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Effect of prolonged use of hormonal contraception on ovarian reserve: A randomized clinical trial

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***Abstract*---**Background and Objective: Contraception is widely used throughout the world, with 62% of reproductive-aged women. This trial was established to assess the effect of prolonged use of hormonal contraception (HC) on ovarian reserve. Methods: This retrospective randomized controlled trial was performed on 150 healthy females aged (20-35) years with normal menstrual history had at least one offspring after spontaneous pregnancy. Participants were subdivided into equal three groups: first group (study group): used the injectable progesterone for more than four years continuously, second group (study group): used combined oral contraceptive (COC) for more than four years continuously, control group: didn't use HC (as intrauterine device, natural and non-users of any contraception). Results: Ovarian volume (OV) and antral follicle count (AFC) were significantly decreased in COC group than control group. There was a significant negative correlation between body mass index and OV was found. There was an insignificant correlation between age, gravidity, parity,

BMI, usage duration and both AFC, AMH among group 3 controls. Conclusion: The prolonged use of HC in COC group had a significant negative effect on volume of ovary and AFC with no effect on AMH. A significant negative correlation between age and AMH was found among COC users.

***Keywords*---**Hormonal Contraception, Ovarian Reserve, Anti-Mullerian Hormone, Ovarian Volume.

Introduction

Contraception is widely used throughout the world, with 62% of reproductive-aged women recently utilizing various forms of contraception (1). Numerous preference-sensitive healthcare decisions, such as contraceptive techniques, contain both desirable and unwanted characteristics, requiring the patient to assess the possible benefits and drawbacks of several options (2). Despite, several women had insufficient knowledge or support for using contraceptive or having unknown values, unrealistic potentials, or social pressures that can confuse decisions (3).

Using of hormonal contraception (HC) for contraception and therapy of different endocrine conditions including polycystic ovarian syndrome and endometriosis (4, 5). Pretreatment with oral contraceptives (OC) among infertile patients (6), is usually utilized for regulating the cycle in anovulatory women before ovulation and ovarian stimulation for in vitro fertilization (IVF) (7, 8). During the reproductive years, anti-Mullerian hormone (AMH) is synthesized by the ovary's granulosa cells and prevents excessive follicular recruitment induced by follicle-stimulating hormone (FSH) (9). Appearance of AMH is highest during folliculogenesis's recruitment stage, in the preantral and small antral follicles (10). This production decreases as follicles increase and enter selection stage, this results in a rise in FSH expression (11).

According to some authors, it is an assessment of particular ovarian function parameters that could be utilized to diagnose polycystic ovary syndrome and premature ovarian failure (12, 13). Given the widespread use of hormonal contraceptives in women who are fertile and infertile, it is critical to ascertain if extended use of hormonal contraceptives alters blood AMH and AFC concentrations (14). This trial was established to assess the effect of prolonged use of HC on ovarian reserve.

Materials and Methods

This randomized retrospective clinical trial was established on 150 healthy females aged (20-35) years with normal menstrual history, fertile women had at least one offspring after spontaneous pregnancy and at comparing the experimental group to age matched controls. The research was done after approval from the Ethical Committee of Faculty of Medicine at Obstetrics and Gynecology department in Tanta University Hospital, Egypt from January 2020 to October 2020.

Exclusion criteria: any disease affects ovarian reserve: (polycystic ovary, premature ovarian failure, resistant ovarian syndrome), ovarian or uterine tumors, ovarian surgery, patient receive radiological treatment, severe medical problems (hepatic, cardiac, diabetic) and obesity "body mass index (BMI) > 30 (kg/m^2)".

Randomization

A statistician unrelated to patient treatment utilized a computer-generated programmed (permuted block technique) to randomize and allocate the included patients into three equal groups: first group (study group): used the injectable progesterone for more than four years continuously, second group (study group): used combined oral contraceptive (COC) for more than four years continuously, third group (control group): didn't use HC (as intrauterine device, natural and non-users of any contraception).All women were subjected to:

1. Detailed history including (medical and surgical, obstetric, and contraceptive), menstrual pattern, fertility status, any previous investigations or treatment given, with a special stress on type and method of contraception.
2. General examination with special stress on anthropometric measurements and clinical manifestations of any general medical disease and gynecological disease,
3. Serum AMH measurement regardless time of menstruation by Ultra-Sensitive AMH/MIS ELISA.
4. On days 2–7 of the menstrual cycle, vaginal ultrasonography is used to determine the antral follicular count by transvaginal 6.5 MHz (Samsung Korea H60 color Doppler.

