

# Effects of Different Progesterone Containing Contraceptive Methods on Endogenous Progesterone Level and Ovulation Rate: prospective cohort observational study

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## Research Article

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# Abstract

## Background

Progestogen-only' contraceptives are presented as injections, implants, oral formulations, hormone-releasing intrauterine methods, and emergency contraceptives. The research designed to assess the influence of progesterone in different progesterone containing contraceptive methods on endogenous progesterone level and ovulation rate.

## Methods

This prospective cohort observational research was involved 80 healthy fertile females aged 20–35 years with normal menstrual history and had at least one offspring after spontaneous pregnancy. Subjects were classified into 4 equal groups according to contraceptive method: D group: used the injectable progesterone of 150 mg every 90 days or 3 months (Depo-Provera), I group: etonogestrel implant which contains 68 mg of etonogestrel, formerly known as Implanon, N group: used norgestrel (Ovrette, with each pill containing 0.075 mg of norgestrel), M group: used IUD (Mirena) containing 52 mg of levonorgestrel.

## Results

women who in M group had higher endogenous progesterone level compared to those who used other contraceptives containing with normal follicle growth and normal follicle size. Incidence of amenorrhea was significantly decreased in M group 20% than D group 75%, I group ,65%, N group 70% and there was an insignificant difference among other three groups. Continuation rate was significantly increased in M group than other three groups after 3 months and 6 months

## Conclusion

Mirena had low systemic absorption of exogenous progesterone so, it had low effect on endogenous progesterone and ovulation rate with low incidence of side effects compared to other contraceptives containing progesterone. Therefore, Mirena is an effective and safe method as contraceptive and can be used with women who had complication with using progesterone containing contraceptive methods in the study.

## Background

Progestins, or progestogens, are a group of synthetic hormone drugs which mimic progesterone's endogenous hormone [1].

Progestogen-only' contraceptives are presented as injections, implants, oral formulations, hormone-releasing intrauterine methods and emergency contraceptives [2]. These substances could be used by females who are breastfeeding or have other contraindications to estrogen treatment, including those who are immediately postpartum, have thalassemia, sickle-cell disease, gallbladder disease, have had or are currently experiencing thrombo-embolic disorders, valvular heart disease, ischemic heart disease, have recently undergone surgery, have migraines, or are elderly [3]. Intrauterine, injectable methods and contraceptive implants, also named long-acting reversible contraceptives (LARC), are the more efficient reversible contraceptive approaches are highly effective, longer-acting contraceptive methods levels in comparison to short-term user-dependent approaches, with both ideal and normal usage failure rates of less than 1% that can be used by most women in most circumstances [4].

Depot medroxyprogesterone acetate (Depo-Provera) is an injectable progestogen that is given in an aqueous microcrystalline solution via deep intramuscular injection into the gluteal or deltoid muscle [5]. This depot produces a peak plasma level of medroxyprogesterone acetate, which rapidly falls subsequently. It is administered once every 90 days at a dose of 150 mg [6]. It has side effects as menstrual disturbances that might manifest as amenorrhea or regular and/or irregular bleeding, weight increase is also a familiar adverse-effect [7].

Subdermal implants release progestogen gradually over an extended time and give reversible, long-term contraception [8]. Nexplanon is an etonogestrel implant that contains 68 mg of etonogestrel, formerly known as Implanon. It is the size of a matchstick, and It is inserted by a competent healthcare expert beneath the skin of the upper arm. As the injectable progestogen-only contraceptives, progestogen implants induce amenorrhoea or regular or intermittent bleeding in the majority cases [9]. Additionally, implants are more expensive than a variety of alternative approaches [9].

Progesterone only Pill (more commonly preparations have drospirenone or norethindrone). Drospirenone inhibits ovulation and acts as an anti-mineralocorticoid. While norethindrone mainly performs by thickening cervical mucus to prevent sperm entrance, inhibiting ovulation, reducing the mid-cycle LH and FSH peaks, that slows the ovum movement within fallopian tubes, and changes endometrium thickness. Certain progestins have more antiandrogenic characteristics, making them more helpful in the treatment of polycystic ovarian syndrome, hirsutism, and acne [10]. It had several side effects as irregular menstruation, breast discomfort, diminished sexual drive (libido), melancholy, headaches, nausea, and ovarian cysts. levonorgestrel-releasing IUD (Mirena) is inserted into the uterus as a small T-shaped device. It is implanted directly into the uterus by a trained healthcare professional [11]. Mirena contains 52 mg of levonorgestrel that is released slowly over time. After implantation, Mirena can help prevent pregnancy for up to seven years and decrease menstrual bleeding for up to five years [12]. Mirena may be preferred for women who have heavy menstrual bleeding and want a form of contraception. In addition, Mirena provides protection from pregnancy longer than Nexplanon at seven years versus three years [13].

