS was lateral to the uterotubal junction in interstitial ectopic pregnancy and pregnancy in rudimentary horn of unicornuate uterus but it was medial to it in the other 3 situations.

Conclusion: Our study described a simple triaging model based on sonographic criteria for four pregnancy situations where the gestational sac appears eccenterically in the early 1st trimester. These four situations are namely; interstitial ectopic pregnancy, ectopic pregnancy in a rudimentary horn of a unicornuate uterus,

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angular pregnancy and pregnancy in one side of a septate or bicornuate uterus. This model will be helpful for early accurate diagnosis to avoid false positive diagnosis that may lead to unnecessary intervention and false negative diagnosis that may lead to maternal morbidity or mortality.

Introduction

Ectopic pregnancy (EP) is implantation of the gestational sac outside the endometrium near the fundus, which is the normal site of implantation. EP accounts for about 1-2% of pregnancies and represents a major cause of maternal morbidity and mortality in early pregnancy especially in developing countries. Most of the complications caused by EP are due to its late detection.[1-3]

The commonest location for ectopic pregnancy is the ampulla of the fallopian tube that accounts for more than 90% of the ectopic pregnancy cases. One of the rare sites of ectopic pregnancy is the interstitial ectopic pregnancy that represent about 2-4% of the all ectopic pregnancies. It occurs in the intramural part of the fallopian tube and though it is less common than the ampullary tubal ectopic pregnancy, its complications are significantly higher and its diagnosis and management are more challenging.[4]

Angular pregnancy is totally different from the interstitial ectopic pregnancy, the first represents a gestational sac implanted inside endometrium at the superior lateral angle of the cavity medial to the uterotubal junction. Gestational sac in pregnancy in one side of septate or bicornuate uterus is also implanted within the endometrium medial to the uterotubal junction. Angular pregnancy and pregnancy in one side of septate and bicornuate uterus are considered intrauterine pregnancies rather than ectopic pregnancies.[5,6]

Cornual pregnancy is a term to describe a pregnancy in a uterus with anomaly. It could be either intrauterine pregnancy in cases where gestational sac implanted in one side of septate/bicornuate uterus or ectopic pregnancy where gestational sac implanted in the rudimentary horn of a unicornuate uterus. The latter represents an extremely rare form of ectopic pregnancy with high rate of complications.[4-6]

With the wide spread use of high-resolution transvaginal 2D and 3D sonography, most of the early pregnancy abnormalities can be diagnosed early, and hence conservative management can be used. Most of the obstetricians have a limited experience in differentiating interstitial ectopic pregnancy & pregnancy in a rudimentary horn of a unicornuate uterus from angular pregnancy and pregnancy in septate or bicornuate uterus. The first two conditions are worrisome, so early detection and management is warranted. The later 2 conditions are of better prognosis and their management will be just follow up.[6]

In our study, we will describe the ultrasonographic diagnostic clues for these 4 situations to establish a triaging model for eccentrically located gestational sac early in pregnancy to avoid false negative diagnosis that may lead to maternal complications and false positive diagnosis that may lead to unnecessary procedures.

Aim of the work

To evaluate the differential diagnosis of eccentrically located gestational sac early in pregnancy.

Patients and Methods

This is a retrospective study, carried out on 26 patients referred to a private referral center for obstetric and gynecology sonography; in the period from November 2019 till November 2020.

All cases were referred due to an unusual eccentric location of the gestational sac in the early 1st trimester sonographic assessment. All cases were evaluated according to age, obstetric history and gestational age at diagnosis.

The ultrasound was done by the same sonographer using Samsung HS 60 apparatus; 2 dimensional (2D) and 3 dimensional (3D)

transvaginal ultrasound (TVUS). In each case we assessed 5 variables which were: relation of the gestational sac (GS) to the endometrium, interstitial line sign, condition of the overlying myometrium, shape of the uterine cavity and the relation of the GS to the uterotubal junction. The first 3 variable were assessed using 2D-TVUS and the last 2 variables were assessed using 3D-TVUS.

Results

This study was carried out on 26 cases, who were classified into five categories; angular pregnancy (11 cases), pregnancy in one side of a septate uterus (6 case), pregnancy in one horn of a bicornuate uterus (4 cases), interstitial ectopic pregnancy (3 cases) and ectopic pregnancy in the rudimentary horn of a unicornuate uterus (2 cases). There was no significant difference between the five categories regarding the age and gestational age. The gravidity and parity were significantly lower in cases of pregnancy in bicornuate uterus and cases of ectopic pregnancy in rudimentary horn of unicornuate uterus. The incidence of previous abortion was also significantly higher in these two categories. (Table 1).

Regarding the ultrasound findings, it was found that the gestational sac (GS) is within the endometrium in angular pregnancy and pregnancy in septate and bicornuate uterus while GS is outside the endometrial interface in interstitial ectopic pregnancy and pregnancy in rudimentary horn of unicornuate uterus.

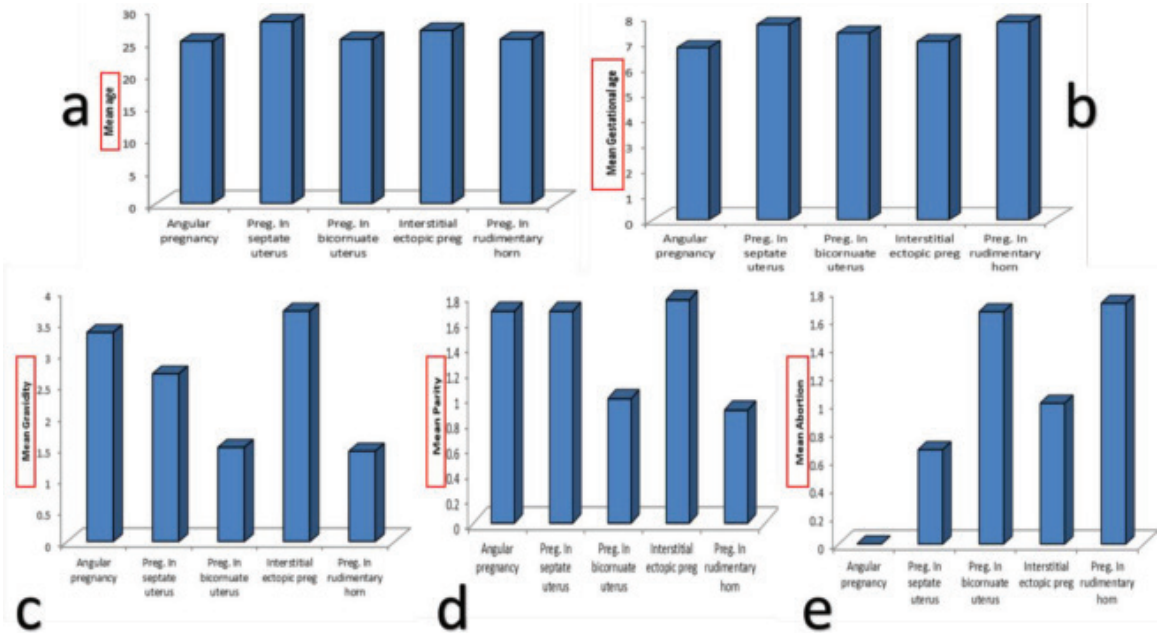
The interstitial line sign is an echogenic line from the endometrium to the eccentric gestational sac (it represents the coapted margins of the interstitial portion of the tube). It is seen in the transverse or semi-axial planes. The interstitial line sign was +ve and the overlying myometrium was thin only in cases with interstitial ectopic pregnancy.

Cavity was normal in angular and interstitial ectopic pregnancy but it has a Mullerian fusion anomaly in cases of pregnancy in rudimentary horn of a unicornuate uterus and cases with pregnancy in one side of a septate or bicornuate uterus. GS was lateral to the uterotubal junction in interstitial ectopic pregnancy and pregnancy in rudimentary horn of unicornuate uterus but it was medial to it in the other 3 situations.

Table (1): Comparison between different categories regarding basic demographic and clinical data.

Variables	Angular pregnancy	Preg. In septate uterus	Preg. In bicornuate uterus	Interstitial ectopic preg.	Preg. In rudimentary horn	P value
Age (years)	25 ± 1.73	28± 4.62	25.3 ±2.21	26.67 ±3.79	25.33± 3.21	0.201 N.S.
Gravidity	3.33± 0.58	2.67± 0.58	1.50±0.36	3.67 ±0.58	1.44±0.41	0.012*
Parity	1.67 ±0.58	1.67 ±0.58	0.98±0.22	1.76 ±0.58	0.89±0.36	0.003*
Abortion	0.00 ± 0.00	0.67± 1.15	1.65±0.52	1.00 ±0.00	1.71±0.61	0.017*
Gestational age (GA: weeks)	6.76± 1	7.67 ±1.15	7.33± 0.58	7.00± 1	7.76 ±1.34	0.208 N.S.

N.S. : not significant , *: clinically significant

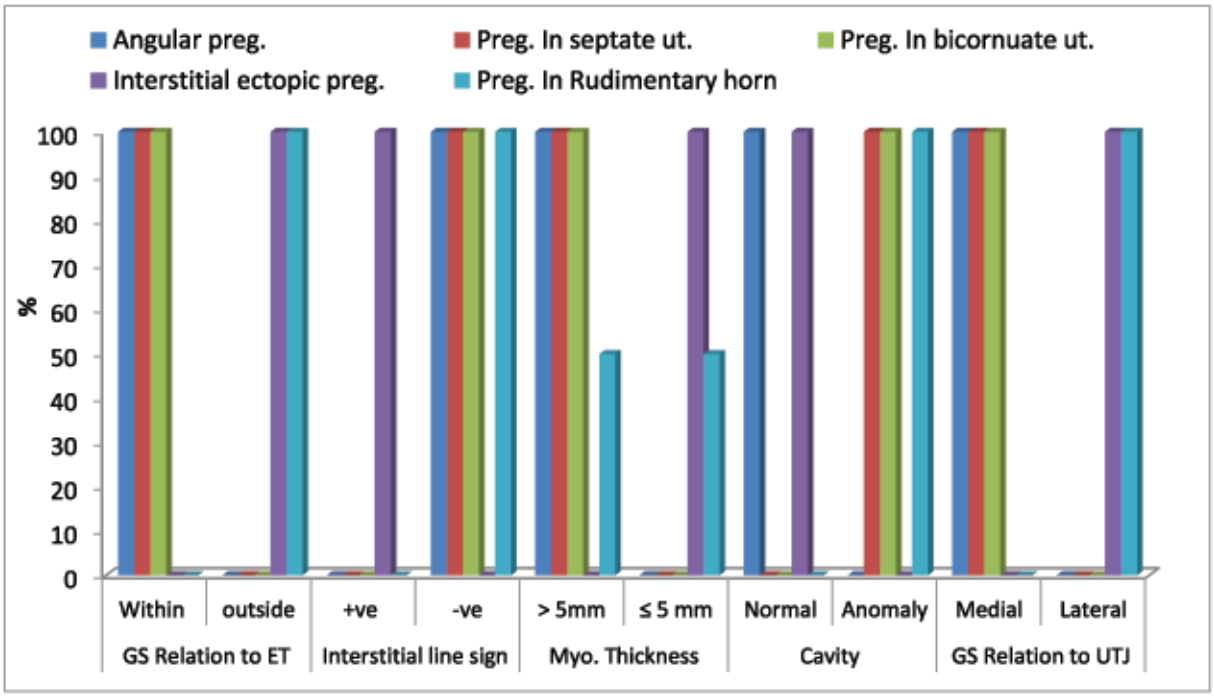


Figures (1): Comparison between different categories regarding basic demographic and clinical data. [a] age. [b] gestational age. [c] gravidity. [d] parity. [e] previous abortions.

