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# Determining the effect of Magnesium Sulfate on Doppler Parameters of Fetal Umbilical and Middle Cerebral Arteries in Women with Severe Preeclampsia: A Prospective Study

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Preeclampsia is best described as a pregnancy-specific syndrome that can affect every organ system. Although preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important objective diagnostic criterion. The aim of this study is to evaluate Doppler velocimetric parameters (resistance index [RI], pulsatility index [PI], and systolic/diastolic [S/D] ratio) of the umbilical and middle cerebral arteries before and after magnesium sulfate administration in pregnant women with severe preeclampsia.
**Methods:** This prospective study had been included 25 women from the emergency department and Obstetrics outpatient clinic Tanta University. Resistance index [RI], pulsatility index [PI] and systolic/ diastolic [S/D] ratio of middle cerebral artery and umbilical artery before and 20 minutes after intravenous administration of 6 grams of magnesium sulfate (loading dose).
**Results:** The maternal age of cases included in the study ranged between 18 year and 40 year with a mean age of 32.03±6.1. The gravidity of cases included in the study ranged between 1 and 5 with a mean of 2.01±1.03.The parity of cases included in the study ranged between 0 and 6 with

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a mean of 2.18±1.04.The number of abortions ranged between 0 and 3whith a mean of 0.61±0.03. The serum level of ALT ranged between 11 and 104 mEq/L with a mean of 49.12±27.81. The serum level of AST ranged between 13 and 84 mEq/L with a mean of 42.5±20.17. The resistance index (RI) before MgSo4 administration ranged between 0.45 and 1.0 with a mean of 0.65 ± 0.15while it ranged between 0.4 and 0.9 after MgSo4 administration with a mean of 0.63± 0.13 .There was statistical significant differences between them ($p<0.001$). The pulsatility index (PI) before MgSo4 administration ranged between 0.6 and 2.15 with a mean of 1.15±0.45 while it ranged between 0.5 and 0.2 after MgSo4 administration with a mean of 1.04± 0.45 .There was statistical significant differences between them ($p<0.001$) .

**Conclusions:** Infusion of MgSO4 significantly decreases the fetal RI-umbilical and PI-MCA and increases C/U ratio indices obtained with color Doppler ultrasound evaluations.

*Keywords: Magnesium sulfate; Doppler; fetal umbilical; middle cerebral arteries.*

## 1. INTRODUCTION

Preeclampsia is best described as a pregnancy-specific syndrome that can affect every organ system. Although preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important objective diagnostic criterion [1,2].

Although preeclampsia affects about 1–2% of pregnancies in some European countries, its prevalence reaches up to 10–15% in some South American and African countries [3].

Indicators of severity of gestational hypertensive disorder including the presence of one or more of the following criteria: diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥160 mmHg, proteinuria ≥3+, headache, visual disturbances, upper abdominal pain, oliguria, elevated serum creatinine, thrombocytopenia, marked elevation of serum transaminase, obvious fetal growth restriction or pulmonary edema [1,4].

Preeclampsia as a two-stage disorder, stage 1 is caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome [3,4].

As a result of impaired utero-placental blood flow, manifestations of preeclampsia may be seen in fetal placental unit. These include intra uterine growth restriction (IUGR), oligohydraminos, placental abruption, and non-reassuring fetal status found on ante-partum surveillance by Doppler ultrasound [5].

High flow resistance in the capillaries of terminal villi leads to a low end-diastolic velocity in the umbilical artery and a subsequent hypoxia [6].

The aim of this study is to evaluate Doppler velocimetric parameters (resistance index [RI], pulsatility index [PI], and systolic/diastolic [S/D] ratio) of the umbilical and middle cerebral arteries before and after magnesium sulfate administration in pregnant women with severe preeclampsia.

## 2. PATIENTS AND METHODS

This prospective study had been included 25 women from the emergency department and Obstetrics outpatient clinic Tanta University.

They had been all diagnosed as severe preeclampsia by the following criteria:

Sustained systolic blood pressure of ≥160 mmHg or a sustained diastolic blood pressure of ≥110 mmHg, Proteinuria measured as +3 or more dipstick or 24 hours urine collection with ≥3 g, Oliguria or creatinine>1.2 mg%.

### 2.1 Inclusion Criteria

1) Gestational age ≥28 weeks.
2) Diagnosed as severe preeclampsia by the following criteria: (Sustained systolic blood pressure of ≥160 mmHg or a sustained diastolic blood pressure of ≥110 mmHg, Proteinuria measured as +3 or more dipstick or 24 hours urine collection with ≥3 g, Oliguria or creatinine>1.2 mg%.).
3) Patients not in labor.
4) Singleton pregnancy.