We hypothesized that Mirena had low systemic absorption and its local effect on endometrium with low incidence of side effects, therefore it could be used in females who had problems with using other

progesterone containing contraceptive methods.

There was a paucity of studies that has directly assessed the endogenous level of progesterone and side effects in different contraceptive containing progesterone among postpartum parous adolescents. Therefore, the purpose of this study was to assess the influence of progesterone in different progesterone containing contraceptive method on endogenous progesterone level and ovulation rate.

## Materials And Methods

This prospective cohort research involved 80 healthy fertile females aged 20–35 years with normal menstrual history and had at least one offspring after spontaneous pregnancy. The study was done after approval from the Ethical Committee of Faculty of Medicine at Obstetrics and Gynecology department in Tanta University Hospital, Egypt between September 2021 to March 2022. All participants provided informed consent.

Cases were divided into four equal groups according to contraceptive method: D group: used the injectable progesterone of 150 mg every 90 days (Depo-Provera). I group: etonogestrel implant which contains 68 mg of etonogestrel, formerly known as Implanon. N group: used norgestrel (Ovrette, with each pill containing 0.075 mg of norgestrel). M group: used IUD (Mirena) containing 52 mg of levonorgestrel.

Exclusion criteria were any disease affects uterus (uterine fibroids, endometriosis, uterine prolapse, uterine tuberculosis), ovarian or uterine tumors, submucous myoma, irregular menstrual cycle, past or family history of Breast disease ,thyroid, DVT, migraine, diabetic patients, medication affecting reproductive or metabolic functions and an endometrial thickness < 7 mm on the secretory transformation day, a history of spontaneous abortions or embryo transfer failure on over three occasions, patients had cortisol medications, patients who received radiological treatment.

### All women were subjected to:

1. Detailed history menstrual pattern, fertility status, any previous investigations or treatment given, with a special stress on type and method of contraception.
2. Endogenous progesterone measurement was performed in all groups at 21 days of cycle every month till for 6 months.
3. Ovulation rate (follicular size, follicular growth) every month till for 6 months.
4. Side effects of different types of progesterone containing contraceptive methods were recorded.
5. Continuation of different contraceptive methods at 3months and 6 months.

## Serum sample preparation

Blood samples were collected from cases into serum tubes which did not contain anti-coagulant and leave to clot for 30 minutes at room temperature. Centrifugation was used to separate serum, and

samples were kept at -80°C until analysis. After defrosting the serum samples on ice, 0.5 mL of serum was transferred to a 10 mL glass centrifuge tube. Triplicate samples were analyzed, requiring 1.5 mL of serum per analysis. Every serum sample was spiked with 10 µL of internal standard, 1 mL 100 mM potassium phosphate, pH 9-, and 4-mL pentane was added.

After centrifugation. After collecting the organic phase in a separate 10 mL glass centrifuge tube, the extraction was done with 2 mL pentane. The dried samples were modified in 100 µL HPLC water/methanol (50/50) taking care to wash down the walls of the tube and mix and then the samples were transported into injection vials for analysis by liquid chromatography-mass spectrometry (LC/MS/MS).

## Sample size

G. power 3.1.9.2 was used to calculate the sample size (Universitat Kiel, Germany). The sample size was estimated as  $N \geq 17$  on each group based on the subsequent considerations: 0.05  $\alpha$  error and 90% power of the study to demonstrate incidence of amenorrhea with Mirena 20% [14] versus Depo-Provera (75%) [15] according to a previous studies. Each group was supplemented with three cases to account for dropout. As a result, each group consisted of twenty patients.

Our outcomes were effect of different contraceptives containing progesterone on endogenous progesterone level, ovulation rate and incidence of side effects.