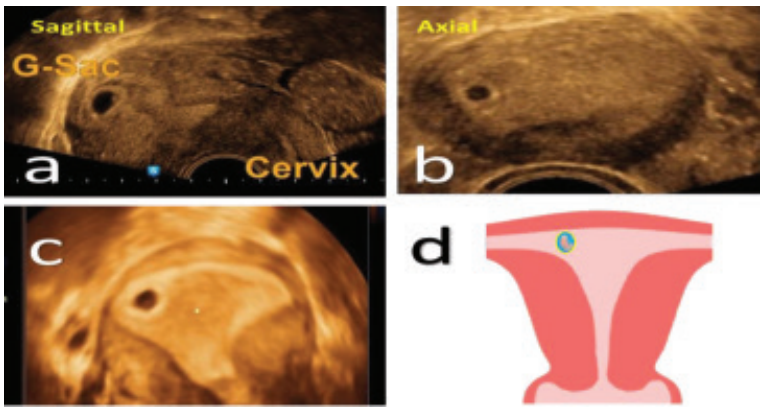
Table (2): Comparison between different categories regarding ultrasound findings.

Variables	Angular preg.		Preg. In septate ut.		Preg. In bicornuate ut.		Interstitial ectopic preg.		Preg. In Rudimentary horn		Total	P value
	No.	%	No.	%	No.	%	No.	%	No.	%		
GS Relation to ET												
Within	11	100	6	100	4	100	0	0	0	0	21	
outside	0	0	0	0	0	0	3	100	2	100	5	0.0028*
Interstitial line sign												
+ve	0	0	0	0	0	0	3	100	0	0	3	
-ve	11	100	6	100	4	100	0	0	2	100	23	0.017*
Myo. thickness												
> 5mm	11	100	6	100	4	100	0	0	1	50	22	
≤ 5 mm	0	0	0	0	0	0	3	100	1	50	4	0.0036*
Cavity												
Normal	11	100	6	100	0	100	3	100	0	0	14	
Anomaly	0	0	0	0	4	0	0	0	2	100	12	0.001*
GS Relation to UTJ												
Medial	11	100	6	100	4	100	0	0	0	0	21	
Lateral	0	0	0	0	0	0	3	100	2	100	5	0.0024*

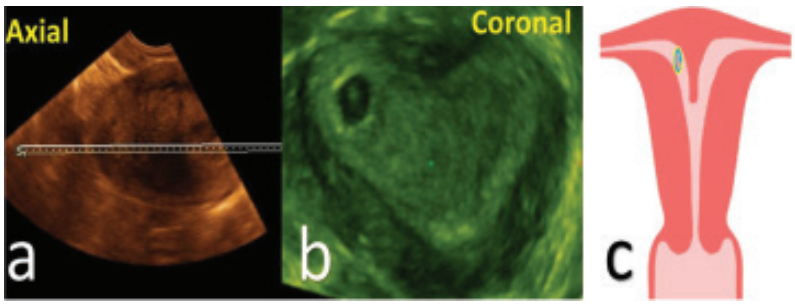
GS: gestational sac. ET: endometrium. Myo.: Overlying myometrial thickness.
UTJ: uterotubal junction.
*P value <0.05 → clinically insignificant



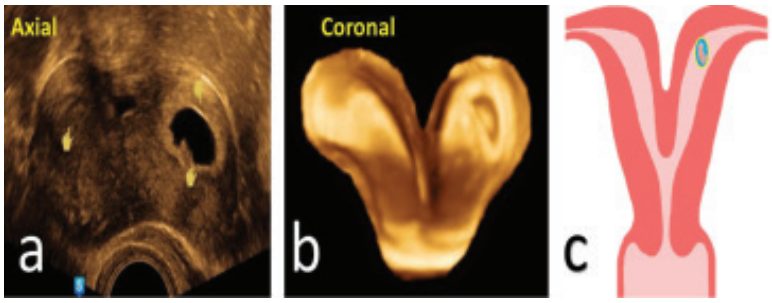
Figures (2): Comparison between different categories regarding ultrasound findings.



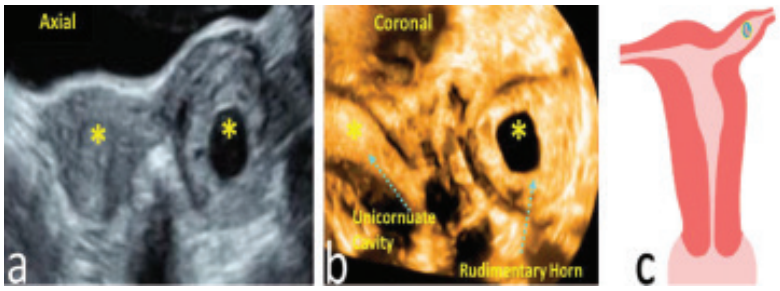
Figures (3): Angular pregnancy. [a] sagittal view using 2D-TVUS. [b] axial view, 2D-TVUS. [c] coronal view using 3D-TVUS. [d] diagram. In angular pregnancy; gestational sac was eccentwerially located but within the endometrial cavity, medial to the uterotubal junction.



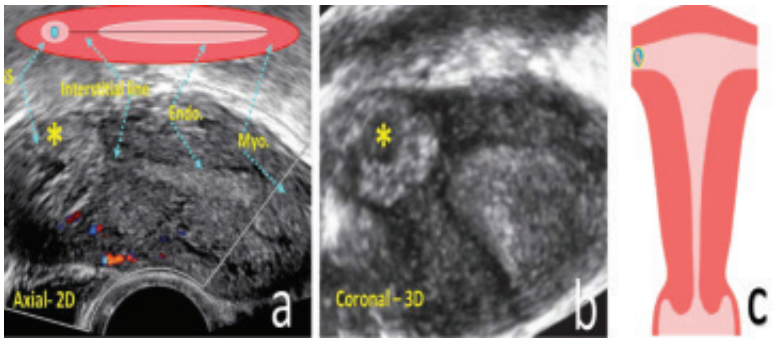
Figures (4): Pregnancy in one side of a septate uterus. [a] sagittal view using 2D-TVUS. [b] coronal view using 3D-TVUS. [c] diagram. In pregnancy in a septate uterus the gestational sac is eccentric but within the endometrial cavity medial to the uterotubal junction in one side of the septum.



Figures (5): Pregnancy in one side of a bicornuate uterus. [a] sagittal view using 2D-TVUS. [b] coronal view using 3D-TVUS. [c] diagram. In pregnancy in a bicornuate uterus the gestational sac is eccentric but within the endometrial cavity medial to the uterotubal junction in one horns of the bicornuate uterus.



Figures (6): Ectopic pregnancy in a rudimentary horn of a unicornuate uterus. [a] sagittal view using 2D-TVUS. [b] coronal view using 3D-TVUS. [c] diagram. In pregnancy in a rudemintary horn the gestational sac is eccentric and is surrounded by a myometrium of variable thickness and it is located lateral to the uterotubal junction of the main horn.



Figures (7): Interstitial ectopic pregnancy. [a] sagittal view using 2D-TVUS. [b] coronal view using 3D-TVUS. [c] diagram.

Discussion

Cornual, angular and interstitial pregnancy are unfortunately still used interchangeably although they are completely different. Cornual pregnancy is a pregnancy in a uterus with anomaly; e.g.: septate, bicornuate or unicornuate uteri. Angular pregnancy is an intrauterine pregnancy near the cornu of the uterus but medial to the uterotubal junction. Interstitial pregnancy is an ectopic pregnancy in the medial part of the Fallopian tube(i.e. the intramural part of the tube).[4-6]

Interstitial ectopic pregnancy and ectopic pregnancy in the rudimentary horn of a unicornuate uterus are rare forms of ectopic pregnancies but they carry a high risk for maternal morbidity and mortality. They could be misdiagnosed with less dangerous conditions; namely: angular pregnancy and pregnancy in one side of septate or bicornuate uterus. This study aimed to differentiate between these 4 situations to allow early detection that will enhance the prognosis.[4-6]

The following table summarize the variables that we had used in our study to objectively assign the type of pregnancy detected in an eccentric location in early pregnancy.

Criteria		Septate - Bicornuate	Angular	Interstitial	Rudimentary horn Of unicornuate uterus
2D- TVUS	Relation to the endometrium	Within the endometrium		Outside the endometrium	
	Interstitial Line Sign	-Ve		+Ve	-Ve
	Overlying Myometrium	Normal		Thin (≤5mm)	Variable
3D- TVUS	Cavity	Mullerian fusion anomaly	Normal cavity		Mullerian fusion anomaly
	Uterotubal Junction (3D)	Gestational sac (GS) is medial to it		GS is lateral to it	

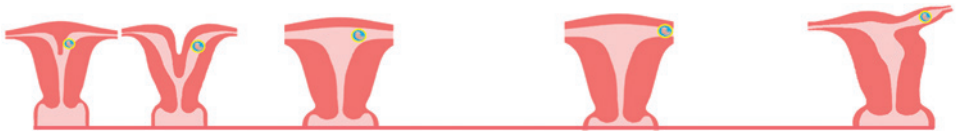


Table (3): Triaging of eccentric gestational sac early in pregnancy based on sonographic criteria using 2D and 3D- TVUS.

Interstitial line sign was positive in the 3 cases of our study who had an interstitial ectopic pregnancy. This finding was comparable to Ackerman et al who studied cases 12 cases of interstitial ectopic pregnancy and concluded that the interstitial line sign had a sensitivity of 98% for diagnosis.[7] Timor-Tritsch et al and Finlinson et al noted that the myometrial thickness overlying the gestational sac in cases of interstitial ectopic pregnancy is thin (5 mm or less), which was matched with our findings.[8,9]

Tanaka et al and Arleo et all described that angular pregnancy and pregnancy in one side of a septate uterus are both considered as an intrauterine pregnancy and are located medial to the uterotubal junction in 3D-TVUS coronal plane. Our results were agreed with theirs.[10,11]

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Coasting Versus GnRH Antagonist administration in Patients at High Risk of Ovarian Hyper stimulation Syndrome and its impact on the ICSI Outcome

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Abstract

Objectives: study the value of GnRH antagonist administration as an alternative protocol to coasting in preventing severe OHSS in cases of long agonist ovarian stimulation protocol and its impact on embryos quality &positive pregnancy in women undergoing ICSI.

Study design: A prospective randomized control trial is done at the assisted Reproduction unit, Al-Azhar university, Egypt to compare Coasting group (n = 150) and GnRH antagonist group (n = 150) in patients detected to be at risk of OHSS during the process OHSS in cases of long agonist ovarian stimulation protocol before ICSI. The primary outcome was high quality embryos, the secondary outcome was days of intervention, number of oocytes, pregnancy outcome, number of cryopreserved embryos and incidence of severe OHSS.

Results: There were statistical significant deference between quality embryos (2.3±1.2 versus 1.6±0.7; P value = 0.001) and more oocytes number (8.2±3.1) versus (6.7±3.2; P value = 0.01) in Antagonist group as compared with coasting group. There were more number of coasting days than with antagonist administration days (2.9±1.4 versus 2.2±1.1; P value = 0.001).

Conclusion: GnRH antagonist was superior to coasting in producing higher numbers of mature oocytes, high quality embryos and reducing the number of days till the HCG injection. There was no statistical significant difference in chemical pregnancy rate between two groups. No early or late OHSS developed in either group.

Introduction

Infertility affects 10%–15% of couples worldwide and has become a public health problem in recent decades(1). In vitro fertilization (IVF) and Intracytoplasmic sperm injection (ICSI) are commonly used in the management of infertility attributable to tubal factor, endometriosis, male factor and unexplained infertility (2).Recruitment and development of multiple follicles in response to go-

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nadotrophin stimulation are necessary for successful assisted reproductive treatment. The response of ovulating women to gonadotrophin therapy is quite variable and difficult to predict. Patient characteristics, rather than the stimulation protocol, seem to determine the individual response; although the dose and duration of gonadotropin treatment required to induce successful ovulation vary among women, even among cycles within a woman. In young ovulating women undergoing IVF treatment, the standard stimulation protocol can result in either poor response or in ovarian hyper-stimulation syndrome (OHSS) (3).