### 2.2 Exclusion Criteria

1) Fetal anomalies.
2) Any maternal chronic diseases esp. diabetes mellitus, renal disease, epilepsy ,CNS lesion and autoimmune disorders.

3) Patients receiving antiplatelet drugs eg.low dose aspirin, or Patients receiving antico agulants eg. heparine (unfractionated or low molecular weight). All participants will be counseled and sign a written informed consent.
4) HELLP syndromemm (Headache, Nausea/vomiting/indigestion with pain after eating, Abdominal or chest tenderness and upper right upper side pain (from liver distention), Shoulder pain or pain when breathing deeply, Bleeding, Changes in vision, Swelling, hemolysis, which is the breaking down of red blood cells, elevated liver enzymes and low platelet count)

## 2.3 Examination

A. General examination

1) Evaluation of vital signs,
2) Measurement weight, height (BMI)

B. Abdominal and local clinical examination:

- To assess fundal level and gestational age
- Scar of previous operation,
- Mass, tenderness or rigidity,
- Any abdominal or pelvic clinically detectable pathology.

The UA color Doppler waveforms

Were obtained from a free floating portion of the umbilical cord during minimal fetal activity and the absence of fetal breathing.

All measurements were performed in the semi recumbent positions with the head and chest slightly elevated.

For measurement of the MCA,
An axial view of the fetal head was obtained at the level of cerebral peduncles,
Then the color Doppler was used to visualize the circle of Willis, and Doppler sample volume was placed within 1 cm of the origin of the MCA that was easily identified as a major branch running anterolateral from the circle of Willis toward to the lateral edge of the orbit.

Doppler studies: Resistance index [RI], pulsatility index [PI] and systolic/ diastolic [S/D] ratio of middle cerebral artery and umbilical artery before and 20 minutes after intravenous administration of 6 grams of magnesium sulfate (loading dose).

## 2.4 Statistical Analysis

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The criteria used for sample size calculation (n>33) were 95% confidence limit, 80% power of the study, expected outcome in in treatment group 90% compared to 60% for control groups.

Analysis of data were performed by SPSS v25 (SPSS Inc., Chicago, IL, USA). Quantitative parametric variables (e.g. age) were presented as mean and standard deviation (SD). They were compared between the two groups by unpaired student's t- test and within the same group by paired T test. Quantitative non-parametric variables (e.g. VAS) were presented as median and range and compared between the two groups by Mann Whitney (U) test and within the same group by Wilcoxon test. P value < 0.05 was considered significant.

## 3. RESULTS

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Age, BMI and duration of infertility). Significance defined by $p < 0.05$.

Table 1 showed that, there was no significant difference between both studied groups as regard to patients characteristics as age, BMI and duration of infertility (P = 0.348, 0.165, and 0 .942).

Mann-Whitney U test was used to compare quantitative data which are not normally distributed (FSH and LH). Student t test was used for the quantitative data which are normally distributed (Prolactin and TSH), Significance defined by $p < 0.05$.

Table 2 showed that, there was no significant difference between both studied groups as regard to serum FSH, LH, Prolactin and TSH level (P = 0.147, 0.311, 0.651 and 0.505).

Chi-square analysis was used for the categorical variable (number of MGF). Mann-Whitney U test was used to compare quantitative data because it is not normally distributed (Size of larger follicle and Endometrial thickness), *Significance defined by $p < 0.05$.

Table 3 showed that, there was significant relation as regard to number of MGF between both studied groups (P = 0.002) as follow; for stair step group there was 4 (13%) versus 16 (53%) in combined group showed no ovulation, 15 (50%) in stair step group versus 11 (37%) in combined group showed one MGF and 11 (37%) in stair step group versus 3 (10%) showed two MGF.

There was no significant relation as regard to the mean size of larger follicle (mm) between both studied groups (P = 0.517) for stair step group was 21.69 ± 1.49 and ranged from 18 to 23 mm while in combined group it was 21.07 ± 2.19 and ranged from 18 to 24 mm.

There was significant relation as regard to endometrial thickness between both studied groups, (P < 0.001); as in stair step group it was 9.67 ± 1.29 and ranged from 8 to 12 mm while in combined group it was 11.47 ± 0.83 and ranged from 10 to 13 mm.

Chi-square analysis was used for the categorical variables (Ovulation rate and Pregnancy rate). Significance defined by p < 0.05. Fig. (1)

Table 4 showed that, there was a statistically significant relation as regards to the ovulation rate in both studied groups (P = 0.001)as it represent 26 (87%) in stair step group versus 14 (47%) in combined group with, Meanwhile there was no statistically significant difference between both studied groups (P = 1) as regards to the pregnancy rate.