## Statistical analysis

SPSS version 25 was used for statistical analysis (IBM Inc., Chicago, IL, USA). The mean and standard deviation (SD) of quantitative variables were calculated and compared using the ANOVA test between the three groups, with a post hoc (Tukey) test used to compare the two groups. The frequency and percentage values of qualitative variables were evaluated statistically using the Chi-square test. Statistical significance was defined as a two-tailed P value of 0.05.

## Results

Demographic data was comparable among the four groups. Regarding menstrual pattern, parity, mode of delivery, there was an insignificant difference among four groups. Table 1

Table 1  
Demographic data among studied groups

		<b>D group (n = 20)</b>	<b>I group (n = 20)</b>	<b>N group (n = 20)</b>	<b>M group (n = 20)</b>	<b>P value</b>
Age/years		27.5 ± 5.09	29.35 ± 3.56	26.7 ± 5.18	27.9 ± 4.3	0.325
Weight (Kg)		67.2 ± 7.29	66.4 ± 7.26	64.8 ± 6.99	66.0 ± 7.04	0.757
Height(m)		1.6 ± 0.08	1.6 ± 0.08	1.6 ± 0.08	1.6 ± 0.09	0.233
BMI(Kg/m <sup>2</sup> )		27.8 ± 4.42	25.9 ± 3.77	25.52 ± 2.66	25.9 ± 3.86	0.196
Menstrual pattern		28.8 ± 4.18	29.9 ± 4.91	26.4 ± 4.44	27.9 ± 4.32	0.094
Parity	Primipara	4 (20%)	3 (15%)	5 (25%)	3 (15%)	0.824
	Multipara	16 (80%)	17 (85%)	15 (75%)	17 (85%)	
Mode of delivery	Vaginal	7 (35%)	8 (40%)	11 (55%)	9 (45%)	0.619
	CS	13 (65%)	12 (60%)	9 (45%)	11 (55%)	
Data presented as Mean ± SD, CS: caesarian section						

Endogenous progesterone level was significantly increased in M group than other three groups (P value = 0.001) at 1st month till 6th month of measurements. There was an insignificant difference among D group, I group and N group at 1st month till 6th month of measurements. Table 2

Table 2  
Endogenous progesterone level among studied groups

Endogenous progesterone (ng/ml)	D group (n = 20)	I group (n = 20)	N group (n = 20)	M group (n = 20)	P value	Post hoc
1st month	1.85 ± 0.88	1.95 ± 0.83	2.2 ± 0.83	11.2 ± 0.83	0.001	P1 = 0.712
						P2 = 0.203
						P3 < 0.001
						P4 = 0.347
						P5 < 0.001
						P6 < 0.001
2nd month	2.1 ± 0.79	2 ± 0.79	2.15 ± 0.81	11.15 ± 0.88	0.001	P1 = 0.692
						P2 = 0.844
						P3 < 0.001
						P4 = 0.559
						P5 = < 0.001
						P6 = < 0.001
3rd month	2.15 ± 0.75	1.95 ± 0.76	2.05 ± 0.89	10.85 ± 0.88	0.001	P1 = 0.406
						P2 = 0.702
						P3 < 0.001

Data presented as Mean ± SD, P value = p among four groups, P1 = P value between D group and I group, P2 = P value between D group and N group, P3 = P value between D group and M group, P4 = P value between I group and N group, P5 = P value between I group and M group, P6 = P value between N group and M group.

Endogenous progesterone (ng/ml)	D group (n = 20)	I group (n = 20)	N group (n = 20)	M group (n = 20)	P value	Post hoc
						P4 < 0.704
						P5 < 0.001
						P6 < 0.001
4th month	2.2 ± 0.95	1.9 ± 0.91	2.05 ± 0.76	11.4 ± 1.23	0.001	P1 = 0.315
						P2 = 0.585
						P3 < 0.001
						P4 = 0.575
						P5 < 0.001
						P6 < 0.001
5th month	1.4 ± 0.5	1.45 ± 0.51	1.5 ± 0.51	11.35 ± 1.14	0.001	P1 = 0.757
						P2 = 0.735
						P3 < 0.001
						P4 = 0.759
						P5 < 0.001
						P6 < 0.001
6th month	1.85 ± 0.88	1.95 ± 0.83	2.2 ± 0.83	11.1 ± 0.79	0.001	P1 = 0.712

Data presented as Mean ± SD, P value = p among four groups, P1 = P value between D group and I group, P2 = P value between D group and N group, P3 = P value between D group and M group, P4 = P value between I group and N group, P5 = P value between I group and M group, P6 = P value between N group and M group.