OHSS is considered a menacing prospective to the patients' health elaborated by iatrogenic influence of controlled ovarian hyper stimulation (COH) thus, it is a particularly alarming complication of IVF-related ovarian stimulation, that has a well-being threatening compass that ranges between admitting the patient to a hospital and in ultimate adverse impact may lead to lethal complication. (4) IVF cycles correspondence to OHSS intensity is outlined with the majority of cases exhibiting mild symptoms (around 33%) (1) The approximate value of moderate OHSS varies between 3%-6%, and the severe forms take place in about 0.1%-3% of all IVF cycles (5). Patients observed (based on undesirable regulatory factors) with elevated chances of OHSS are evaluated up to 20% (6).

OHSS foundation is directly proportional to the enhancement of multiple follicles, a critical phase for evolving a severe OHSS is supplied either by an exogenous human chorionic gonadotrophin (HCG) administration for final occasion of oocytes maturity peak or by endogenous production of HCG as a result of embryo-maternal signaling (pregnancy) (4)Exhibition of severe OHSS is displayed through extensive ovarian enlargement, peritoneal effusion, pleural effusion, hypo uresis, hemoconcentration, and thromboembolism (7).Coasting implies a refraining exogenous gonadotrophin therapy that maintains a realizing hormone agonist/antagonist administration to the point where serum E2 levels set down to a safe level. GnRH antagonists could disaffect the phenomenon of OHSS in by assigning a fast E2 levels suppression. (8) Aboulghar et al studied the anticipation of women with high risk of OHSS throughout the consequences of utilizing coasting and GnRH antagonist administration during randomized controlled cycles of ovarian stimulation for IVF, accompanied by a GnRH agonist long protocol, with a scouting prospect of preventing a downside outcome of prolonged coasting (9).

Aim of the Work

The aim of this study is to evaluate the GnRH antagonist subcutaneous administration as an alternative protocol to coasting in prevention of OHSS and its impact on embryos number, quality and ICSI outcome.

Patients and Methods

A prospective randomized control study was done after approval by the internal ethical committee. All women gave an informed written consent at the beginning of the research. The study population consists of 300 infertile women at high risk of developing OH, during COH using long GnRH agonist protocol for ICSI-ET. They were recruited from the International Islamic Centre for population studies and researches, assisted reproduction unit, Al- Azhar University during the period from January 2013 to June 2014.

Inclusion criteria:

During the ovarian stimulation process using long GnRH agonist protocol, women were considered at high risk of developing OHSS if they have a large number of follicles (>20) on both ovaries, with 90% of the follicles being small (<14 mm in mean diameter), and E2 concentration ≥ 3500 pg/ml. These women were included in the study. All women were subjected to: Full history taking general examination specially body mass index; Pelvic examination and full Investigations: FSH, LH, E2,prolactin,TSHusing ELFA technique

(Enzyme linked Fluorescent Assay) (Vidas-Biomerieux). Routine preoperative investigations (HB%, fasting blood sugar, 2 hours postprandial blood sugar, liver function ,kidney function tests, HBS Ag and HCV Ab). TVS for determination of AFC, folliculometry and detection of normally stimulated and hyper stimulated ovaries.E2 levels monitoring to ensure pituitary down regulation and for follow up during folliculometry) using ELFA technique (Enzyme linked Fluorescent Assay) (VidasBiomerieux).

Female patients in the study were divided randomly into 2 groups:

Coasting group

Involves 150 patients who experienced gonadotropin administration for no less than 24 hours prior to ovulation triggering, aided with HCG injection GnRH agonist in a quotidian manner. E2test is performed uniformly up to a descending desired concentration of ≤ 3000 pg/ml, 5000 IU of HCG was then supplied.

Antagonist group

Involved 150 patients that sustained a daily intake of GnRH antagonist (subcutaneous injection Cetrorelix acetate 0.25 mg (Cetrotide, Serono, UK)) up to the point in time for HCG administration. A daily E2 level assessment was carried out until the required concentration was achieved: ≤ 3000 pg/ml and vouched with TVS that visualized the follicles diameter of ≥ 18 mm, subsequently 5000 IU of HCG was given.

Oocyte Retrieval

TVS directed oocyte recovery was performed UGA, 34-36 hours after HCG administration, under full aseptic technique. The oocytes then were assessed for maturity (quality) according to **Hill et al. (10)** grading system.

Semen assessment

All semen parameters were recorded and evaluated in accordance to the WHO standards 2010 of semen evaluation.

ICSI

The ICSI procedure involved the injection of a single motile sperm into the cytoplasm of mature oocyte. The assessment of fertilization and cleavage was evaluated depends on the numbers, sizes of blastomeres and presence of a cytoplasmic fragments. The cleavage embryos are scored according to equality of size of the blastomeres and proportion of a nucleate fragments(10).

Embryo Transfer

On day 3, the embryos that would be transferred were loaded into the ETcatheter. The catheter used is Labotect catheter that is a 150 mm long atraumatic catheter having a precurved guiding cannula with spherical finish). (Labotect GmbH, Labor -Technik - Gottingen - Germany).

Luteal phase support (LPS)was given to all females, Prontogest (Shire Pharmaceuticals Ltd., Andover, UK) 100 mg intramuscular injection once daily for 2 weeks was give till the day of pregnancy test after two weeks. If the pregnancy test came positive; Prontogest 400 vaginal or rectal suppository was given instead of the injections until 8 weeks gestation. Clinical pregnancy was confirmed at 5-6 weeks gestation by visualization of a viable fetus by U/S examination.

Main outcome measure

Good quality embryos

Secondary outcome measures

number of intervention days, number of mature oocytes, pregnancy rate (PR), number of cryopreserved embryos and the incidence of severe OHSS.

Statistical analyses

- **Descriptive analysis** of the results in the form of percentage distribution for qualitative data.
- **Student t- test: Fisher's exact test and the Chi-square test.**
- **P:** The probability/significance value
- Statistical analysis: Statistical package was used for social science (SPSS) software version 17

Results

Table 1: Biodemographic 'characteristics for female patients at risk of OHSS in Coasting versus GnRH antagonist groups:

	Coasting	Antagonist	P value
Females age (years)	28.2±4.6	28.3±5.3	0.889
Duration of Infertility (years)	6.9±4.9	6.5±4.1	0.444
Primary infertility (%)	116(77.3%)	120(80%)	0.573
Secondary infertility (%)	34(22.7%)	30(20%)	0.573
PCO cases(%)	44(29.3%)	40(26.7%)	0.607
BMI	33.1±35.0	28.9±5.2	0.144
Basal FSH (mIU/ml)	6.1±2.0	7.6±9.7	0.070
Basal LH (mIU/ml)	4.8±3.5	4.5±2.5	0.409
Basal PRL (ng/mL)	17.6±7.3	18.7±9.5	0.277
Basal E2 (pg/ml)	46.4±18.6	46.0±16.7	0.845
Basal TSH (mIU/L)	2.0±1.0	1.8±1.0	0.212

Table 2: The distribution of the underlying aetiology of infertility

(%)	Coasting	Antagonist	P value
Male factor	92(61.3%)	84(56%)	0.348
Azoospermia	18(12%)	22(14.7%)	0.497
Ovarian factor	4(2.7%)	6(4%)	0.520
Tubal factor	16(10.7%)	22(14.7%)	0.298
Endometriosis	2(1.3%)	2(1.3%)	1
Asherman syndrome	2(1.3%)	0(0%)	0.156
Adhesions	4(2.7%)	6(4%)	0.520
Unexplained infertility	30(20%)	34(22.7%)	0.573

Table 3: Comparison between Coasting and Antagonist groups regarding the stimulation characteristics of the cycle.

	Coasting	Antagonist	P value
No. of HMG injections	26.7±8.3	28.8±10.4	0.133
Days of stimulation	10.8±1.8	11.4±2.7	0.124
Peak E2 (pg/ml)	4759.5±1160.8	4953.9±1301.2	0.322
E2 on day of hCG (pg/ml)	2257.8±715.3	2120.0±715.0	0.342
Days of intervention	2.9±1.4	2.2±1.1	0.001**

The table represents a significantly prolonged coasting period in variance to antagonist pattern. The GnRH antagonist injections delivered a median value of 2.2±1.1. The average E2 concentration within the antagonist criteria manifested a decline continuously after 24 hours till the day of hCG administration. Inceptive observation acknowledges the ascending concentration of E2 within the first 24 hours of coasting, followed by a falling pursuit of E2 concentration until the day of hCG administration.

Table 4: %Coasting and Antagonist groups in relation to the number of days of intervention.

No. Days of intervention	Coasting No. (%)	Antagonist No. (%)
1	16(10.7)	44(29.3)
2	48(32)	62(41.3)
3	50(33.3)	18(12)
4	16(10.7)	22(14.7)
5	16(10.7)	4(2.7)
7	2(1.3)	0(0)
8	2(1.3)	0(0)

In Antagonist group, 44 women (29.3%) required only one injection of GnRH antagonist, 62 women (41.3%) required two injections of GnRH antagonist and 44 women (29.4%) required more than two injections before hCG administration. In coasting group, only 16 women (10.7%) underwent coasting for 1 day, 48 women (32%) were coasted for 2 days, and 86 women (57.3%) were coasted for 3 days or more.

Table 5: Comparison between Coasting and Antagonist groups regarding the embryology lab characteristics:

%	Coasting	Antagonist	P value
Sperm collection by ejaculate	130(86.7%)	130(86.7%)	1
Sperm collection by PESA	4(2.7%)	2(1.3%)	0.409
Sperm collection by TESE	16(10.7%)	18(12%)	0.716
No. of oocytes	6.7±3.2	8.2±3.1	0.001**
No. of MII oocytes	3.7±2.0	4.7±2.3	0.001**
No. of MI oocytes	1.8±1.0	1.9±1.3	0.487
No. of GV oocytes	2.4±1.9	1.9±0.8	0.059
No. of atretic oocytes	2.4±1.4	2.3±1.6	0.583
No. of fertilized oocytes	2.9±1.8	3.8±2.4	0.001**
No. of grade 1embryos	1.6±0.7	2.3±1.2	0.001**
No. of embryos grade 2	1.5±0.7	1.7±0.8	0.179
No. of embryos grade 3	2.0±1.3	1.7±1.3	0.415
No. of embryos transferred	1.9±0.8	2.1±0.8	0.042*
No. of cryopreserved embryos	0.0±0.0	0.1±0.6	0.157

The table displays a notable difference of average oocytes number picked up from the antagonist group that was higher by almost 18% compared to the coasting group. An elevated value of the number of metaphase II oocytes obtained from the antagonist group is distinguished in contrast to the coasting group. The antagonist group regarding fertilization rate of oocytes is distinctly advanced in figures compared to the coasting group. Amount of the developed high-quality embryos in the antagonist group exceeds that of the coasting group by around one-third the number of embryos (grade1). The mean

number of embryos transferred was significantly higher in the antagonist arm than in the coasting arm.

Statistical rates acquired of clinical pregnancy and multiple pregnancy displayed unremarkable dissimilarity between the two groups. On the other hand, resemblance of late severe OHSS was identified in both groups including two patients in each group. Early severe OHSS was not observed among patients without significant difference.

Table 6: Comparison between Coasting and Antagonist groups regarding the Pregnancy rates (PRs) and latesevere OHSS rate.