Statistical analysis

The statistical analysis was performed using SPSS v27 (IBM, Chicago, IL, USA). The Shapiro-Wilks test and histograms were used to determine the normality of the data distribution. We generated and examined the mean and standard deviation (SD) of quantitative parametric data using the ANOVA (F) test with a post hoc test (Tukey). To assess qualitative data expressed as frequency and percentage, the Chi-square test was applied. A two-tailed P value of 0.05 was considered statistically significant.

Results

In this trial, 195 cases were assessed for eligibility. After screening, 48 patients were excluded from allocation. Thirty - five cases did not match the inclusion criteria and thirteen cases refused participating in the trial. 150 patients were allocated into equal three groups. The trial was completed by 150 patients and were eligible for analysis during follow-up into injectable progesterone, COC and control group. (Figure 1)

Age, gravidity, parity, duration of contraception, and BMI were insignificantly different among the three groups. (Table 1)

As regard OV and AFC, there was a significant difference among the three groups (p=0.02,0.04 respectively). OV and AFC were significantly decreased in COC group in comparison to control group. As regard AMH, an insignificant difference among

the three groups. (Table 2). There was an insignificant correlation between each of age, gravidity, parity, usage duration and OV among group 3 controls. However, there was a significant negative correlation between BMI and OV. There was an insignificant correlation between each of age, gravidity, parity, BMI, usage duration and both AFC, AMH among group 3 controls. (Table 3)

Discussion

AMH is a granulosa cells product in ovarian follicles. Now, it is a critical indicator of ovarian reserve (15). Numerous previous research have been conducted to determine the effect of HC on blood AMH levels (16). However, the findings remain inconclusive. The majority of these studies (17, 18) concentrated on the effects of HC consumption. Various research examining the lifestyle, demographic, and clinical factors which might affect AMH concentrations have been conducted because of the common use of AMH as a indicator for ovarian reserve (19). Furthermore, Clinicians who counsel individuals requiring a fertility evaluation while on hormonal contraceptives have been particularly interested in the influence of contraceptives on AMH levels (20).

Statistical analysis of recent trial presented that there was an insignificant difference between women of both groups regarding age, gravidity, parity, duration of contraception and BMI. There was an insignificant correlation between each of age, gravidity, parity, BMI, usage duration and OV and both AFC and AMH among group 1 cases (injectable progesterone). There was a significant correlation between each of gravidity, parity, BMI, usage duration and OV, AFC and AMH among COC cases. However, a significant negative correlation between age and AMH was found. There was an insignificant correlation between each of age, gravidity, parity, usage duration and OV, AFC and AMH among group 3 controls. However, a significant negative correlation between BMI and OV was found.

Shalabi et al. (21) aimed to quantify endocrine and sonographic parameters of O.V in women using COC pills and comparing them with IUCD and non-contraceptive users. A cross sectional investigation included 100 healthy volunteer women divided into 35 COC users (all using monophasic preparations, ethinyl estradiol 30&35ug and progestin, norgestimate and gestodene) and 65 non-users (35 IUCD users and 30 non contraceptive users). On day 2–5 of the menstruation or throughout withdrawal bleeding, blood sampling to measure AMH and transvaginal ultrasonography to measure AFC and OV were performed. They agreed with current results and stated that there was an insignificant difference between women of both groups regarding age, weight, height, parity and BMI.

Consistent with existing findings, Shalabi et al. (21) showed substantial reduction in the mean of total AFC among COC users than nonusers with p value=.006 with reduction in total AFC in COC than IUCD users but of insignificance and there is highly significant decrease in the mean of total OV among COC userscompared to IUCD users (B) and none users with p value =0.001. They showed a significant decrease in the proportion of AFC sized 5-7mm and 8-10 mm in COC users compared to IUCD users and nonuserswith P value=0.001. While there is a significant increase in the proportion of AFC 2-4mm among COC users than IUCD

users and nonusers with P-value=.001. They showed a significant reduction in total AFC and total O.V in women using COC ≥ 6years than who were using it 1-5 years. They disagreed with current results and demonstrated that there is statistically considerable decrease in the average of AMH level among COC users than IUCD users and non-users with p- value<.001. There is reduction in AMH with increasing duration of COC use but of no statistical significance. Bas-Lando et al. (22) performed a research comparing 41 HC users to 57 non-HC users who underwent preimplantation genetic diagnosis during IVF with the goal of determining the influence of HC on AMH, small (2–5 mm), large (6–10 mm), and total AFC levels, as well as their potential to predict IVF finding . They concurred with current findings, stating that the most of demographic parameters did not reveal significant variations between the two groups.