Endogenous progesterone (ng/ml)	D group (n = 20)	I group (n = 20)	N group (n = 20)	M group (n = 20)	P value	Post hoc
						P2 = 0.203
						P3 < 0.001
						P4 = 0.347
						P5 < 0.001
						P6 < 0.001
Data presented as Mean ± SD, P value = p among four groups, P1 = P value between D group and I group, P2 = P value between D group and N group, P3 = P value between D group and M group, P4 = P value between I group and N group, P5 = P value between I group and M group, P6 = P value between N group and M group.						

Follicle size was significantly increased in M group than other three groups (P value = 0.001) and there was an insignificant difference among D group, I group and N group at 1st month till 6th month of measurements. Table 3

Table 3  
Follicle size(mm) among studied groups

Follicle size	D group (n = 20)	I group (n = 20)	N group (n = 20)	M group (n = 20)	P value	Post hoc
1st month	10.8 ± 0.77	11.05 ± 0.94	10.95 ± 0.83	20.2 ± 1.51	0.001	P1 = 0.364 P2 = 0.555 P3 = 0.000 P4 = 0.723 P5 = 0.000 P6 = 0.000
2nd month	10.95 ± 0.89	11 ± 0.86	11 ± 0.86	20.2 ± 1.28	0.001	P1 = 0.857 P2 = 0.857 P3 = 0.000 P4 = 1 P5 = 0.000 P6 = 0.000
3rd month	11 ± 0.92	11 ± 0.79	11 ± 0.79	20.35 ± 1.35	0.001	P1 = 1 P2 = 1 P3 = < 0.001 P4 = 1 P5 = < 0.001 P6 = < 0.001
4th month	11.3 ± 0.73	10.95 ± 0.89	11.3 ± 0.86	19.55 ± 1.43	0.001	P1 = 0.182 P2 = 1 P3 = 0.000 P4 = 0.214 P5 = 0.000

Data presented as Mean ± SD, P value = p among four groups, P1 = P value between D group and I group, P2 = P value between D group and N group, P3 = P value between D group and M group, P4 = P value between I group and N group, P5 = P value between I group and M group, P6 = P value between N group and M group.

Follicle size	D group (n = 20)	I group (n = 20)	N group (n = 20)	M group (n = 20)	P value	Post hoc
						P6 = 0.000
5th month	11.05 ± 0.89	11.15 ± 0.88	11 ± 0.73	19.85 ± 1.46	0.001	P1 = 0.722
						P2 = 0.846
						P3 = 0.000
						P4 = 0.559
						P5 = 0.000
						P6 = 0.000
6th month	10.7 ± 0.86	10.85 ± 0.88	11 ± 0.86	19.6 ± 1.43	0.001	P1 = 0.589
						P2 = 0.278
						P3 = 0.000
						P4 = 0.587
						P5 = 0.000
						P6 = 0.000
Data presented as Mean ± SD, P value = p among four groups, P1 = P value between D group and I group, P2 = P value between D group and N group, P3 = P value between D group and M group, P4 = P value between I group and N group, P5 = P value between I group and M group, P6 = P value between N group and M group.						

Incidence of amenorrhea was significantly decreased in M group 20% than D group 75% I group 65%, N group 70% while there was an insignificant difference among other three groups. Table 4

Table 4  
Incidence of amenorrhea among studied groups

	<b>D group (n = 20)</b>	<b>I group (n = 20)</b>	<b>N group (n = 20)</b>	<b>M group (n = 20)</b>	<b>P value</b>	<b>Post hoc</b>
Incidence of amenorrhea	15 (75%)	13 (65%)	14 (70%)	4 (20%)	0.014	P1 = 0.731 P2 = 0.731 P3 = 0.001 P4 = 1.00 P5 = 0.015 P6 = 0.015
Irregular bleeding	16 (80%)	13 (65%)	14 (70%)	9 (45%)	0.126	
Data presented as frequency (%),P value = p among four groups ,P1 = P value between D group and I group,P2 = P value between D group and N group,P3 = P value between D group and M group, P4 = P value between I group and N group,P5 = P value between I group and M group,P6 = P value between N group and M group						

Continuation rate was noticeably greater in M group than other three groups after 3 months and 6 months while there was an insignificant difference among other three groups. Table 5