	Coasting	Antagonist	P value
Clinical pregnancy (%)	50(33.3%)	54(36%)	0.627
Multiple pregnancy (%)	14(9.3%)	16(10.7%)	0.874
Severe OHSS (late) (%)	2(1.3%)	2(1.3%)	1

Discussion

Most of the previous studies on coasting are either observational or case-control trials. However, there is enough evidence in the literature that coasting is effective in reducing the incidence and severity of OHSS. (11). A demonstration of extended coasting of 4 days or further correlation to pregnancy rate expresses a low outcome (12). A substantial retrospective study that incorporated 1223 women disclosed the end-result of adopting coasting for excelled period of more than 3 days, that had diminishing consequences in terms of average number of oocytes retrieved, accomplishing implantation and successful clinical PRs (12).The follicular fluid was assessed in a programmed arrangement of coasting by two embryologists concurrently to point out the oocyte- cumulus complexes (OCC), an illustration of advanced research is necessary for gathering precise aspects of OCC, on account of negative impact of extended coasting to the number of granulosa cells neighboring the oocytes. (12). In addition to the effect of carrying out coasting for 4 days or more a study on egg donor cycles has described the counteraction to bring down the pregnancy rate. (13) This negative impact is assumingly affiliated to the poor quality of oocytes and embryos, as in traditional prolonged coasting IVF (regular-donor egg) cycles. Therefore, elimination of endometrial factor as a principal for lower pregnancy rates is crucial, a designated protocol was attained to halt the threatening disorders of prolonged coasting in women showing high risk of OHSS. The protocol hypothesis encourages the E2 concentration to drop down to a secure degree by the response of GnRH antagonist (8).

In our study on 300 women undergoing ovarian stimulation before ICSI; women were at high risk of developing OHSS, if they have a large number of follicles (>20) on both ovaries with 90% of the follicles being small (<14 mm in diameter), and E2 concentration ≥ 3500 pg/ml. They were divided into coasting group (150 patients) and antagonist group (150 patients) who received daily S.C injection of GnRH antagonist. When E2 concentration levels fell to < 3000 pg/ml all female patients subjected to HCG administration. None of them developed early onset severe OHSS. The mean number of oocytes gathered from the antagonist group had a considerable high difference from that of the coasting group by variance of 1.5±0.1 mean value. Finest embryo quality percentage was uplifted in the antagonist group with almost 30% better quality embryos that that of coasting group. Additional days were required in the coasting column. The primary approach applied in initial studies to weigh up the inhibitory practice for OHSS (coasting) (12) utilizing an original protocol of GnRH antagonist administration simultaneous to 75 IU of HMG in women at risk of OHSS. The central intention of averting severe OHSS in women at risk was established by coasting and administration of GnRH antagonist out of the 300 women in the study. The mode of action was achieved by minimizing the E2concentration to below 3000 pg/ml on the day of hCG administration. Nevertheless, timeframe accomplished to attain the desired concentration before administration of hCG, was brief ($P < 0.0001$) as stated in the antagonist arm with only 14.9% of patients that required ≥3 days of antagonist, while in comparison to the coasting group with 61.5% of patients that required protracted coasting of

≥3 days. Directing a small dose of HMG in a sustained manner, alongside the short intervention interval might be credible to unlikely nurturing granulosa cells and bearing a satisfactory classification of good quality oocytes and embryos. This study validated the hypothesis assumption of generating more oocytes (P = 0.0001) and high-quality embryos (P = 0.0001) in the antagonist arm. This relatively matches up with a study by Aboulghar et al. (9).

GnRH antagonist treatment of patients down-regulated with the long GnRH agonist protocol on patients with potential risk of OHSS prompted a significant drop in E2 concentration with avoidance of generating unfavorable results regarding assessment of oocyte maturation, evaluation of fertilization rate or embryo quality, the controlled non-randomized also supported a higher pregnancy rate in this group of women at risk of OHSS (8). The difference between PR in extended coasting and GnRH antagonist administration is not of a prime purpose in this study due to the extensive analytical requirements in each arm with a power of 80% and an alpha error of 0.05 presuming the pregnancy rate is 30%-35% which concludes a demand of 1307 women (9) Regardless of HMG suppression in the coasting group, E2 concentrations escalated within the first 24 hours with a later subsequent drop. Appropriately matching the work described by Isaza et al. (13). While the E2 concentration in the antagonist group fundamentally descended. E2 concentration dropped in coasting group following a cascade of events of follicular growth in lack of FSH stimulation to a point of apoptotic occurrence of granulosa cells (14). This clarifies the uprising concentrations of E2 prior to initiating coasting and elucidating the longer durations needed to drop below 3000 ml/pg. Allegedly this prohibits interchangeable reaction of chemical mediators from triggering OHSS (14). The sole machinery of antagonist that conducted an exclusive fall in E2 concentration explicitly not yet recognized. In a pilot retrospective study that conducted down-regulation with the long protocol (8 women) and flare-up protocol (39 women) Gustofson et al. (8) reported mild OHSS in a couple of patients and a single patient had to be treated of ascites as a result of severe OHSS. GnRH antagonist provided following a malfunction feedback of E2 concentration to a depletion of gonadotrophin dose. Controlled GnRH agonist has restorative ability towards the pituitary during directed administration with GnRH antagonist (15). Yet, the effect of GnRH antagonist to the pituitary after down-regulation by GnRH agonist was not anticipated (16).

In our study the mean drop in E2 concentration in 150 women after 1 day of antagonist administration was 34% in agreement with t Aboulghar et al. study in 2007;as the percentage of drop in E2 levels in 94 women after 1 day of antagonist administration was 36% .In Gustafson et al. study in 2006 the mean drop in E2 in 8 women was 49.5%.The riddle of sudden E2 level drop adherent to the effect of GnRH antagonist is yet incomprehensible. Although a substantiate amount of material was delivered proposing the action of GnRH antagonist at the cellular level in extra pituitary tissues, including physiological ovarian cycles. The synthesis of growth factors might be halted back due to the interference to the cell cycle (16). The likelihood of GnRH antagonist and the GnRH receptor interaction are of high chances as being reported (17). Mannaeils and Gordon. (18) opposed the fact of a direct extra pituitary tissues effect regulated by GnRH antagonist; claiming studies recited in this proposal are in-vitro studies, testing supra-pharmacological doses of GnRH antagonist in cancer cell lines.

Prolonged coasting represents a deficiency in oocytes, and specifically MII oocytes, which might potentially be refrained by the enrollment of GnRH antagonist as portrayed in the current study. The clinical PR in patients with prolonged coasting (4—8 days) was 27.7% in comparison with the preferable stats of 36% in the GnRH antagonist group, although a favorable percentage is not adequate against proportionally inconsiderable sample size. adversely, a committed approach nonrandomized large study from the present study proclaimed a feasible evaluation of pregnancy rate outcomes, in support of operating coasting for 3 days or less as compared with prolonged coasting. (12). Patients demanding extended coasting for more than 3 days took place in 24% of accumulative coasting patients. OHSS progress is usually bridged by uplifted levels of E2 concentrations that ambiguously has a parallel influence on complex evolvement of OHSS (19).

OHSS risk diminishing possibility is conditioned rationally by the potential depletion of E2 concentration. A study of categorized groups was executed to evaluate incidence of OHSS which represented 0.001 of the affected group from the study population and 0.01 concerning the women at risk (12). For an applicable, fitted study in a randomized clinical trial, the sustainable sample size acquired to minimize OHSS prevalence chances towards at risk population by 15 % is 17211 women in each treatment arm with an alpha error of 0.05 and 80% power. Manifestly this number would be immensely difficult to attain in a RCT.A conventional appropriate manner of managing coasting, as well as GnRH antagonist anticipated a constructive avoidance of OHSS development. None of the 300 patients at risk of OHSS elaborated early onset OHSS developments.

Conclusion

Coasting alone and GnRH antagonist protocol are effective methods for prevention of OHSS. GnRH antagonist protocol was superior to coasting in producing more number of oocytes and more good quality embryos as well as reducing the time until hCG administration. There was no statistical significant difference in PR between the studied groups. No early onset OHSS developed in either group.

Recommendation

GnRH antagonist administration during coasting is a valuable alternative protocol for prevention of OHSS during COH. We require to larger randomized studies compare coasting with or without GnRH antagonist to determine if there is any difference in PR and the incidence of OHSS between two protocols.

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Luteal phase Vitamin C supplementation on the outcome of in-vitro fertilization

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Abstract

Background: In-vitro fertilization is successful Assisted Reproductive Technology for infertility became one of the best modalities for achieving the dream of having children in face of many obstacles in fertility, many works have been done to enhance the outcome of IVF especially the live birth rate and all methods tried to support the luteal phase with many medications.

Objective: To evaluate the effect vitamin C supplementation at dose of 1000mg per day on the day of oocyte retrieval on the outcome of the In-vitro fertilization.

Methodology: A randomized open-label study was carried out on 200 women undergoing In-vitro fertilization for infertility treatment conducted at AlShorouk IVF clinic Benha city egypt. They were randomly divided in two groups; one group received 1000 mg/day oral Vitamin C supplementation 1000mg divided into two capsules by day and night on the day of oocyte retrieval along with the standard treatment protocol of In-vitro fertilization and other group received standard treatment long protocol for the In-vitro fertilization only. Pregnancy test done after 14 days and pregnant patient followed by regular visits till reaching term and any morbidity recorded.

Results: Significant outcome regarding reaching full term pregnancy occurred in the vitamin c group with number of full term pregnancies 65 out of 100 (65%) compared to only 45 out of 100 in the control group (45%) with p value 0.004 also the rate of early miscarriage is higher in the control group 20% and only 8% in the vitamin c study group with p value 0.01.

Conclusion: Vitamin C supplementation has significantly improved the outcome of In-vitro fertilization techniques with reduced incidence of spotting and miscarriages along with improved term pregnancy.

However a multimodal approach of analgesia/anaesthesia for TUGOR is recommended to further improve on clients' satisfaction and acceptance.

Keywords: In-vitro fertilization, Vitamin C, Infertility, full term pregnancy.

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Introduction

Vitamin C functions as a cofactor in many enzymatic reactions that mediate a variety of essential biological functions, includingcollagen synthesis.

Vitamin C deficiency leads to impaired collagen synthesis, contributing to the more severe symptoms of scurvy.Another biochemical role of vitamin C is to act as an antioxidant (a reducing agent) by donating electrons to various enzymatic and non-enzymatic reactions.[10]

Dietary sources of vitamin C are guava, lime, lemon, green leafy vegetables,Milk, and Animal products like liver and fish.

Ascorbic acid is necessary for the post translational hydroxylation of proline and lysine residues to form hydroxyproline&hydroxy lysine that make collagen strong by cross liking collagen fibers which constitutes most of connective tissue and intercellular cement substances of capillaries

Vitamin c also involved in Hydroxylation of tryptophan to 5-hydroxy tryptophanwith formation of serotonin; serotonin is the key hormone that stabilizes our mood, feelings of well-being, and happiness.

Vit C reduces ferric iron to ferrous state, which is preferentially absorbed from intestine and consequently raising Hemoglobinlevel and correct anemia. Also vitamin c involved in Folic acid metabolism and Helps the enzyme folatereductase to reduce folic acid to tetrahydrofolic acid thus helps in maturation of RBC.

Unexplained infertility affects 15% of couples in the United States;Its pathophysiology remains unclear; Evidence suggests that oxidative stress (OS) and low antioxidant status may be associated with infertility of both known and idiopathic origin (1).

Lower total antioxidant status (TAS) is observed in serum of women with polycystic ovarian syndrome (a known risk factor for female infertility) and the peritoneal fluid of women with idiopathic infertility compared with fertile control women (2,3).

Ascorbic acid is essential for maintenance and synthesis of collagen during tissue development and at sites of tissue damage, and also for the maintenance of the slow collagen turnover which occurs in mature tissues.

Vitamin c acts as an electron donor, it is an essential co-factor for the enzymes that hydroxylateproline and lysine residues during the post-translational processing of pro-collagen. Collagen synthesis is required for follicle growth, for repair of the ovulated follicle and for corpus luteum development.

