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Ovarian Reserve Dynamics in Users of Hormonal Contraceptives: A Comparative Analysis

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ABSTRACT

Background: Hormonal contraception (HC) is a cornerstone of family planning, which is preferred over non-hormonal contraceptive methods. However, the long-term impact of HC use on ovarian reserve (OR) and fertility remains an area of ongoing investigation. **Objective**: This study aimed to evaluate the difference in OR between hormonal contraceptive users, and non-users. **Methods**: A cross-sectional study was conducted with 200 women, divided equally into two groups; HC-Users: 100 women using hormonal contraception for more than one year; Non-Users: 100 women not using any contraception for at least 6 months, as a control group. OR was assessed in all participants during days (2-4) of their menstrual cycle through measurement of serum Anti-Mullerian Hormone (AMH), Antral Follicle Count (AFC), and serum Follicle Stimulating Hormone (FSH). **Results:** The comparative analysis of HC-Users versus non-users revealed statistically significant differences across ovarian reserve markers. HC-Users exhibited significantly lower serum AMH levels (2.47±1.04) ng/mL compared to non-users (3.32±1.52) ng/mL, $p < 0.0001$. AFC was significantly reduced in HC-Users (10.21±7.41) relative to non-users (14.81±9.63), $p = 0.0002$. HC-Users displayed lower FSH levels (4.23±3.51) IU/L compared to non-users (6.12±1.1) IU/L, $p < 0.0001$. **Conclusion:** HC use is associated with significant reductions in OR markers; AMH, AFC, and FSH. These findings highlight an inhibitory impact of HC which may influence fertility assessments.

Keywords: Hormonal contraception, ovarian reserve, anti-müllerian hormone, antral follicle count, follicle stimulating hormone

1. Introduction

Contraceptive use has become common among women throughout their reproductive years, with approximately 65% of women of childbearing age utilizing some form of contraception, according to the National Survey of Family Growth (Daniels *et al.*, 2022). Concurrently, the trend of delaying childbearing has become widespread, leading to an increase in maternal age at first birth and a decline in total fertility rates (Martin *et al.*, 2019).

In the United States, a growing number of women in their reproductive years are choosing hormonal contraception (HC) over non-hormonal methods for a variety of reasons. Beyond family planning, hormonal contraceptives are also widely used for their ovulation-suppressing effects in the management of conditions like polycystic ovarian syndrome (PCOS), endometriosis, and menstrual cramps. This highlights the importance of assessing their potential impact on fertility and ovarian reserve (OR) (Siegel *et al.*, 2023).

The growing utilization of HC has been paralleled by an increasing number of women seeking fertility evaluations and fertility preservation services (Jones *et al.*, 2018). Consequently, assessment of OR has become a common clinical request. Currently, the most frequently employed markers for evaluating OR are measuring level of serum anti-Müllerian hormone (AMH), level of serum follicle-

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stimulating hormone (FSH), and evaluating antral follicle count (AFC). While AFC is considered the most reliable test for assessing ovarian reserve, its utility can be limited by the requirement for a skilled sonographer. As a result, AMH serum levels offer a practical alternative, particularly for evaluating ovarian follicle depletion related to age (Rooij *et al.*, 2005). AMH, a glycoprotein secreted by granulosa cells of large preantral and small antral follicles, serves as a reliable biomarker due to its correlation with the number of developing primordial follicles (Dewailly *et al.*, 2014). Furthermore, AMH is considered superior to FSH for assessing ovarian reserve due to its stability throughout the menstrual cycle (Kissel *et al.,* 2014), its stronger correlation with antral follicle count (Rooij *et al.,* 2005), and its independence from cycle phase (Tal *et al.,* 2014).

Evidence regarding the influence of HC on OR markers, including serum AMH levels, AFC, and FSH, has been mixed. While several studies suggest a negative influence of HC on these markers, others report no significant effects. These discrepancies highlight the need for further investigation into the potential effects of HC on fertility to guide clinical management, particularly in cases of infertility (Siegel *et al.*, 2023).

Objective of this study

This study sought to assess the difference of OR between HC-users, and non-users.

2. Material and Methods

2.1. Study design

This study was a cross-sectional study, included 200 women.

2.2. Ethical approval

This study was approved by ethics committee at Faculty of Medicine, Fayoum University [No. R520]. The study followed the guidelines of Helsinki Declaration on the conduct of human research. A written informed consent was designed by each patient.

2.3. Subjects

A sample of two hundred (200) Egyptian women were conducted at Infertility Clinic from January 2024 to June 2024.