Table 5  
Continuation rate among studied groups

Continuation rate	D group	I group	N group	M group	P value	Post hoc
3rd month	7 (35%)	9 (45%)	8 (40%)	16(80%)	0.012	P1 = 0.746
						P2 = 0.744
						P3 = 0.010
						P4 = 0.749
						P5 = 0.048
						P6 = 0.022
6th month	3 (15%)	7 (35%)	5 (25%)	15 (75%)	< 0.001	P1 = 0.273
						P2 = 0.694
						P3 = 0.000
						P4 = 0.730
						P5 = 0.026
						P6 = 0.004
Data presented as frequency (%),P value = p among four groups ,P1 = P value between D group and I group,P2 = P value between D group and N group,P3 = P value between D group and M group, P4 = P value between I group and N group,P5 = P value between I group and M group,P6 = P value between N group and M group.						

Regarding endometrium thickness, measurements at 1st month till 6th month of were insignificantly different among the four groups. Figure 1

## Discussion

LARCs are increasingly prevalent among females looking for contraception [16]. Progestogens are the primary active ingredient in hormonal contraception, as they have essentially three modes of action, their structure and the action profile are different, they show a multifocal form of action in contraception. Moreover the normal progestogenic effect, each progestogen has a partial effect pattern, and different effects on endogenous progesterone and ovulation rate with different side effects[17].

In our study we compared between four types of contraceptives containing progesterone.

Menstrual pattern, parity, mode of delivery was insignificantly different among four groups.

In our study, women who used Mirena had higher endogenous progesterone level compared to those who used other contraceptives containing progesterone (oral, Implanon and injectable progesterone), this was due to high systemic absorption of exogenous progesterone from other methods while Mirena had low systemic absorption of progesterone.

Also, women who used Mirena had normal follicle size and ovulation rate p compared to other three groups (P value = 0.001) but with other groups (D group, I group and N group) had low follicle size.

In Barbosa et al.[18] who study the effect of IUD on ovarian function and found that the dose of levonorgestrel get out from the IUD is so low, it almost certainly influences gonadotrophin secretion. which impairs follicular growth in a significant proportion of the women investigated, additionally to the local effect on the endometrium, adds to its high contraceptive effectiveness.

In current research, endometrium thickness was significantly lower with the four contraceptive methods < 8mm.

Incidence of amenorrhea was substantially decreased in M group 20% than D group 75% I group 65%, N group 70% while there was an insignificant difference among other three groups.

Consistent with our findings, Pedro et al, found that incidence of amenorrhea with women who had used Mirena was 13% while in women who had used Depo Provera was 75%.

Also, in Sergison et al.[19] who showed prevalence of amenorrhea with IUD and found that, 18.2% of participants underwent amenorrhea for at least 90-day interval throughout the 1st year.

In our study incidence of irregular bleeding was 80% with D group, 65% with I group 70% with N group and 45% with M group.

In Regidor et al,[20] found that incidence of irregular bleeding with women who had used Mirena was 50% while in women who had used Depo Provera was 75%.

Continuation rate was notably greater in M group than other three groups after 3 months and 6 months while there was an insignificant difference among other three groups.

In Peipert et al.,[21] who studied maintenance and satisfaction of reversible contraception and found that the greatest rate of continuation for LNG-IUS (88%).

Limitations: insufficient sample size, follow-up period is brief and absence of randomization as Participants were not assigned a contraceptive technique at random, their expectations of a contraceptive method may be different from the outset. We did not believe that randomizing patients to a method of contraception was ethical, and that randomization could have a negative effect on continuance, which was one of our outcomes.

## Conclusions

Mirena had low systemic absorption of exogenous progesterone so, it had low effect on endogenous progesterone and ovulation rate with low incidence of side effects compared to other contraceptives containing progesterone. Therefore, Mirena is an effective and safe method as contraceptive and can be used with women who had complication with using progesterone containing contraceptive methods in the study