Mann-Whitney U test was used to compare quantitative data which are not normally distributed (FSH and LH). Student t test was used for the quantitative data which are normally distributed (Prolactin and TSH), Significance defined by p < 0.05.

Table 5 showed that, there was no statistically significant relation between the hormonal profile and the ovulation status as regard to serum FSH, LH, Prolactin and TSH level (P = 0.976, 0.123, 0.940 and 0.273).

Student t test was used to compare normally distributed quantitative data (FSH, LH, Prolactin and TSH), Significance defined by p < 0.05.

Fig. 2-4 showed that, in Clomiphene and Gonadotropin group (n=30), there was no significant difference in the hormonal profile according to the ovulation status as regard to serum FSH, LH, Prolactin and TSH level (P = 0.398, 0.648, 0.727 and 0.803).

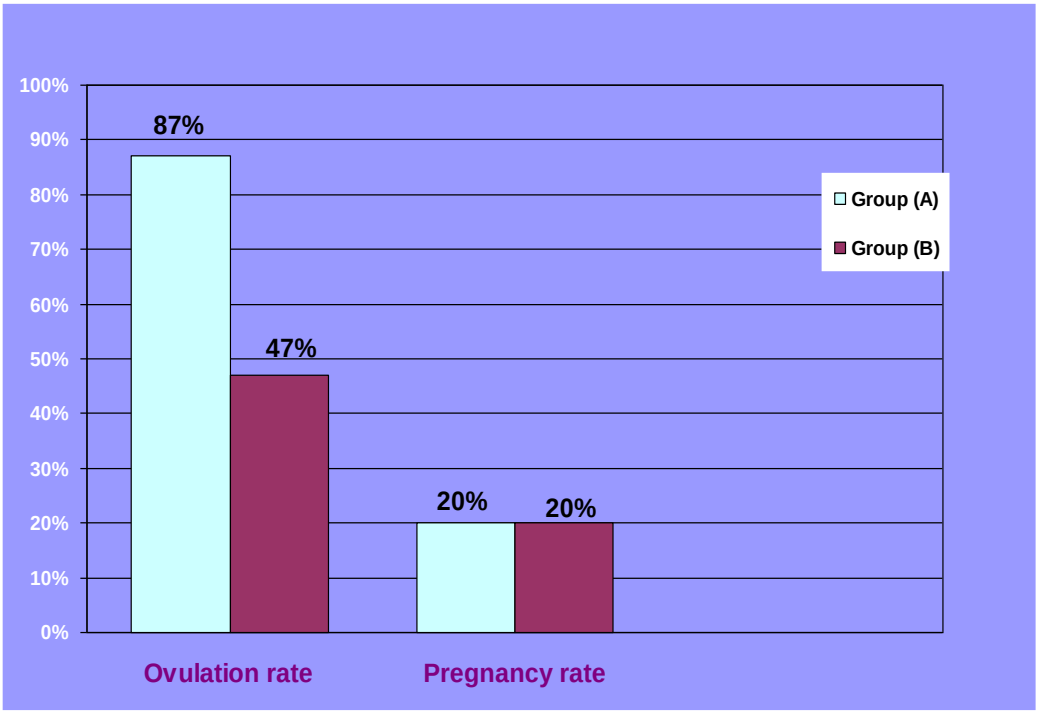


**Fig. 1. Showing the difference between both studied groups as regard to the ovulation and pregnancy rate**

**Table 1. Patients characteristics of the studied groups**

| Variable name | | Stair-Step (n = 30) | Clomiphene and Gonadotropin (n = 30) | P value |
|---|---|---|---|---|
| Age (y) | Mean ± SD | 26.00 ± 3.26 | 26.70 ± 3.18 | 0.348 |
| | Median (range) | 25 (22 – 33) | 26 (22 – 33) | |
| BMI (kg/m$^2$) | Mean ± SD | 25.51 ± 1.37 | 26.08 ± 1.27 | 0.165 |
| | Median (range) | 25.6 (23.4 – 27.8) | 25.8 (24.2 – 29.1) | |
| Duration of infertility | Mean ± SD | 2.60 ± 0.80 | 2.58 ± 0.72 | 0.942 |
| (y) | Median (range) | 2 (1.5 – 4) | 2 (2 – 4) | |