2.4. Criteria of inclusion

All the 200 women participated in the present study were of age range between 20 to 40 years. All of the included women had no history of anovulation and/or its causes, no endocrinal disorders, no gynecological disorders and/or infections, and no medical disorders. All of these 200 women were non-smokers. In this study, women using hormonal contraception were doing so primarily for contraception/family planning purposes, rather than for the management of endocrine or gynecological conditions. Hormonal contraception methods in this study were: combined oral contraceptive pill (COCP), progestogen only pills (POP), contraceptive injectables, or contraceptive implants.

2.5. Study groups

The 200 women were equally divided into two groups:

- **HC-Users**: as a study group; 100 women using hormonal contraception, for more than one year.
- **Non-Users**: as a control group; 100 women not using any contraception for at least 6 months.

2.6. Criteria of exclusion

In the present study we excluded women younger than 20 years, older than 40 years, women with history of anovulation and/or its causes, women with endocrinal disorders, women with gynecological disorders and/or infections, women with medical disorders, and smokers. In addition, we excluded from this study women using hormonal contraception for any purpose rather than contraception/family planning and women using other contraceptive methods rather than hormonal.

2.7. Assessment of ovarian reserve

Participating women in the present study were undergone ovarian assessment on day (2-4) of menstrual cycle. Transvaginal ultrasound examination were done to investigate AFC. Then, blood samples were collected to determine serum levels of AMH and FSH.

2.8. Statistical analysis

The data were gathered, reviewed, coded, and entered into the Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 23.0, released in 2015, Armonk, NY, USA). Quantitative data were expressed as mean and standard deviation and analyzed using an independent t-test, while qualitative data were summarized as frequencies and percentages. A 95% confidence interval was used, with an acceptable margin of error of 5%. A p-value of less than 0.05 was considered statistically significant.

3. Results

This cross-sectional study included 200 women divided equally into two groups: the HC-Users group (n = 100) as the study group and the Non-Users group (n = 100) as the control group.

3.1. Demographic characters

The demographic data of participants revealed no statistically significant differences between the two groups (Table 1). The mean age in the HC-Users group was 31.3 ±5.7 years, compared to 29.8 ± 5.1 years in the Non-Users group, yielding no significant statistical difference ($t = 0.34$, $p = 0.75$). Similarly, body mass index (BMI) showed no significant variation between HC-Users (28.8 ±4.89 kg/m²) and Non-Users (29.6 ±5.48 kg/m²; $t = 0.19$, $p = 0.86$). Age at menarche also exhibited no notable difference, with a mean of 12.5 ±1.3 years in HC-Users and 12.8 ±1.2 years in Non-Users ($t = 0.29$, $p = 0.78$). Gravidity was comparable between groups, with a mean of 1.3 ±1.5 in HC-Users and 1.4 ±1.7 in Non-Users, showing no statistical significance ($t = 0.08$, $p = 0.94$).

Table 1: Demographic Data

Variable	HC Users n =100	Non-users n = 100	T-test	P-value
Age (years), Mean±SD	31.3±5.7	29.8±5.1	0.34	0.75
BMI (kg/m^2), Mean±SD	28.8±4.89	29.6±5.48	0.19	0.86
Age of menarche (years), Mean±SD	12.5±1.3	12.8±1.2	0.29	0.78
Gravida, Mean±SD	1.3±1.5	1.4±1.7	0.08	0.94

3.2. Ovarian reserve markers

Assessment of OR markers revealed significant differences between the two groups **(Table 2)**.

Anti-Müllerian hormone (AMH): The mean AMH level in HC-Users (2.47 ± 1.04 ng/mL) was significantly lower than in Non-Users (3.32 ±1.52 ng/mL), with a confidence interval (CI) of 0.49 to 1.21, standard error (SE) of 0.18, degree of freedom (DF) of 198, $t = 4.62$, and $p < 0.0001$.

Table 2: Ovarian Reserve Markers

Variable	HC-Users n=100	Non-Users n=100	95% CI	SE	DF	t-test	p-value
AMH(ng/mL),Mean ± SD	2.47±1.04	3.32±1.52	0.49 to 1.21	0.18	198	4.62	<0.0001
AFC # Mean ± SD	10.21±7.41	14.81±9.63	2.20 to 6.99	1.22	198	3.79	0.0002
FSH (IU/L), Mean ± SD	4.23±3.51	6.12±1.1	1.16 to 2.62	0.37	198	5.14	<0.0001

Antral follicle count (AFC): The mean AFC was also significantly reduced in HC-Users (10.21 ± 7.41) compared to Non-Users (14.81 ±9.63), with a CI of 2.20 to 6.99, SE of 1.22, DF of 198, t = 3.79, and p = 0.0002.