## Abbreviations

**LARC:** Long-acting reversible contraceptives

**Depo-Provera:** Depot medroxyprogesterone acetate

**IUD:** intrauterine device

**DVT:** Deep vein thrombosis

**HPLC:** High performance liquid chromatography

**LC/MS:** Liquid chromatography-mass spectrometry

**SD:** Standard deviation

**LNG-IUS:** levonorgestrel-releasing intrauterine system

## Declarations

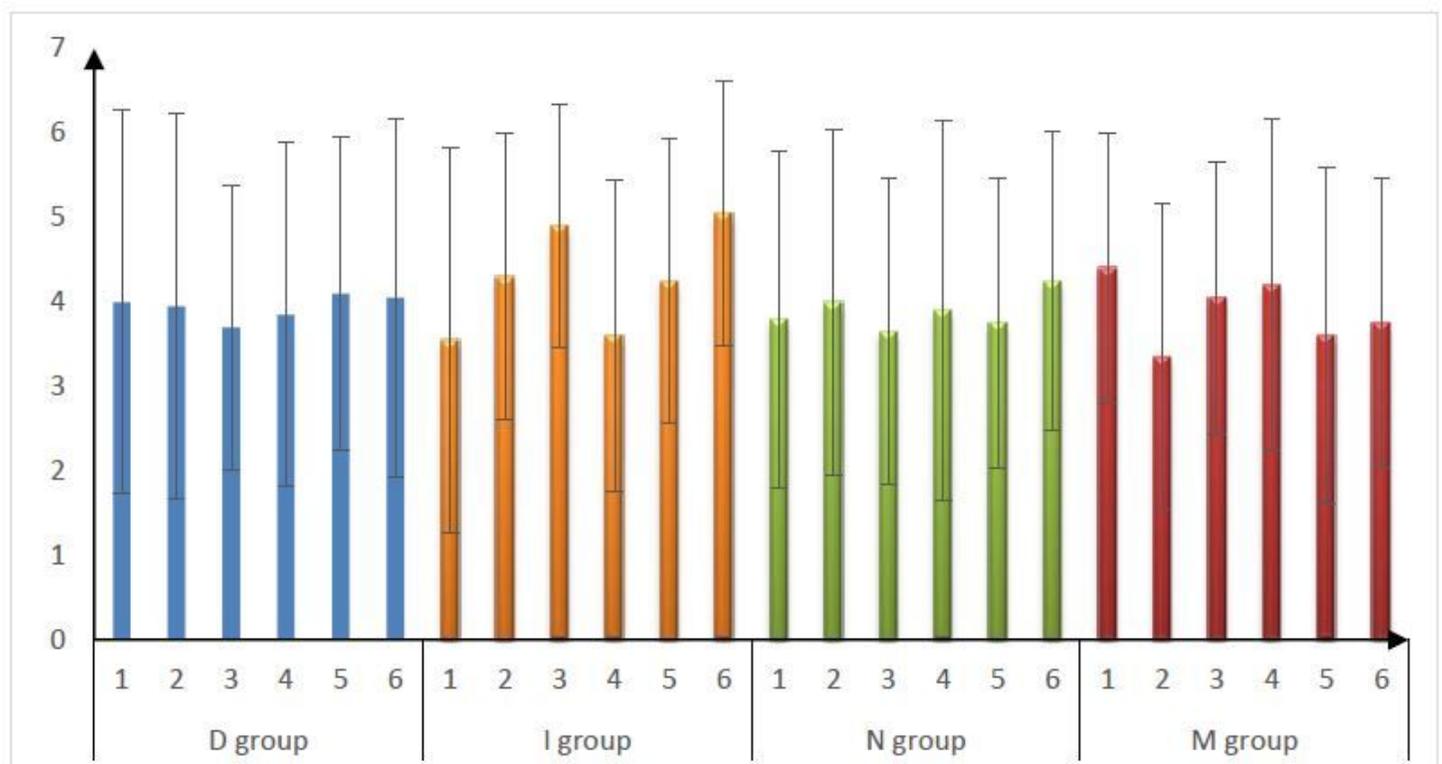
- **Ethics approval and consent to participate:** The study was done after approval from the Ethical Committee of Faculty of Medicine at Obstetrics and Gynecology department in Tanta University Hospital, Egypt between September 2021 to March 2022. All participants provided informed consent.
- **Consent for publication:** All authors give their consent for publication in the journal.
- **Availability of data and materials:** Data and material are available on a reasonable request from the author.
- **Competing interests:** The authors declare no conflict of interest.
- **Funding:** Nil
- **Authors' contributions:** Mona Omar conceived and supervised the study; Ahmed Ossman were responsible for data collection. Ahmed Ossman and Mona Omar analysed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.
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## Figures



**Figure 1**

Endometrium thickness among the studied groups