*BMI, body mass index;Data are presented as mean ± SD and median (range)*

**Table 2. Hormonal profile of the studied cases**

| Variable name | | Stair-Step (n = 30) | Clomiphene and Gonadotropin (n = 30) | P value |
|---|---|---|---|---|
| FSH | Mean ± SD | 5.55 ± 1.96 | 6.33 ± 1.53 | 0.147 |
| | Median (range) | 6.3 (2.4–8.5) | 6.6 (3.2–9.2) | |
| LH | Mean ± SD | 12.70 ± 4.67 | 13.11 ± 3.26 | 0.311 |
| | Median (range) | 11.1 (5.6–23.1) | 12.5 (9.2–20.1) | |
| Prolactin | Mean ± SD | 19.59 ± 6.51 | 20.28 ± 5.09 | 0.651 |
| | Median (range) | 19.5 (8.6–35.6) | 20.6 (9.8–28.5) | |
| TSH | Mean ± SD | 2.02 ± 0.74 | 1.91 ± 0.57 | 0.505 |
| | Median (range) | 2.2 (0.8–3.5) | 2.1 (0.7–3.1) | |

*FSH, follicular stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone; Data are presented as mean ± SD and median (range)*

**Table 3. Number of MGF & its diameter and endometrial thickness of the studied groups**

| Variable name | | Stair-Step (n = 30) | Clomiphene and Gonadotropin (n = 30) | P value |
|---|---|---|---|---|
| Number of MGF | 0 N (%) | 4 (13.3) | 16 (53.3) | |
| | 1 N (%) | 15 (50.0) | 11 (36.7) | 0.002* |
| | 2 N (%) | 11 (36.7) | 3 (10.0) | |
| Diameter of larger | Mean ± SD | 21.69 ± 1.49 | 21.07 ± 2.19 | 0.517 |
| follicle (mm) | Median (range) | 22 (18–23) | 22 (18–24) | |
| Endometrial thickness | Mean ± SD | 9.67 ± 1.29 | 11.47 ± 0.83 | < 0.001* |
| | Median (range) | 10 (8.0–11.5) | 11.5 (10.0–12.5) | |

*MGF, Mature graffian follicle; Data are presented as mean ± SD and median (range) or number (%)*

**Table 4. Ovulation and pregnancy rate of the studied cases**

| Variable name | Stair-Step (n = 30) | Clomiphene and Gonadotropin (n = 30) | P value |
|---|---|---|---|
| Ovulation rate | 26 (86.7) | 14 (46.7) | 0.001* |
| Pregnancy rate | 6 (20.0) | 6 (20.0) | 1 |

*Data are presented as n (%)*

**Table 5. Correlations between the hormonal profile and the ovulation status in Stair-Step group (n=30)**

| | | Ovulation | | |
|---|---|---|---|---|
| **Variable name** | | **No (n = 4)** | **Yes (n = 26)** | **P value** |
| FSH | Mean ± SD | 5.64 ± 2.26 | 5.54 ± 1.96 | 0.976 |
| | Median (range) | 5.12 (3.8–8.5) | 6.3 (2.4–8.1) | |
| LH | Mean ± SD | 9.67 ± 3.47 | 13.17 ± 4.70 | 0.123 |
| | Median (range) | 8.9 (6.4–14.5) | 12.0 (5.6–23.1) | |
| Prolactin | Mean ± SD | 19.83 ± 4.65 | 19.55 ± 6.82 | 0.940 |
| | Median (range) | 18.2 (16.5–26.5) | 20.1 (8.6–35.6) | |
| TSH | Mean ± SD | 2.39 ± 0.85 | 1.96 ± 0.72 | 0.273 |
| | Median (range) | 2.4 (1.4–3.5) | 2.1 (0.8–3.2) | |

*FSH, follicular stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone;Data are presented as mean ± SD and median (range).*