Petersen et al. (23) established a study to determine the extent to which OC compromises ovarian reserve characteristics in females seeking fertility testing and advising to determine if their reproductive lifetime has been diminished. In their study, all females were checked by a fertilization expert on a random cycle day. They concurred with our findings, stating that both groups (OC users and non-users) were equivalent in terms of BMI, age, maternal age at menopause and smoking.

In contrast to our results, Petersen et al. (23) found that AMH was 19 % decreased (95 % confidence interval [CI] 9.1–29.3 %) in OC users than non-users. AMH comparison at 10 pmol/l concentrations. OC exerted a substantial detrimental effect on AMH (OR1.6, 95% (CI) 1.1; 2.4, P = 0.03). They concurred with us and claimed that 244 (27.5%) of the 887 females utilized OC. In a linear regression analysis corrected for age, OC users had a 50% reduction in OV (95 % [CI] 45.1–53.7%) and an 18% reduction in AFC (95 % CI 11.2–24.8%) in comparison to non-users. Additionally, they discovered a substantial decline in antral follicles measuring 5–7 mm (P value= 0.001) and 8–10 mm (P value <0.001), but a rise in antral follicles measuring 2–4 mm (P value = 0.008) among OC users.

Kucera et al. (16) agreed with us and stated that the moderate level of AMH in the group of long-term users of HC was 2.89 ng/ml. They found an insignificant difference between the groups (P value = 0.3261). Landersoe et al. (24) established the trial to determine if the ovarian reserve markers AMH and AFC were decreased in females utilizing the progestin-only pill or levonorgestrel-releasing intrauterine system and like the detected reduction in women using the COC pill. This disagreed with current results and stated that age significantly different between the groups.

Statistical evaluation of recent trial presented that There was a substantial difference in OV and AFC amongst the three study groups, it was revealed that the significant difference was between COC group and control group only. But AMH was insignificantly different among the three study groups. In accordance with our findings, Amer et al. (25) assessed the effect of HC on circulation of AMH and other ovarian reserve indicators and stated that no variation in circulating AMH in females applying cyclical combined hormonal contraceptive for 1to 6 cycles.

In disagreement with our results, Amer et al. (25) stated that all long- and diverse investigations (six studies, n = 1601) a significant decrease in AMH, AFC, and OV was consistently seen. Three of this research showed AMH recovery following HC cessation.

Corresponding to our findings, Bentzen et al. (26) stated that After correcting for age, users of HC had poorer ovarian reserve characteristics in all follicle size categories than non-users: AFC by 30.4 % (95 % confidence interval [CI] 23.6 to 36.7 %) and OV by 42.2 percent (95 % CI 37.8 to 46.3%). In disagreement with our results, Bentzen et al. (26) stated a negative correlation between period of HC usage and ovarian reserve indicators. They observed that Serum AMH concentrations were significantly decreased in HC users than in non-users by 29.8% (95% CI 19.9 to 38.5%).

Conclusion

The prolonged use of HC especially in COC group had a significant negative effect on OV and AFC and had no effect on AMH. There was a significant negative correlation between age and AMH among COC users, while among non-hormonal contraceptive users, a significant negative correlation between BMI and OV was found.

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Author's Contributions:
Ahmed M.E. Ossman: Conceived and designed the analysis**; Esmat H. Abo Zeid:** Collected the data**, Samaa A. Shahin:** Contributed data or analysis tools**; Mona K. Omar:** Performed the analysis.
Conflict of Interest: Nil

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Table 1: Comparison between personal and medical data among three groups

		Injectable Progesterone (n=50)	COC (n=50)	Controls (n=50)	P value
Age		28.58 ±3.01	28.04 ± 3.17	27.82 ± 2.93	0.4*
Gravidity		2.84 ± 0.93	2.88 ± 1.21	2.90 ± 1.18	0.96*
Parity		2.32 ± 0.96	2.38 ± 1.07	2.32 ± 0.91	0.94*
Duration		5.04 ± 1.05	5.02 ± 1.12	4.76 ± 0.95	0.32*
BMI	**≤25**	23 46.0%	27 (54.0%)	22 (44.0%)	0.57**
	>25	27 (54.0%)	23 (46.0%)	28 (56.0%)	

Data presented as mean ± SD, frequency (%) *ANOVA test, **Chi-Square Tests, BMI: body mass index, COC: combined oral contraceptive

Table 2: Comparison as regard of ovarian volume, AFC and AMH among the three groups