Follicle-stimulating hormone (FSH): The mean FSH level was significantly lower in HC-Users (4.23 ± 3.51 IU/L) than in Non-Users (6.12 ± 1.1 IU/L), with a CI of 1.16 to 2.62, SE of 0.37, DF of 198, t = 5.14, and p < 0.0001.

Therefore, the analysis of OR markers highlighted the potential suppressive effects of hormonal contraceptives on ovarian function. Both AMH levels and AFC were markedly reduced in HC-Users compared to Non-Users, indicating a diminished OR. Additionally, FSH levels were significantly lower in HC-Users, further supporting this finding (Figure 1).

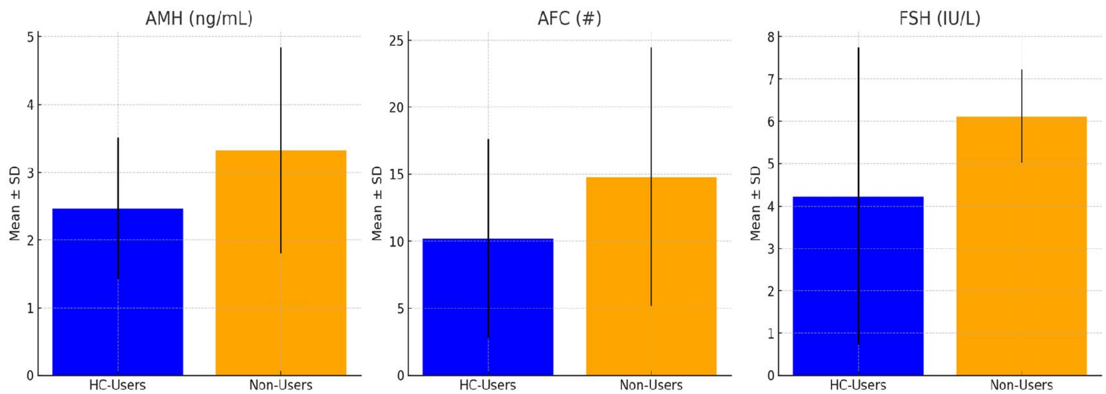

Fig. 1: Mean values and standard deviations for AMH, AFC and FSH, comparing HC-Users and Non-Users

4. Discussion

HC is a cornerstone of family planning, functioning primarily by upsetting the hypothalamic-pituitary-ovarian axis through the administration of synthetic hormones. Combined oral contraceptive pills (COCP), which include both estrogen and progestin, work by suppressing FSH and luteinizing hormone (LH), effectively inhibiting follicular development and ovulation. Progestogen-only methods act by altering cervical mucus to impede sperm penetration and modifying the endometrium to inhibit implantation. Although HC is highly effective in preventing pregnancy, research has highlighted its suppressive effects on OR markers, including AMH and AFC, with these effects generally reversing after cessation. Nonetheless, the long-term influence of HC use on ovarian function and fertility remains under investigation, with studies yielding mixed findings (Siegel *et al.*, 2023; Amer *et al.*, 2019).

In this cross-sectional study, we examined the OR of 200 women, divided equally into HC-users and non-users, by measuring serum AMH, AFC, and FSH levels. Baseline demographic characteristics, including age, BMI, age at menarche, and gravidity, showed statistically insignificant difference between the two groups. However, the analysis of OR markers revealed significant suppressive effects associated with HC use.

Specifically, AMH levels were significantly lower in HC-users (2.47 ±1.04 ng/mL) compared to non-users (3.32 ±1.52 ng/mL; p < 0.0001). Similarly, AFC was significantly reduced in HC-users (10.21 ±7.41) compared to non-users (14.81 ±9.63; p = 0.0002). Serum FSH levels were also lower in HC-users (4.23 ±3.51 IU/L) compared to non-users (6.12 ±1.10 IU/L; p < 0.0001). These findings highlight a clear inhibitory impact of HC on OR markers.

Our findings are consistent with several prior studies. Bentzen *et al.* (2012) assessed OR markers in 228 HC-users compared to 504 non-users. They reported a reduction in AMH by 29.8% (95% CI: 19.9%–38.5%) and a 30.4% decrease in AFC (95% CI: 23.6%–36.7%) in HC-users. Additionally, ovarian volume was reduced by 42.2% (95% CI: 37.8%–46.3%). This study concluded that AMH and

AFC may not provide a precise representation of OR during HC use, highlighting the need for careful interpretation of these markers in clinical practice.

Birch *et al.* (2015) provided additional evidence in their cross-sectional study involving 887 women, including 244 HC users. Their findings revealed that AMH levels were 19% lower (95% CI: 9.1%–29.3%), and AFC was 18% lower (95% CI: 11.2%–24.8%) in HC users compared to non-users. They also observed fewer antral follicles measuring 5–7 mm and 8–10 mm (both $p < 0.001$), alongside an increase in smaller follicles measuring 2–4 mm ($p = 0.008$), indicating complex effects of HC on follicular development.