Ascorbate will also be needed for secretion of collagen and proteoglycans into follicular fluid. To gauge the requirement during follicle growth, the follicular basement membrane and theca can be considered as the surface of a growing sphere whose quantity will increase as the square of follicular radius.

The radius of the graffian follicle may double on a daily basis so the local demand for collagen synthesis, and for ascorbate, will be intense. (4).

These concepts have yet to be investigated directly, but shown relevance in an early study of infertility in scorbutic guinea pigs The antioxidant properties of ascorbic acid are known to protect tissues from reactive oxygen species such as 02-, OH-, H202, 02, OCI-, NO, and metal-oxygen complexes (5,6).

The ovary has long been recognized as a site of ascorbic acid accumulation and turnover, with the highest concentrations in the theca interna, granulosa, and luteal compartments. (6)

LH blocks the uptake of ascorbic acid by gonadotropinprimed ovaries. A change in the retention and excretion of ascorbic acid occurs at mid-cycle in women, associated with LH secretion and temperature rise, and has been proposed as a definitive marker of ovulation [7].

There appears to be a biphasic change such

that excretion increases in the late follicular phase, declines immediately prior to ovulation, and increases again immediately after the rise in body temperature.; these changes was assumed due to changes in the uptake of ascorbic acid by the periovulatory ovary.

It has been suggested that changes in retention before ovulation facilitate luteal steroidogenesis, and this explains its cycle-protective effects.

Recent studies with luteinizing granulosa cells show that ascorbate is stimulatory to progesterone and oxytocin secretion, consistent with its known roles in hormone biosynthesis, and synergizes with neurotransmitters in stimulating hormone secretion.the concentration of ascorbic acid in the corpus luteum appears to be greatly in excess of that required to facilitate hormone production [8].

In the present study, we explored a factor of high Ascorbic Acid intake by the female partner undergoing IVF and its relation to various parameters and outcome of pregnancy.

Methodology

A randomized open-label study spread over 1 year from the period of January 2020 to January 2021was carried out in the specialty Alshorouk IVF clinic located in Benha city Egypt. All the patients were explained clearly about the purpose and nature of the study and those who are willing to given written informed consent were enrolled for the study.

Participant Selection

Sample size: 200 hundred patients undergoing IVF in that period with one undred as cases with vitamin c supplementation and one hundred as controls and not given vita

Inclusion criteria: Patients who were <40years of age, had >2 years of infertility and required infertility treatment by IVF-ET and came to hospital for the infertility treatment were included in this study.

Exclusion criteria:

endocrine diseases such as diabetes mellitus, hypothalamic pituitary dysfunction, or thyroid dysfunction; autoimmune disease, cardiovascular disease, and liver and kidney dysfunction; treatment with oral contraceptives and gonadotropin-releasing hormone agonists within 3-months

Study Duration

These 200 patients were enrolled from January 2020 to January 2021.

Study Procedure in Detail

Written informed consent was obtained before including them in the study. All the patients fulfilling the inclusion-exclusion criteria were interviewed for the first time on the day of enrolment, and their case sheets were reviewed to gather necessary information.

History and examination were carried out. All the demographic, disease related parameters, clinical examinations, details of IVF technique and antenatal visits, spotting/bleeding occurred or not and outcome of pregnancy was recorded.

Group Allocation

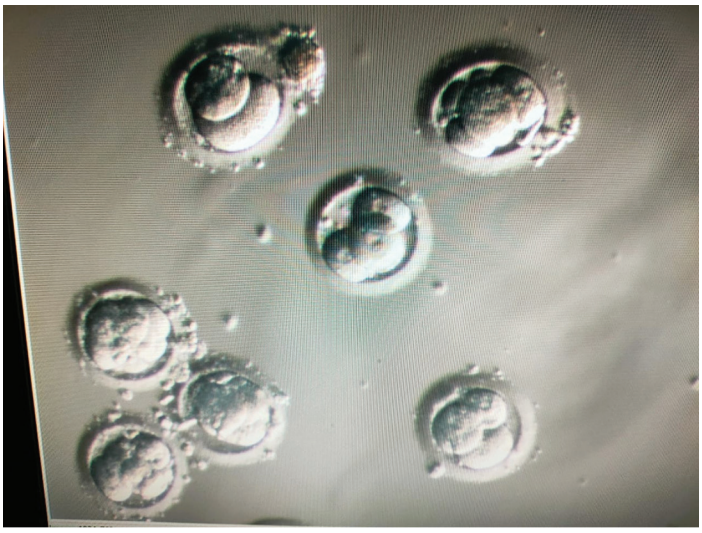
All patients were randomly assigned into groups A and B using random number table. Group A patients received 1000 mg/ day of oral Vitamin C. The vitamin C supplementation was started on the day of follicle aspiration and continued for entire duration of gestational period. Group B patients did not the vitamin C supplementation as oral tablets.

Fertilization Assessment, Embryo Assessment and Pregnancy Evaluation

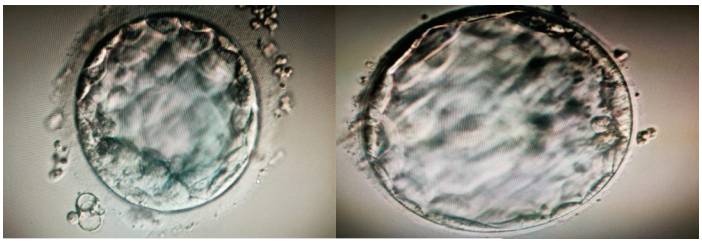
All oocytes were inseminated or injected with sperm using the standard intracytoplasmic sperm injection (ICSI) technique. Fertilization was confirmed by the presence of two pronuclei and extrusion of the second polar body.

A preferable embryo was defined as one that had reached the four-cell stage on day 2, reached the seven-cell stage on day 3, and had less than 20% of its volume filled with fragments and a preferable blastocyst was defined as being in a full blastocyst stage. A pregnancy test was performed two weeks at day 12-14 post transfer. Pregnancy was confirmed when fetal heart activity was detected

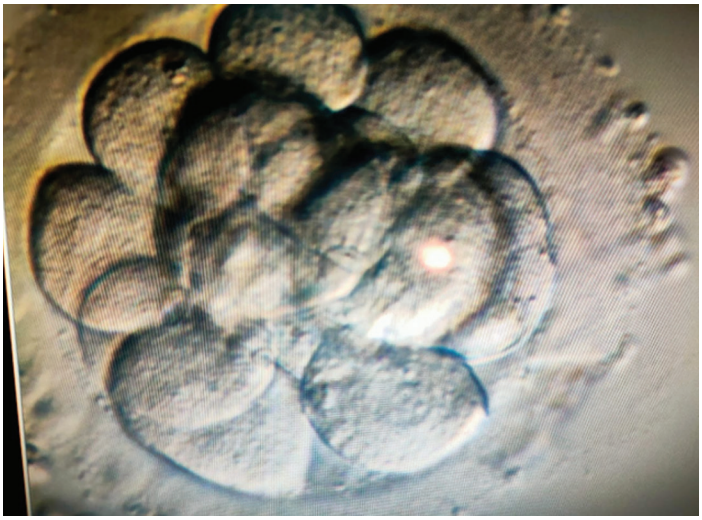
M2 oocyte



Embryos at different stages



Blastocyst embryo



Good quality 16 cells embryo

Patients Follow up

Routine check-up of patients was done with respect to blood pressure, heart rate, weight, complete gestational assessment throughout pregnancy till delivery period.

Warning sign and symptoms are given in a written format for reminding and confirmation that they understandlike vaginal spotting,bleeding, and frequent abdominal pain referred to the back. If any of the warning symptoms were encountered we got an instant feedback by telephony and an emergency visit arranged to assess and treat.

Statistical Analysis

Outcome assessment pertaining to the bleeding/spotting events, need of hospitalization during pregnancy, duration of term pregnancy, any cases of preterm delivery and miscarriages recorded and then by using Fischer's exact test we compared the results of patients prescribed with Vitamin C against the control group of patients. P value less than 0.05 was considered significant.

Result

Out of 200 patients, 100 patients were randomized in the vitamin C group and remaining 100 patients were randomized in the control group and analyzed. There were no significant differences between the two groups at baseline in relation to age, parity and BMI (Table 1).

Table 1: Epidemiological data

variable	Vitamin c group	Control group	P value
age	32(20-40)	31(20-40)	>0.05
BMI(kg/m2)	26 (18-29)	25(18-28)	>0.05
Duration of infertility	4.5	5	>0.05

Table 2: Efficacy related parameters in both study groups.

variable	Vitamin c (cases)group	Control group	P value
Spotting	15	25	0.07
miscarriage	8	20	0.01
Preterm pregnancy	27	35	0.2
Term pregnancy	65	45	0.004

significant difference in result of Term pregnancy was achieved in Vitamin C group, 65 out of 100 women (65%) compared to 45 out of 100 (45%) in the control group with p value 0.004.

A Total of 8 women out of 100 (8%) in vitamin C group compared to 20 from100 in the control group who experienced miscarriage (p Value 0.01) which is statistically significant.

Also, there was no statistically significant difference found in the results of spotting between two groups.

Discussion

In this cohort of women enrolled in a randomized controlled study to evaluate the role of antioxidant for unexplained infertility outcome, we found evidence that increased intake of certain antioxidants as ascorbic acid is associated with higher levels of term pregnancies compared to preterm pregnancy and miscarriages.

It is hypothesized that female antioxidant intake and oxidative stress may influence the timing and maintenance of a viable pregnancy.

Many preliminary studies have also emphasized the importance of Ascorbic acid in luteal formation and regression, but no examination of dietary supplementation during luteal phase has been reported.

Studies have revealed that relatively high bioavailability of vitamin C inside the Graafian follicle and the results obtained from clinical trial suggest a very important role of the vitamin C in follicular genesis, follicular maturation, ovulation and term pregnancy. The efficacy of supplemental use of vitamin C above a level that can be supplied by means of diet alone has been evidently playing beneficial role in reduced spotting and miscarriages [9-11].

Low level of Ascorbic acid disturbs the Follicular Fluid (FF) microenvironment which adversely influences IVF outcome parameters such as oocyte quality, fertilization rate, and high-grade embryos.

Ascorbic acid restores the balance between oxidation and antioxidant action and associated with the maturation of oocytes as shown by the positive correlation between appropriate Reactive oxygen species levels in free fluid and the term pregnancy [12,13].

Low plasma ascorbic acid leads to elevated ROS levels which appear to be responsible for oxidative stress injury, leading to denaturation of oocyte DNA and cytoskeletal damage, an increase of embryonic debris, and abnormal embryonic development. (18-20)

Supplemental Vitamin C maintains balance of the ROS level and antioxidant capacity in the free fluid follicular environment proves to be essential for the acquisition of high-quality oocytes and embryos following IVF treatment [14,15].

Ascorbic acid performs a major biological role; it is required for the biosynthesis of collagen, for the biosynthesis of steroid and peptide hormones, and to prevent or reduce the oxidation of biomolecules.

Ascorbic acid concentrations at the time of oocyte recovery in women undergoing IVF procedures revealing a strong correlation between follicular fluid and serum concentrations of ascorbic acid to facilitate rapid follicular expansion during the approach to ovulation and/or post-ovulatory steroidogenesis[16-17].

In present study supplementation of Ascorbic acid provided important clinical signs in the group of women treated.

A high percentage of term pregnancies were achieved in group A with vitamin c supplementation 65% compared to only 45% in the control group B which received no vitamin c and this could be interpreted as more related to the continuous follow up and regular multivitamin supplementation.

Significantly lower incidence of spotting was observed in women undergoing IVFET with vitamin C supplementation compared to control group. It is suggested that Vitamin C supplementation help in reducing incidence of spotting and bleeding incidences which helps psychologically also to the mothers in early phase of embryo transfer by reducing anxiety and hospitalization.