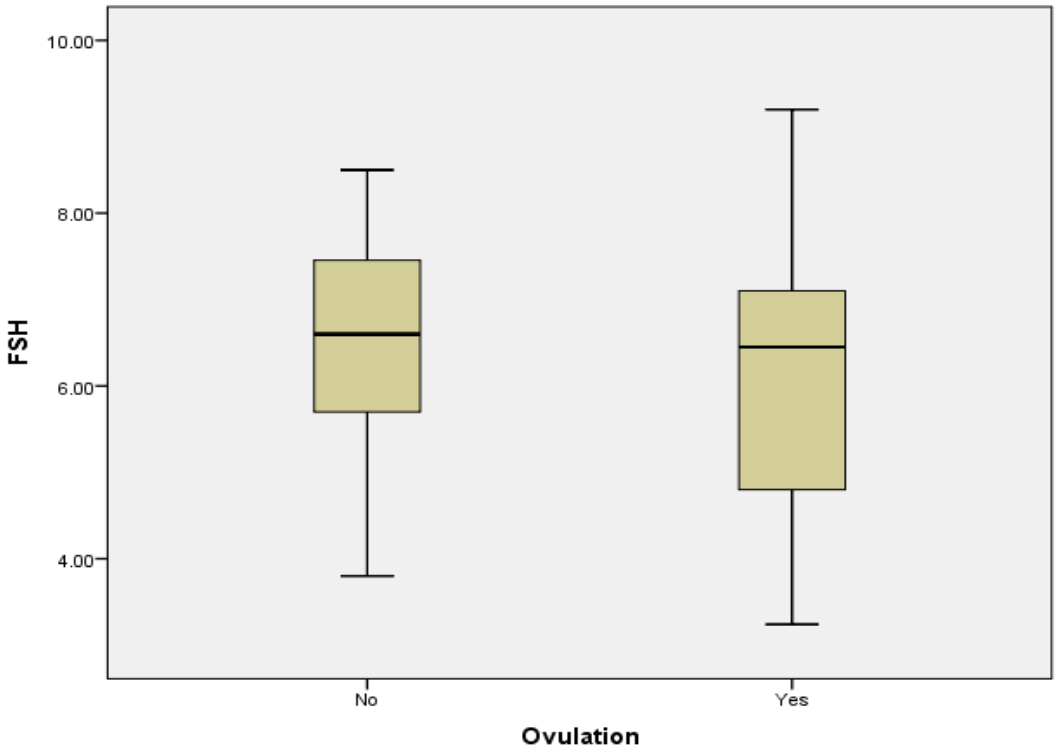


**Fig. 2. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum FSH**

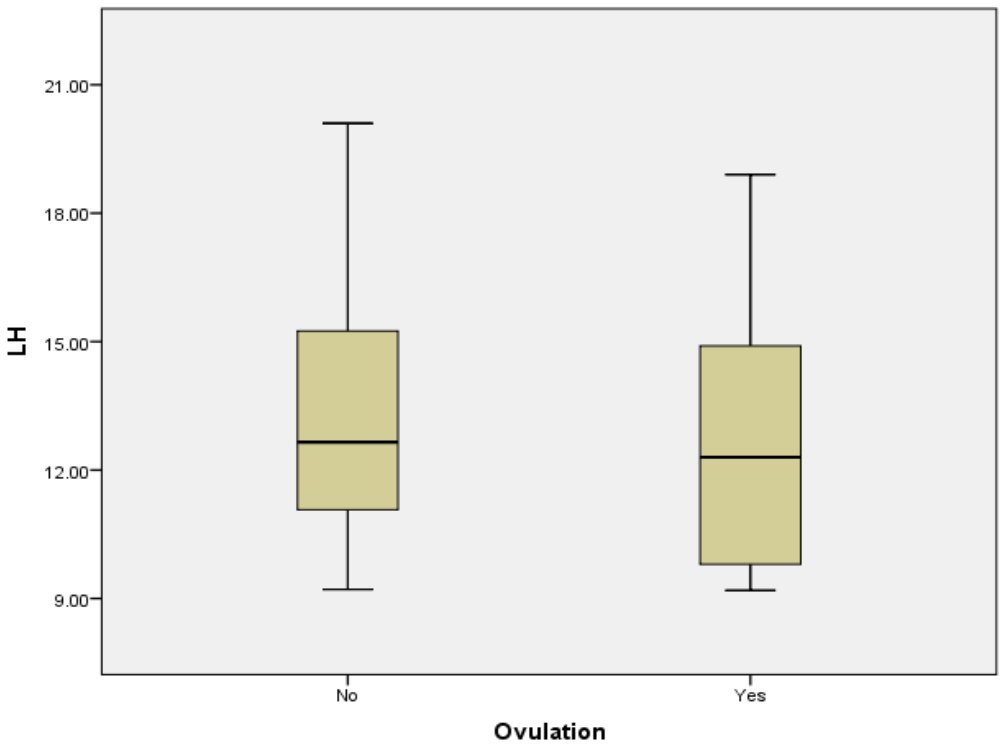


**Fig. 3. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum LH**

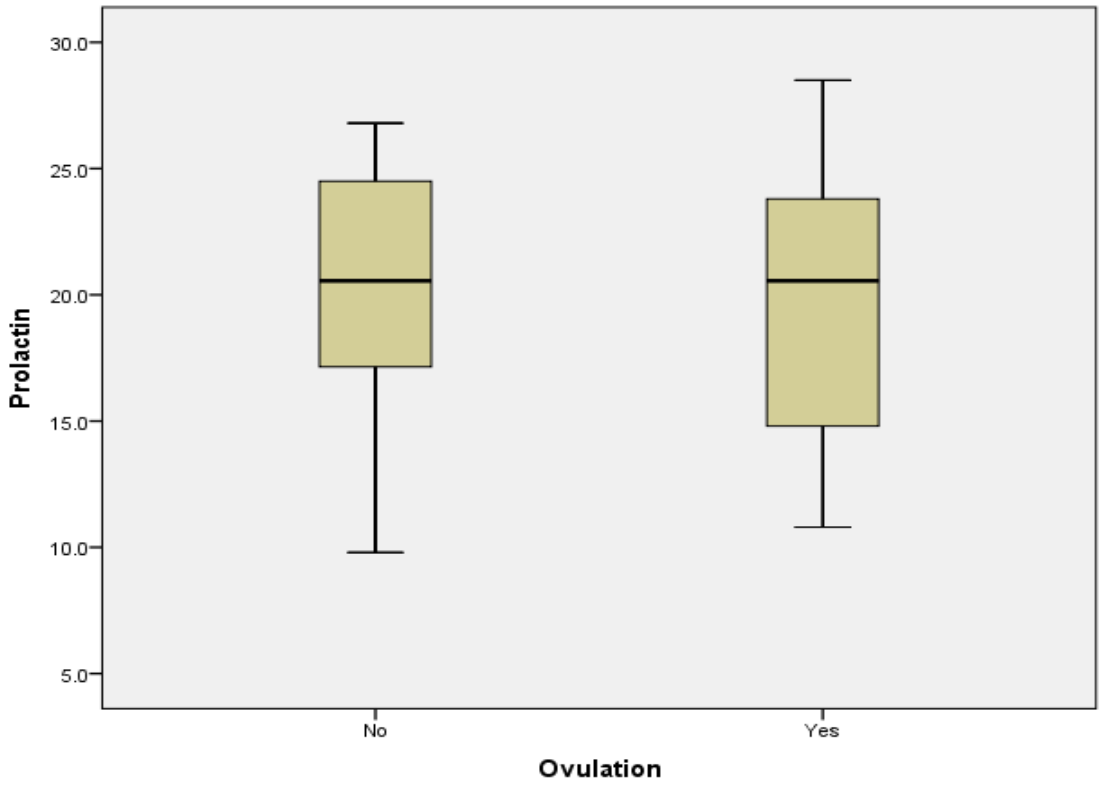


**Fig. 4. Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the serum prolactin**

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Table 6 showed that, there was no statistically significant relationship as regards to the endometrial thickness between women who showed no ovulation while in women who showed ovulation (P = 0.105) in stair step group (n=30), with the mean of endometrial thickness was 8.50 ± 0.71 and ranged from 8 to 10 mm in women who showed no ovulation while in women who showed ovulation it was 9.67 ± 1.29 and ranged from 8 to 12 mm.

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Fig. 5 showed that, in Clomiphene and Gonadotropin group (n=30), the mean of endometrial thickness was 11.47 ± 0.62 and ranged from 10.5 to 12.5 mm in women who showed no ovulation while in women who showed ovulation it was 11.43 ± 0.85 and ranged from 10 to 12.5 mm with no statistically significant difference between both studied groups (P = 0.949).