	Injectable Progesterone (n=50)	COC (n=50)	Controls (n=50)	P*	
O. V	10.18 ± 2.15	9.74 ± 2.30	10.86 ± 1.54	0.02*	P1=0.271
					P2=0.09
					P3=0.006*
AFC	12.32 ± 3.46	11.68 ± 3.94	13.38 ± 2.65	0.04*	P1=0.34
					P2=0.12
					P3=0.013*
AMH	2.20 ± 0.93	2.22 ± 1.02	2.54 ± 1.06	0.17	

Data presented as mean ± SD, O.V: ovarian volume, AFC: Antral follicle count, AMH: Anti-Mullerian Hormone, COC: combined oral contraceptive, *: significant as P value <0.05, P1: between injectable progesterone and COC, P2: between injectable progesterone and Controls, P3: between COC and controls

Table 5: Correlations between personal and medical data and OV, AFC and AMH in the studied participants

	O. V		AFC		AMH	
	r	**p**	**r**	**p**	**r**	**p**
Age	-0.051	0.727	-0.052	0.722	0.026	0.858
Gravidity	-0.130	0.368	-0.092	0.526	0.001	0.993
Parity	-0.079	0.584	-0.043	0.768	0.079	0.587
BMI	-0.286	0.044	-0.278	0.050	-0.274	0.054
Duration	-0.137	0.344	-0.068	0.638	0.069	0.632

*Pearson Correlation, O.V ovarian volume, AFC: Antral follicle count, AMH: Anti-Mullerian Hormone, BMI: body mass index

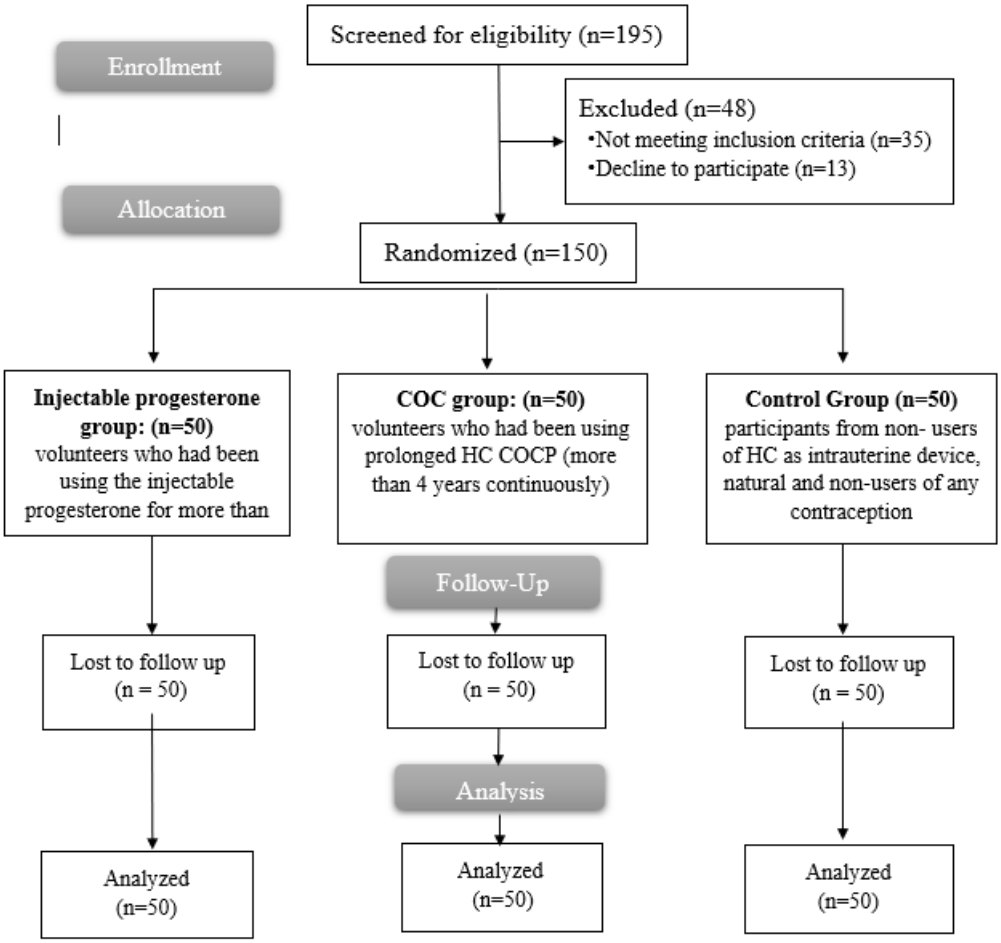

Figure 1: Consort flow diagram of the participants through each stage of the trial