The present investigation has investigated role of vitamin C supplementation post embryo transfer and its influence on various clinical parameters like term pregnancy, and miscarriages.

Conclusion

Oxidative stress has been identified as major factor adversely affecting outcome of IVF. Vitamin C has been identified as one of the nutrients which help in reducing oxidative stress. Supplementation of large dose of Vitamin C post embryo transfer orally, has shown statistically significant improvement in the outcome of IVF techniques with reduced incidence of spotting and bleeding, reduced hospitalization and miscarriages along with improved term pregnancy.

Conflict of interest: The author has no competing interests to declare.

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Placental thickness and Transcerebellar diameter for accurate estimation of gestational age in the second trimester (A cross sectional study)

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Abstract

Objective: To assess the accuracy of combined measurement of placental thickness and transcerebellar diameter in estimation of fetal gestational age in second trimester.

Patients and Methods: A cross sectional study was conducted at ultrasound unit, department of obstetrics and gynecology, Ain shams University Maternity Hospital in the period between January 2020 and March 2020.The population studied included 161 pregnant ladies at 14 to 26 weeks.Trans-abdominal ultrasound (Samsung H60, Convex Pro = CV1 = 8MHz - probe 4.9 MHz) was used to asses placental thickness and transcerebellar diameter.

Results: Our results showed that there is positive correlation between Placental thickness and gestational age r= 0.44 which is highly significant (P value < 0.001). Also highly statistically significant positive correlation between TCD and G.A (P value < 0.001) r= 0.92. Statistical analysis of our results showed that trans-cerebellar diameter was more accurate than placental thickness for accurate estimation of gestational age with almost perfect agreement (0.91) between gestational age by last menstrual period and gestational age by trans-cerebellar diameter.

Conclusion: Client's aged 32.8 ±3.4. More than half had primary infertility with mean duration of 4.6 ± 2.4. Female factor infertility was the commonest cause of infertility. The pregnancy rate per embryo transfer was 36.4%, miscarriage rate was 9.1%, while the live rate was 27.3%. The mean VAS scores at 1hour, 6 hours, 24 hours and at embryo transfer were 7.1 ± 2.8, 4.6 ±1.4, 2.8 ±1.2 and 1.0 ± 0.9 respectively. The mean Likert score was 2.4 ± 0.9.

Conclusion: Both placental thickness and TCD are useful fetal biometric parameters that can be used for assessment of gestational age. Although placental thickness is positively correlated to G.A, it is not as accurate as TCD. Unfortunately, combined use of placental thickness and TCD is not superior to TCD alone in accurate estimation of gestational age.

Keywords: Ultrasound, placental thickness, transcerebellar diameter,gestational age.

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INTRODUCTION

Determination of gestational age depends onaccurate recall of the last menstrual period with regular rhythm and ultrasound assessment of fetal biometry. Over or under estimation of gestational age may result from inaccurateрecalling of the last menstrual period and the affection of the fetal biometry by multiple factors.(1)

Worldwide the most common used fetal parameters for detection of the gestational age arebiparietal diameter, head circumference, abdominal circumference and femur length. In the first trimester, the ultrasound assessment of gestational age is the most accurate. By the second trimester, ultrasound accuracy is reduced. By the third trimester,ultrasound accuracy becomes markedly reduced. Recently, studies have shown that fetal transcellebellar diameter is the most precise ultrasound parameter for estimation of the gestational age. (2)

The most accurate ultrasound singletool for estimation of gestational age in third trimester is transcerebellar diameter then FL, and then BPD. By combination of a TCD and FL we can know the gestational age in many women with unsure dates.(3)

The efficacy of the placenta to transfer the amount of nutrients, oxygen, and carbon dioxide that passes from the mother to fetus is in direct relation to the surface area of the placenta. By the third trimester, the placental growth is ended while the placental thickness continues to grow until the late third trimester.(4)

Placental thickness is a reliable biometry in the assessment of gestational age in singleton pregnancies is the placental thickness. This is due to the linear association between placental thickness and gestational age. It is measured at the site of cord insertion.(5)The placental thickness measurement is very easy and useful.(6)

The aim of the present study is to detect accuracy of combined measurement of placental thickness and transcerebellar diameter in estimation of fetal gestational age in second trimester of pregnancy.

PATIENTS AND METHODS

This cross sectional study conducted at ultrasound unit, department of obstetrics and gynecology, Ain shams University Maternity Hospital in the period between January 2020 and March 2020.

The population of the study was pregnant ladies aged 18 to 41 years old with confirmed last menstrual period, regular cycles and not used hormonal pills 3 months prior to conception attended outpatient clinics in the second trimester for antenatal care with singleton and low risk pregnancy.

Women who had any disorder affecting the size of the placenta or fetal growth, fetal anomalies, liquor abnormalities and/or abnormal placentation were excluded from our study.

The study included 161 pregnant female who fulfilled inclusion criteria. They were subjected to full detailed history taking. Accurate last menstrual period date was obtained and gestational age was calculated using Neagle's rule or first trimester ultrasound (CRL). General and abdominal examinations were done including fundal level and Leopold's maneuvers. Placental thickness, trans-cerebellar diameter and estimated fetal weight were measured using trans-abdominal ultrasound.

Study procedure:

Detailed history was taken to exclude the previous exclusion criteria in selected cases: Personal history including name, age, occupation and special habits, Present, past history, family history, obstetric history including gravidity, parity, gestational age and menstrual history by Naegele's rule.

Examination:

General examination

Abdominal examination: fundal level and Leopold's maneuvers.

Investigation:

Trans-abdominal ultrasound (Samsung H60, Convex Pro = CV1 = 8MHz - probe 4.9 MHz) was used to asses:

The placental thickness: was measured by placing the ultrasound probe perpendicularly to the placental plane, at the site of the cord insertion. The maximum thickness was measured in the cross section. The placenta was measured to 1 mm precision, at its greatest thickness, which was perpendicular to the uterine wall. Both the uterine wall and retro placental vein were excluded.

Trans-cerebellar diameter: This plane of TCD was at lower level than that of the transventricular plane with posterior tilting. It included the visualization of the frontal horns of the lateral ventricles, CSP, thalami, cerebellum and cisterna magna.

Ethical Considerations: Approval of the ethical committee of the department of obstetrics and gynecology, Faculty of medicine, Ain shams university was obtained. The study was conducted in accordance with the current approved clinical protocol and relevant policies, requirements and regulations of the Ain Shams University Maternity Hospital.

Data analysis:

Analysis of data was done using SPSS program version 23. To describe the studied sample, quantitative data were presented as minimum, maximum, mean and standard deviation. Qualitative data were presented as count and percentage. Pearson correlation test was used to compare correlation between different continuous variables. Linear regression analysis was done to measure predictive ability of TCD and PT for prediction of GA.Intra-class correlation was used to measure agreement between GA by LMP and GA by TCD. P value < 0.05 was considered statistically significant.

RESULTS

Determination of gestational age depends onaccurate recall of the last menstrual period with reg

Table (1): Demographic characteristics among the studied groups

Items			
Age	Mean ± SD	28.66± 5.49	
	Range	19 – 41	
		N	%
Gravidity	PG	48	29.8%
	G2	30	18.6%
	G3	32	19.9%
	G4 or more	51	31.7%

Parity	PG	48	29.8%
	P1	43	26.7%
	P2	34	21.1%
	P3	23	14.3%
	P4 or more	13	8.1%
Mode of previous delivery	NVD	37	32.2%
	CS	78	67.8%
	Total	115	100.0%
Fetal sex	Female	56	46.7%
	Male	64	53.3%
GA in weeks	Mean ± SD	22.09 ± 3.13	
	Range	14 – 28	

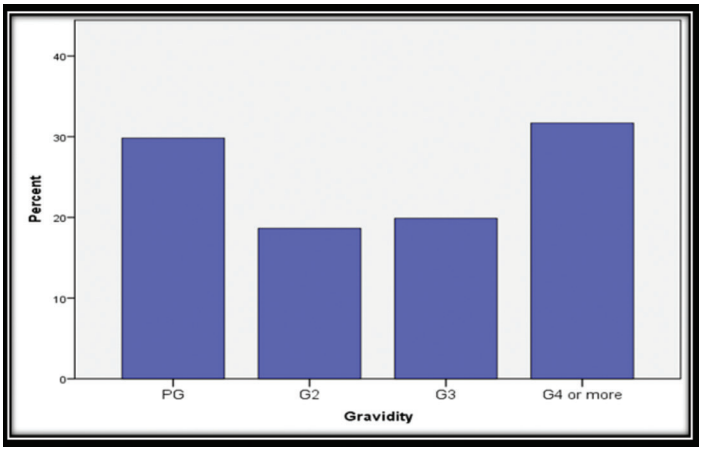

Figure (1): Gravidity

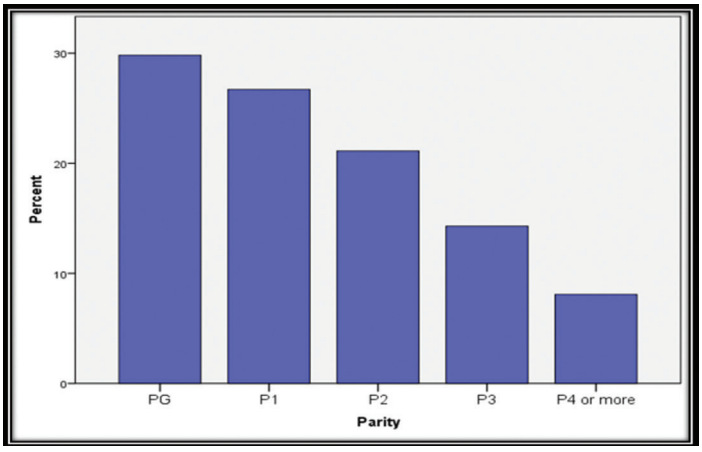

Figure (2): Parity

Table (2): Mean values of PT in relation to gestational age

Items		Placental thickness in mm	
		N	Mean ± SD
GA in weeks	14.00	1	21.00 ±
	15.00	2	22.00± 5.66
	16.00	7	21.43±4.76
	17.00	6	22.67± 5.79
	18.00	8	27.88± 3.60
	19.00	13	23.54± 5.90
	20.00	10	29.60± 5.50
	21.00	13	28.85± 5.26
	22.00	19	29.58± 5.77
	23.00	25	30.72± 4.80
	24.00	16	37.06± 11.12
	25.00	20	31.15± 7.98
	26.00	12	31.25± 6.06
	27.00	7	32.00± 8.83
	28.00	2	41.50± 2.12

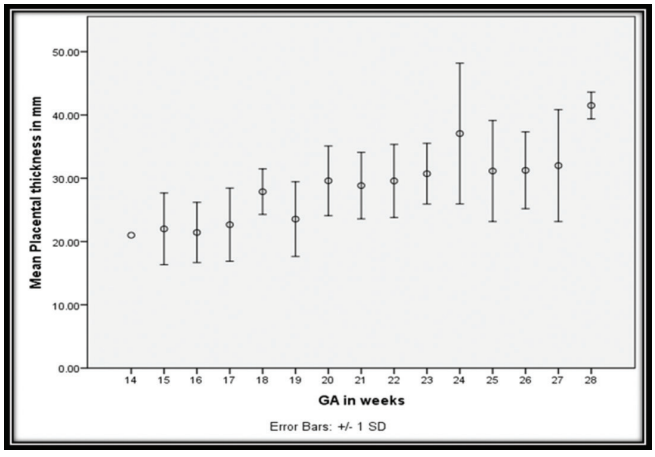

Figure (3): Mean values of PT in relation to gestational age

Table (3): Mean values of TCD in relation to gestational age:

Items		N	Mean ± SD
GA in weeks	14.00	1	13.00 ±
	15.00	2	15.00±1.41
	16.00	7	15.43± 1.13
	17.00	6	16.00± 0.89
	18.00	8	17.88± 1.13
	19.00	13	18.69± 1.55
	20.00	10	21.20± 1.32
	21.00	13	21.62± 1.61
	22.00	19	23.37± 2.41
	23.00	25	24.16± 1.91
	24.00	16	26.00± 1.83
	25.00	20	27.00± 1.69
	26.00	12	27.67± 1.97
	27.00	7	30.71± 1.98
	28.00	2	32.50± 2.12

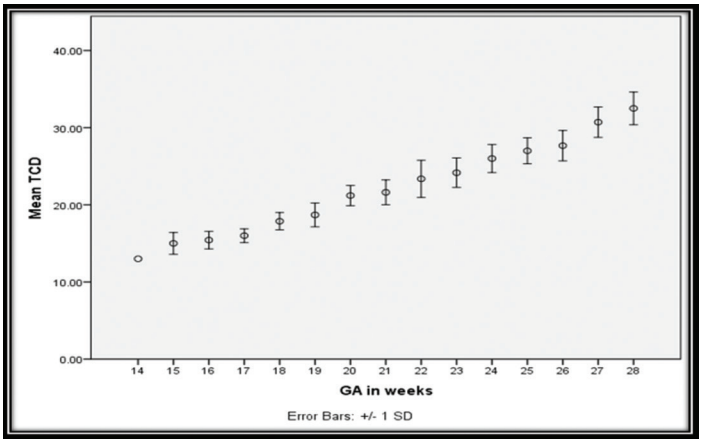

Figure (4): Mean values of TCD in relation to gestational age

Table (4): Correlation between GA and PT:

Items		Placental thickness in mm
GA in weeks	Pearson Correlation	0.44
	P value	<0.001 HS

Table 4 shows there is highly statistically significant positive correlation between Placental thickness and gestational age (P value < 0.001) r= 0.44
Person Correlation Coefficient (r) between (-1 to + 1) correlation coefficient (r) more close to +1 indicates more strength of association.

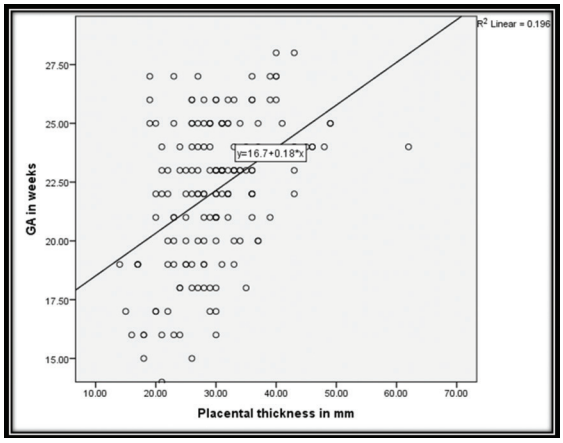

Figure (5): Correlation between GA and PT

Table (5): Correlation between GA and TCD:

Items		TCD
GA in weeks	Pearson Correlation	0.92
	P value	<0.001 HS

Table 5 shows there is highly statistically significant positive correlation between TCD and G.A (P value < 0.001) r= 0.92.
P-value > 0.05: Non significant, P value < 0.05: Significant, P value < 0.001: Highly significant.

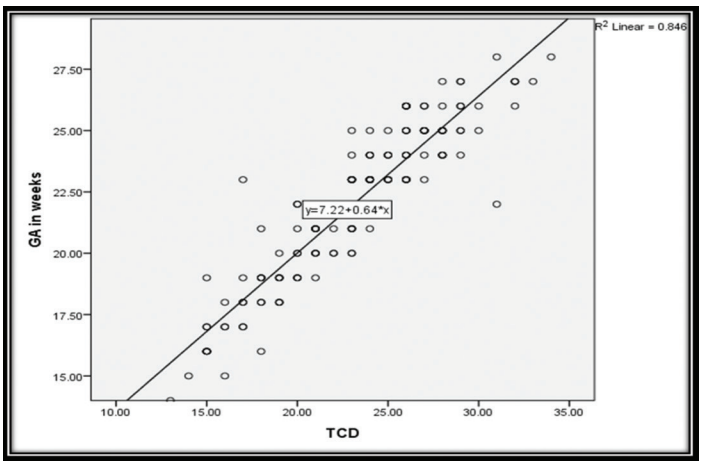

Figure (6): Correlation between GA and TCD

Table (6): Intra-class correlation for agreement between GA by LMP and GA by TCD:

Cronbach's Alpha		N of Items		
0.96		2		
Items		Mean ± SD		
GA by LMP		22.09± 3.13		
GA by TCD		21.71 ±3.16		
Intra-class Correlation	95% Confidence Interval		F Test with True Value 0	
	Lower Bound	Upper Bound	Value	Sig
0.91	0.88	0.93	21.506	<0.001

F-test is a test will null hypothesis that the true value of ICC=0.
Cronbach's alpha tells you how reliably the two methods agree.

ICC tells you how reliable is for you to use GA by TCD to inquire for GA (0-0.2 indicates poor agreement, 0.3-0.4 indicates fair agreement, 0.5-0.6 indicates moderate agreement,0.7-0.8 indicates strong agreement, and >0.8 indicates almost perfect agreement).

Table (7): Linear regression analysis for predictive ability of PT for prediction of GA:

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	16.697	.894		18.677	<0.001	14.932	18.463
Placental thickness in mm	.182	.029	.443	6.224	<0.001	.124	.239

We can predict G.A from PT by The following equation

Equation: GA = 16.697 + (0.182 * PT), Model R^2 = 0.19

Table (8): Linear regression analysis for predictive ability of TCD for prediction of GA:

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	7.223	.512	Model R^2 = 0.85	14.108	<0.001	6.212	8.234
TCD	.640	.022	.920	29.570	<0.001	.597	.682

We can predict G.A from TCD by the following equation.

Equation: GA = 7.223 + (0.64 * TCD), Model R^2 = 0.85

Table (9): Linear regression analysis for predictive ability of combined TCD and PT for prediction of GA:

	Unstandardized Coefficients		Standardized Coefficients	Significance	95.0% Confidence Interval for B	
	B	Std. Error	Beta		Lower Bound	Upper Bound
(Constant)	7.169	.538		<0.001	6.106	8.232
Placental thickness in mm	.005	.015	.012	0.738	-.024	.034
TCD	.636	.025	.914	<0.001	.587	.684

GA = 7.169 + 0.005*PT + 0.636*TCD

Model R^2 = 0.85

DISCUSSION

A crucial step in proper antenatal care is accurate pregnancy dating. Accurate gestational age is vital in managing pregnancy. In many cases it is the key for determination of timing of certain intervention.(6)

Inaccurate pregnancy dating is associated with increased incidence of iatrogenic preterm and posterm deliveries. It is associated with high perinatal morbidity and mortality. In case of uncertain gestational age theclinician is in dilemma searching for best way for accurate dating.The best way for accurate pregnancy dating in absence of sure and reliable last menstrual period is ultrasound(7)

Among the most commonly used parameters in ultrasound for estimation of the gestational age in the second trimester are the Bi Parietal Diameter, Head Circumference, Abdominal Circumference and Femoral Length. A recently added ultrasound parameter is Transverse cerebellar diameter (TCD). (8)

Anatomically the cerebellum liesin the posterior cranial fossa and it is surrounded by the occipital bone. This is a natural protection from any external pressure.This is very important fact that makes TCD the least ultrasound parameter to be affected by external factors.(9)

Another promising ultrasound parameter used for assessment of fetal gestational age is Placental thickness. This is due to the presence of linear relationship between placental thickness and the gestational age . (10)

This is cross sectional study assessed the accuracy of combined measurement of placental thickness and trans-cerebellar diameter in estimation of fetal gestational age in second trimester of pregnancy and the use of these two ultrasound measurements as another method for accurate estimation of gestational age in absence of accurate pregnancy dating.

According to our knowledge, there are no previous studies that evaluate the use of combined measurement of placental thickness and trans-cerebellar diameter for estimation of fetal gestational age (GA) during second trimester.

Our findings have shown that, there is a positive correlation between TCD and GAwhich is highly statistically significant (P value < 0.001) r= 0.92.Linear regression analysis for predictive ability of TCD for detection of GA, We can predict G.A from TCD by The following equation: Equation: GA = 7.223 + (0.64 * TCD), Model R2 = 0.85.

In the current study, we evaluated the role of placental thickness in assessment of gestational age and we found a positive correlation between PT and GAwhich is highly significant (r= 0.44, P value < 0.001).Linear regression analysis for predictive ability of PT for detectionof GA, We can predict G.A from PT by The following equation:

Equation: GA = 16.697 + (0.182 * PT), Model R2 = 0.19.

According to regression analysis, linear regression analysis for predictive ability of combined TCD and PT for prediction of GA

GA = 7.169 + 0.005*PT + 0.636*TC ,Model R2 = 0.85

Statistical analysis of our results showed that trans-cerebellar diameter was more accurate than placental thickness for accurate estimation of gestational age with almost perfect agreement (0.91) between gestational age calculated from last menstrual period and gestational age by trans-cerebellar diameter. Unfortunately, combined use of placental thickness and TCD measurement is not superior to TCD alone in accurate estimation of gestational age.

A prospective case control study by Alalfy et al.assessed the accuracy of the transcerebellar diameterin comparison to other ultrasound parameters in detection of thegestational age with normal and complicated pregnancies. This study concluded that trans-cerebellar diameter, in comparison to other biometric measurements, is the most accurate ultrasound parameter.This is because the growth of cerebellum is not affected by any disorder. [11]

Another prospective pilot study by Reddy et al. evaluated the accuracy of fetaltranscerebellar Diameter (TCD) in prediction of the gestational age in pregnant ladies between 15 to 40 weeks. The study compared between TCD and the other ultrasound parameters. They showed that TCD is the best gestational age predictor. [9]

A prospective cohort study, by Uikeyet al. aimed to assess the degree of accuracy of trans-cerebellar diameter in detection of gestational age. The study included 500 women. Their gestational age ranged from 7 and 11 weeks of gestation. The follow up continued to 40 weeks of gestation. Ultrasound performed once in each trimester. They concluded that, TCD is the most reliable ultrasound parameter in estimation of gestational age. [7]

A prospective cross sectional study, by Nageshet al.included 100 women with normal singleton pregnancies from 15 to 40 weeks. They evaluated the development of fetal cerebellumusing ultrasound and its role in assessment of the fetal gestational age. They showed that TCD was well correlated with gestational age. [8]

An observational cross-sectional study, byNjeze et al supports our findings as regard the correlation between placental thickness and gestational age. They examined the relation between placental diameter and thickness with gestational age in 400 women during the third trimester. They concluded that placental thickness is correlated to the gestational age. [12]

Another study by Pant and Dashottar evaluated the use of placental thickness for detection of the gestational age and the pattern of growth of the placenta. The study included 110 pregnant women from 14 weeks to 40 weeks. They agreed with us and stated that placental thickness corresponds with the gestational age in second trimester and is useful as an additional parameter for gestational age estimation. [13]

Mahaleet al. evaluated the relationship between placental thickness and gestational age. The study included 225 women from 12 to 40 weeks with sure and reliable LMP. Pregnancy dating was confirmed by first trimester ultrasound. When comparing theplacental thickness with the gestational age, a coefficient of correlation (r) = 0.972 was obtained which was statistically significant [$p < 0.001$]. [14]

CONCLUSION

Both placental thickness and TCD are useful fetal biometric parameters that can be used for assessment of gestational age. Although placental thickness is positively correlated to G.A, it is not as accurate as TCD. Unfortunately, combined use of placental thickness and TCD is not superior to TCD alone in accurate estimation of gestational age.