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Table 7 showed that, there was a highly significant relation between endometrial thickness and pregnancy rate in stair step group (n=30), women with mean endometrial thickness of 9.13 ± 1.13 and ranged from 8 to 11 mm have not got pregnant while those with endometrial thickness of 11.08 ± 0.20 and ranged from 11 to 12 mm have got pregnant (P < 0.001).

Mann-Whitney U test was used to compare quantitative data because it is not normally distributed, *Significance defined by p < 0.05.

Fig. 6 showed that, in Clomiphene and Gonadotropin group (n=30), the mean of endometrial thickness was 11.25 ± 0.66 and ranged from 10 to 12.5 mm in non-pregnant women while in pregnant women it was 12.25 ± 0.27 and ranged from 12 to 12.5 mm with highly statistically significant difference (P= 0.002).

**Table 6. Relation between the ovulation status and endometrial thickness in Stair-Step group (n=30)**

| | | Ovulation status | | |
|---|---|---|---|---|
| Variable name | | No (n = 4) | Yes (n = 26) | P value |
| Endometrial thickness | Mean ± SD | 8.50 ± 0.71 | 9.67 ± 1.29 | 0.105 |
| | Median (range) | 8.25 (8.0–9.5) | 10.0 (8.0–11.5) | |

*Data are presented as mean ± SD and median (range)*

**Table 7. Relation between the pregnancy status and endometrial thickness in Stair-Step group (n=30**

| | | Pregnancy status | | |
|---|---|---|---|---|
| Variable name | | No (n = 24) | Yes (n = 6) | P value |
| Endometrial thickness | Mean ± SD | 9.13 ± 1.13 | 11.08 ± 0.20 | <0.001* |
| | Median (range) | 8.75 (8.0–11.0) | 11.0 (11.0–11.5) | |