Amer *et al.* (2019), in a systematic review encompassing 3,280 HC users, reported a significant decline in AMH levels after one year of HC use, with recovery after discontinuation. Interestingly, no notable changes in AMH levels were observed during the first six months of HC use, pointing to a time-dependent impact on OR markers.

Landersoe *et al.* (2019) conducted a large retrospective study comparing 565 HC users and 983 non-users. They found that AMH levels were reduced by 31.1% among COCP users ($p < 0.001$), 35.6% among POP users ($p < 0.001$), and 17.1% among hormonal intrauterine device users ($p = 0.052$) relative to non-users. AFC was also significantly lower among COCP and POP users by 31.3% and 29.7%, respectively ($p < 0.001$). However, vaginal ring users did not exhibit significant differences in AMH or AFC levels, suggesting that the impact of HC may vary depending on the formulation.

In contrast, a cross-sectional study conducted by Siegel *et al.* (2023) examined OR markers among HC users (n = 98) and non-users (n = 25). Although HC users exhibited signs of reduced OR, the differences were not statistically significant. For instance, the mean AMH level was 2.4 ng/mL in HC users compared to 3.2 ng/mL in non-users ($p = 0.20$), AFC was 18 in HC users versus 26 in non-users ($p = 0.10$), and FSH levels were 7.6 IU/L in HC users compared to 6.3 IU/L in non-users ($p = 0.26$). Notably, the study observed a higher utilization of assisted reproductive technologies (ART) among HC users, suggesting possible reproductive implications.

Other studies have yielded mixed outcomes. Hariton *et al.* (2021) analyzed data from 27,125 women and identified significantly lower AMH levels associated with various HC methods. These included reductions of 23.68% with COCP, 22.07% with vaginal rings, and 6.73% with hormonal intrauterine devices, with variability in the extent of suppression.

Conversely, several studies have found no significant differences in OR markers between HC users and non-users. For example, a prospective case-control study by Deb *et al.* (2012) compared OR parameters in 34 women who used COCP for over a year with 36 women who did not use HC. While HC users showed significantly fewer antral follicles ≥6 mm ($p < 0.001$) and smaller ovarian volumes ($p < 0.001$), there was no statistically significant difference in serum AMH levels between the two groups (2.75 ±1.59 ng/mL in HC users vs. 3.06 ±1.27 ng/mL in non-users; $p = 0.440$). However, serum FSH levels were significantly lower in HC users (4.73 ±3.86 IU/L) compared to non-users (6.59 ±0.93 IU/L; $p < 0.05$). The study concluded that while COCPs suppress pituitary gonadotropins and influence the development of larger antral follicles, they do not significantly affect AMH levels.

Similarly, Kucera *et al.* (2016) investigated the impact of HC on levels of AMH in 105 users and 44 non-users. The median AMH level was 2.89 ng/mL in HC users and 3.37 ng/mL in non-users, with no significant difference observed ($p = 0.326$). The study concluded that HC does not appear to have a substantial effect on AMH levels.

Li *et al.* (2011) conducted a prospective study on AMH levels in 95 women, both before and four months after starting HC. This study also reported no significant differences in AMH levels pre- and post-initiation of HC, reinforcing the idea that certain OR markers remain unaffected by HC use.

Our study adds to the body of evidence supporting the suppressive effects of HC on ovarian reserve markers, as indicated by significant reductions in AMH, AFC, and FSH levels among HC users. These results emphasize the importance of considering a patient's HC history when interpreting ovarian reserve markers in fertility evaluations. The findings also highlight the reversible nature of HC's impact upon discontinuation, while calling for further investigation into the long-term implications of HC use on reproductive potential.

5. Conclusion

This study demonstrates that HC use is associated with significant reductions in OR markers, including AMH, AFC, and FSH. These findings highlight a suppressive effect of HC on ovarian function, which may influence fertility assessments. Given the reversibility of these effects upon discontinuation, it is critical to consider a patient's contraceptive history when interpreting ovarian reserve markers in clinical practice. Further research is needed to better understand the long-term reproductive consequences of HC use and to enhance fertility management strategies based on these insights.

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Conflict of interest

All authors have no conflict of interest.

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Author contribution

Kareem El-Nahhas: (corresponding author): Research idea, design of work, manuscript writing, data collection, clinical assessment; **Mahmoud Zaatar:** Data collection, supervision, clinical assessment: **Sameh Abdelmoneim Abdelhamed:** Data collection, supervision, clinical assessment. All the authors have read and approved the final version of the manuscript. **Kareem El-Nahhas**, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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