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Intra-umbilical Oxytocin versus Methyl Ergometrine in the Third Stage of Labor: A Comparative Study from an Egyptian Tertiary Care Hospital

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Abstract

Recently, the active management of the third stage of labor has become a routine practice. In this study we compared two different ecobolics which were oxytocin and methyl ergometrine through intra-umbilical route. The method: the trial divided the included pregnant full term (>37 weeks) women in two groups randomly; one for 0.2 mg methyl ergometrine and the second 10 units oxytocin. The outcomes were on the short term; estimated blood loss (EBL), the need to add another ecobolic, vomiting, blood pressure changes and the duration of the third stage, and the long-term outcomes were hemoglobin levels and the need for surgical or medical uterine evacuation. The results: the mean blood loss was 155± 50.45ml and 167± 45.76 in the methyl ergometrine and the oxytocin groups respectively. Three cases in the oxytocin group (3%) required additional methyl ergometrine while in the ergometrine group only one case was given an additional oxytocin (1%). No vomiting was reported in both groups and there were trivial changes in blood pressure. In the oxytocin group, the third stage duration was average 3.03± 1.02 min in comparison to 2.98± 1.54min in the ergometrine group. Neither did those cases who were injected methyl ergometrine have significant changes in the hemoglobin levels nor did they need uterine evacuation. However, only one case in the oxytocin side required blood transfusion due to uterine atony. Conclusion: intra-umbilical methyl ergometrine should be considered as an effective safe ecobolic in the third stage of labor.

Keywords: Third stage, ecobolics, postpartum hemorrhage, intra-umbilical, oxytocin, ergometrine.

Introduction

Postpartum hemorrhage

MBRRACE (mother and baby reducing risks through audit and confidential enquiries) declared that there is a potentially concerning, although non-significant, 99% increase in maternal deaths from hemorrhage (95% CI 4% decrease–392% increase). [1] This is due to a small increase in the number of deaths of women with abnormal placentation. Consequently, it is imperative that there should be a definitive protocol for early recognition and prevention of the consequences of third stage abnormalities. [2]

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Third stage of labour

Placental delivery in the third stage of labor has three successive steps; (1) placental separation as a result of discordant surface of attached placenta to contracting uterine surface, (2) placental descent owing to uterine contraction and (3) finally placental expulsion and bleeding bed controlled by contracting uterus. That means myometrial contractions leads to effective uterine contractions to deliver the placenta and stop bleeding. In other words, active management is a valid prophylactic intervention to prevent third stage complications for example; postpartum hemorrhage or retained placenta. [3] It is conceivable that an ideal ecobolic should have a dual action; contract the uterus to deliver the placenta and stop the bleeding.

According to the recommendations in NICE (national institute of clinical excellence in the UK) for intrapartum care 2014 updated 2017 that third stage is the period after delivery of the baby and before delivery of the placenta that should be no more than 30 minutes in case of active management and 60 minutes if passive management was used. In order to prevent the risks of bleeding and the need for blood transfusion active management is offered to shorten the third stage and to avoid these side effects of passive management where no ecobolics use, no controlled cord traction and delivery of the placenta by maternal effort. 4 Although benefits of active management by oxytocin 10 IU intramuscularly, deferring cord clamping followed by controlled cord traction (CCT) outweighs its side effects of nausea and vomiting, woman wish not to actively managed her third stage should be respected especially in low risk cases. However, she should be offered all the information she needs about both methods and the increase risk of bleeding and retained placenta and membranes in the passive method. [4]

From a comparison point of view, it is noted that ergometrine is considered as a versatile uterotonic in third stage causing sustained uterine contractions but it also acts on all smooth muscles in the body particularly intestinal muscles. Consequently, the reported nausea and vomiting after ecobolics in third stage were apparently related to ergometrine use and not with oxytocin which works only on uterine muscles.3 Moreover, a growing body of research recommends avoiding the use of ergometrine in hypertensive patients or vascular diseases (migraine, Raynaud's). [5]

Research Hypothesis

Two questions were asked; what the difference would be if injected locally intra-umbilical and what is the mechanism behind the possible reduced mean blood loss and duration of the third stage of labor with the use of intra-umbilical vein injection of oxytocin or ergometrine?

This may be due to the fact that an ecobolic agent injected into the umbilical vein reaches the placental bed in relatively high concentrations. This stimulates uterine contractions, thus decreasing the area of the placental attachment site. The resulting tension causes the decidua spongiosa to give way with the formation of a hematoma. This accelerates the process of placental separation and expulsion, thus resulting in a shorter duration of the third stage of labor and a smaller amount of blood loss

Materials and method

Type of study: randomized prospective comparative study was conducted between January 2019-January 2020

Population: 200 women who delivered vaginally in labour ward at Mansoura University hospital after thorough history and detailed examination. Labor in all recruited women was spontaneous with no induction or augmentation during labor. Management of third stage was active and no passive management included.

Inclusion criteria: women aged 25 to 35 were included in this study their blood groups were Rh +, parity two or less, body mass index (BMI) less than 30, and singleton pregnancy with cephalic presentation.

Exclusion criteria: no risk factor for bleeding; no previous history of bleeding or blood transfusion, no medical comorbidities; hypertension or diabetes, no prolonged labor, no fever, no premature rupture of membrane history.g

Ethical Considerations

Institutional Ethics Committee approval was obtained. Consent was obtained from women who participated in the sample. They were reassured about the confidentiality of the information. They were informed about their rights to refuse participation or withdraw at any time. The study maneuvers couldn't entail any harm to participation.

The study groups: Group 1 included women who received methyl- ergometrine 0.2 mg in 10 ml saline slow intra-umbilical injection over one minute after delivery of the baby. Group 2 was for women who received injection Oxytocin 10 IU in 10 ml saline within one minute after delivery of the baby. Injection was done through neonatal aspiration catheter along the umbilical vein. The Catheter was hold in place by finger pressure all around to prevent back flow. Then milking of the cord towards the placenta was carried out.

The delivery was conducted with the patient at the edge of the table and 10 IU of injection Oxytocin intramuscular were given at the delivery of anterior shoulder of the baby according to NICE recommendation. Once the baby is delivered, apex of the episiotomy was sutured. Placenta is delivered by controlled cord traction and time taken for placental separation was noted with a stopwatch. Controlled cord traction was done by clamping the cord close to the perineum and held in one hand, the other hand is placed above the pubic symphysis and the uterus is stabilized by applying counter pressure. Slight tension is kept on the cord awaiting a strong uterine contraction (2 - 3 min). During the third stage, blood loss for one-hour duration was collected in a clean dry container fixed to the tail end of the delivery table and then measured in a graduated jar. [6]

The outcomes were on the short term; estimated blood loss EBL, the need to add another ecobolic, vomiting, blood pressure changes and the duration of the third stage, and the long-term outcomes were hemoglobin levels and the need for surgical/medical uterine evacuation or blood transfusion.

Analysis

Tools of data collection: One tool was used for data collection.

A Structured Interviewing Questionnaire Schedule: It was designed by the researchers after reviewing related literatures. It consisted of:

Part I: to assess general and obstetrics characteristics including age, parity, gestational age, level of education.

Part II: to assess duration of placental delivery and need for manual delivery of placenta, side effects of ecobolics used and measurement of the amount of blood loss through collection of blood in calibrated container. Complete blood count to assess hemoglobin level before and 6 hours after labor.

Results

There were no significant differences in the studied demographic characteristics; age, parity, BMI, gestational age in weeks, and hemoglobin level at delivery and neonatal birth weight.

Table 1: Shows women demographic criteria and baseline data.

	Group 1 ergometrine (n. 100)	Group2 oxytocin (n. 100)	P value
Age	26.92± 2.55	25.19± 3.02	0.604
Parity **Primigravida** **Para 2**	 **55 (55%)** **45 (45%)**	 **58 (58%)** **42 (42%)**	0.726
BMI (BODY MASS INDEX) at booking	26.45± 3.55	26.19±4.06	0.590
Hemoglobin level before delivery	10.85±1.34	10.65± 1.89	0.223
Gestational age in weeks at delivery	39.87±0.67	38.84±0.39	0.213
Neonatal birth weight	3.21±0.43	2.99±0.55	0.059

Estimated blood loss (EBL), the need to add another ecobolic, vomiting, blood pressure changes and the duration of the third stage as short-term outcomes demonstrated no statically significant difference among the two studied groups.

Table 2: Illustrates the short-term outcomes

	Group 1 ergometrine (n. 100)	Group2 oxytocin (n. 100)	P value
Duration of third stage	2.98± 1.54	3.03± 1.02	0.304
Blood pressure Systolic **Before delivery** **After delivery** **Diastolic** **Before delivery** **After delivery**	 125.76±5.13 125.54±5.45 75.30±4.90 76.60±4.89	 124.96±6.95 123.54±7.85 77.10±3.60 74.05±2.97	0.476 0.396
EBL	155± 50.45	167± 45.76	0.456
Vomiting	0	0	
Need for secondary ecobolic	1 (1%)	3(3%)	0.281

In regard of long-term outcomes; hemoglobin levels and the need for surgical/medical uterine evacuation or blood transfusion were not different significantly (P value < 0.05)

Table 3: Delineates the long-term outcomes

	Group 1 ergometrine (n. 100)	Group2 oxytocin (n. 100)	P value
Hemoglobin level	9.98±1.54	9.83±1.32	0.205
Uterine evacuation **Medical** **Surgical**	 0 0	 0 0	
Blood transfusion	1	2	0.284

DISCUSSION

Labor is critical time in a woman life. One of the most leading causes for maternal mortality in developing countries is bleeding in the 3rd stage. Various uterotonics used in active management of third stage of labor like oxytocin, methyl ergometrine and prostaglandins. 7 Despite of the powerful effect of ergometrine as an ecobolic, it has gastrointestinal side effects. [8]

In this prospective randomized trial, we compared different route of administration; intra-umbilical for both ergometrine and oxytocin to overcome these systemic side effects. Recently, oxytocin has been recomended as the ecobolic of choice in active management of third stage. Consequently, the rate of postpartum hemorrhage has been found to decrease owing to the implementation of this protocol in practice. However, the use of oxytocin may not be superior to ergometrine particularly in a case of atonic postpartum hemorrhage. There are uncertainties about type, dose, route of administration of ecobolic drugs that provide the better safety profile and efficacy. [9]

A randomized study in 2008 reported less blood loss in ergometrine group than oxytocin when administered intravenously after delivery of anterior shoulder; 149.33±145.47and 196.57±192.30 respectively. P=0.003. 10 Using the intra-umbilical route in our study had no difference between the two agents in amount of blood loss; 155± 50.45 for ergometrine group and 167± 45.76 for oxytocin group. p=0.456

Orji, E et al 2008, 6.9% of women had retained placenta in ergometrine group and 4.1% in oxytocin group but no retained placenta in our study. There were three cases that needed further ecobolic doses in the oxytocin group versus one case extra-dose in the ergometrine group. [10]

A running clinical trial in the UK (IMox) investigates three different ecobolics via intra-muscular route. [11] In this study, we changed the route to be intra-umbilical to avoid the generalized smooth muscle effect of ergometrine in order to compete with other ecobolics. The proposed route had been used with oxytocin in retained placenta management but technical obstacles prevented the routine use. [12] Herein study, the method adopted from Pipingas etal 1993.[13] It was a trial and error experience that can be adapted according to the local protocols and facilities.

Limitation of the study was the small sample size and restricted options. In other words, the next study would aim to include more groups with variable ecobolics; for example: Carbetocin or Syntometrine to extend the options available.

Conclusion

In this study, the results agree with previous data that both oxytocin and ergometrine proved to be effective in preventing postpartum hemorrhage. These agents have been used in various doses and routes with variable success. This study showed that intra-umbilical route is viable option that should be considered.

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