*Data are presented as mean ± SD and median (range)*

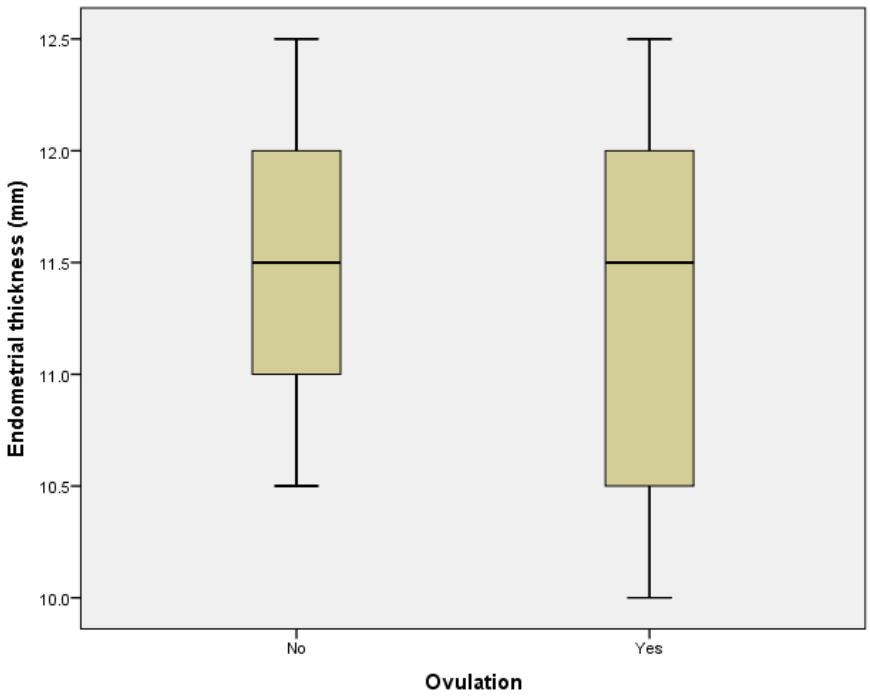


**Fig. 5.Box plot graph showing the difference between women with and with-out ovulation in Clomiphene and Gonadotropin group as regard to the endometrial thickness**

## 4. DISCUSSION

The maternal age of cases included in the study ranged between 18 year and 40 year with a mean age of 32.03±6.1 years. The gravidity of cases included in the study ranged between 1 and 5 with a mean of 2.01±1.03. The parity of cases included in the study ranged between 0 and 6 with a mean of 2.18±1.04. The number of abortions ranged between 0 and 3 with a mean of 0.61±0.03. The gestational age ranged between 28 and 38 weak with a mean of 33.6 ± 2.8 weeks. Our results were supported by study of Guzein et al., [7] as they reported that the gravidity of cases included in the study was with a mean of 1.92±1.6. The parity of cases included in the study was a mean of 0.48± 0.83. The gestational age was with a mean of 28.08 weeks.

In the study of Maged et al., [8], the mean age of the studied mothers was 26.82 ± 6.31years. The mean of their gravidity was1.66 ± 1.75. Their parity mean was± 1.28 1.55. The mean of their gestational age was 35.18± 3.45 weeks. The

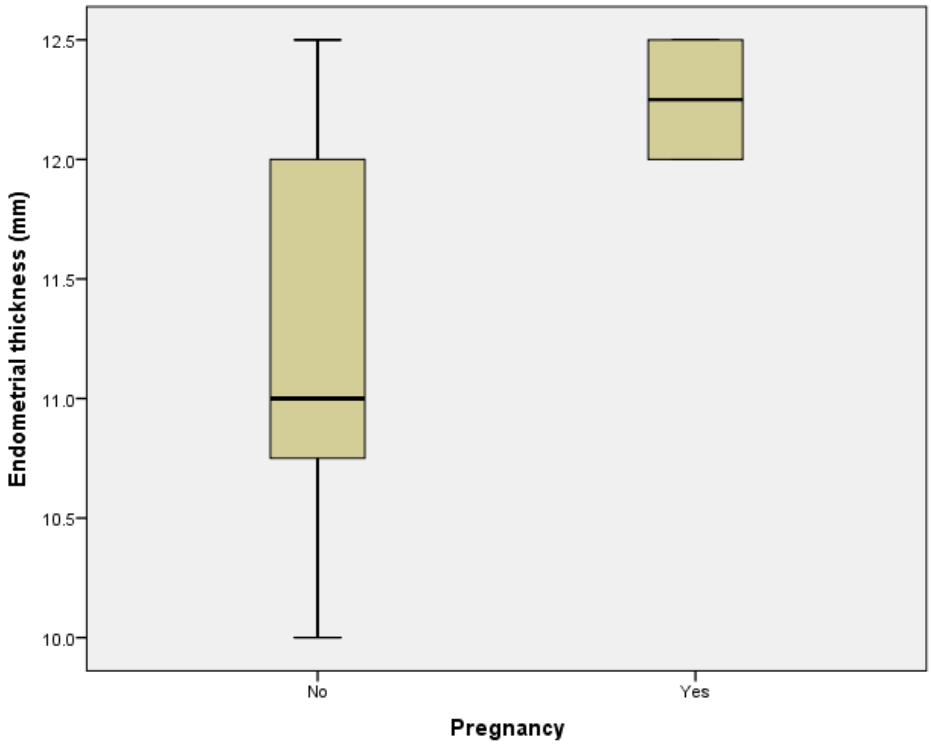


**Fig. 6. Box plot graph showing the difference between pregnant and non-pregnant women in Clomiphene and Gonadotropin group as regard to the endometrial thickness**

present study showed that the serum level of ALT ranged between 11 and 104 mEq/L with a mean of 49.12±27.81. The serum level of AST ranged between 13 and 84 mEq/L with a mean of 42.5±20.17. Our results were supported by study of Dacaj et al., [9] as they demonstrated that there was a significant statistically difference in serum value of AST, ALT, LDH and total cholesterol between women with preeclampsia and IUGR and healthy pregnant women. There was a significant statistically difference in serum value of AST, ALT, LDH.

Our results were supported by study of AlSheeha et al., [10] as they demonstrated significantly lower PC (platelet count) and PC to MPV (mean platelet volum) ratio in patients with preeclampsia compared with the normal controls but failed to show similar trend when MPV and PDW were evaluated in the same study groups. Doğan et al [11] observed significantly lower PC and PC/MPV in preeclamptic women compared with the controls. The same study documented significantly higher MPV in preeclamptic women than the control group. Likewise, Freitas et al, [12] reported lower PC in women with preeclampsia. Preeclampsia is defined as increase in systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg and proteinuria ≥300 mg protein/24 hours urine and starts after 20 weeks of pregnancy. Eclampsia is the condition in which generalized seizure occur in the absence of other neurologic defects [13].

Our results were in agreement with study of Guzein et al., [14] as they found that before magnesium sulfate therapy, the mean of systolic and diastolic BPs was 165.8 + 16.4 and 104.6 + 13.2 mmHg, respectively. According to Maged et al., [15], they reported that the mean proteinuria of the studied mothers was 3.36± 0.60 gm.

Our results were supported by study of Mateus et al., [16] as they revealed that 0f 2462 women analyzed, 2296 (93.3%) were normotensive, 63 (2.6%) had mild gestational hypertension, 54 (2.2%) mild preeclampsia, 32 (1.3%) severe preeclampsia, and 17 (0.7%) unspecified hypertension. Compared with normotensive women, those with severe preeclampsia had estimated fetal weights that were reduced between 22 and 38 weeks (all weekly pairwise values of P < .008). Women with severe preeclampsia compared with those without hypertension also had significantly smaller fetal abdominal circumference between 23-31- and

33-37-weeks' gestation (weekly pairwise values of P < .04). Scattered weekly growth differences were noted on other biometric parameters between these 2 groups.

Our results were supported by study of Sedek et al., [17] as they found that umbilical artery Doppler velocimetry indices (RI, PI, S/D) show significant decrease after administration of the loading dose of magnesium sulfate. Houlihan et al. [18] showed that there is evidence that magnesium sulfate promotes vasodilatation of the umbilical artery with consequent decrease of vascular resistance. Souza et al. [19] reported a reduction of umbilical artery Doppler velocimetry indices (RI, PI, S/D) in pregnant women with preeclampsia, after intravenous administration of magnesium sulfate. Souza et al. [20] reported that while in patients with normal blood pressure levels the vasodilator effect of magnesium is not evident; in patients with pre-eclampsia this effect is significant.

Our results were supported by study of Farshchian et al., [21] as they revealed that after injection of MgSO4, C/U ratio had a significant increase, which shows that the fetal blood supply had improved. Various studies confirmed the efficacy of Doppler ultrasound examination for assessing the vascular status of the fetus and have introduced the C/U ratio as a parameter in assessing fetal blood supply [22].

## 5. CONCLUSIONS

Infusion of MgSO4 significantly decreases the fetal RI-umbilical and PI-MCA and increases C/U ratio indices obtained with color Doppler ultrasound evaluations.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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