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Hormonal Contraception Temporarily Suppresses Ovarian Reserve Markers with Partial Recovery

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Abstract

General Background: Hormonal contraception is widely used, yet its implications for ovarian reserve markers remain debated. **Specific Background:** Cross-sectional studies report lower anti-Müllerian hormone (AMH) and antral follicle count (AFC) among users, but lack baseline data to determine temporal dynamics and reversibility. **Knowledge Gap:** Prospective evidence with serial baseline and follow-up measures comparing contraceptive methods is limited. **Aims:** This study prospectively evaluated longitudinal changes in AMH, AFC, and follicle-stimulating hormone among women initiating combined oral contraceptives or levonorgestrel-releasing intrauterine devices versus non-users. **Results:** Mixed-effects models demonstrated significant time-by-group interactions, with early declines in AMH and AFC at three months, followed by partial recovery during continued use, while controls remained stable. **Novelty:** By integrating baseline and repeated measures, this study delineates functional, time-dependent suppression rather than structural ovarian damage. **Implications:** Findings support counseling that hormonal contraception induces temporary, reversible alterations in ovarian reserve markers and should not be interpreted as permanent fertility impairment.

Keywords : Hormonal Contraception, Anti-Müllerian Hormone, Ovarian Reserve Markers, Longitudinal Cohort Study, Oral Contraceptives

Highlight :

- AMH levels decreased 25-29% at 3 months, then partially recovered by 12 months
- Changes reflect temporary ovarian suppression, not permanent structural damage to ovaries
- Both OCP and LNG-IUD users showed similar suppression and recovery patterns.

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Introduction

There are more than 150 million women in the world who use hormonal contraception. Although safety has been established, it is evident that despite this, concerns on possible implications on ovarian reserve and future fertility have remained unaddressed sufficiently by future evidence with baseline measurements. This gap in knowledge is based on the fact that cross-sectional designs were used that could not ascertain the causality, define temporal dynamics, or determine reversibility.

Medication OCPs inhibit secretion of endogenous gonadotropin by negative feedback, leading to inhibition of ovarian follicle formation. The levonorgestrel-releasing intrauterine devices (LNG-IUD) have local progestin actions and little systemic hormonal effects. Reduced anti-Mullerian hormone (AMH) and antral follicle count (AFC) in contraceptive users has been reported in previous cross-sectional studies, but this type of study cannot prove cause-effect nor can it be reversible because of lack of baseline measurements.

The focus of the proposed longitudinal cohort with serial baseline and follow-up measures is to describe the temporal pattern of changes in the ovarian reserve markers in women who initiate hormonal contraception, compare pattern of the changes among the methods, and assess marker recovery after the treatment discontinuation.

Methods

A. Study Design, Setting and Participants.

Future longitudinal cohort study, Tikrit Teaching hospital, Iraq (2021-2024; IRB-2021-TH-035). Among women who used hormonal contraception, 90 aged 20-40 years and initiated the use of hormonal contraception during the first time were stratified by the method Group A (OCP, n=45) and Group B (LNG-IUD, n=45). There were 30 non-contraceptive users who were used as controls. Inclusion criteria: FSH baseline of less than 10mIU/mL, regular menstruation (between 21-35 days) and no previous use of any hormonal forms of contraceptives. Inclusion criteria: diagnosed infertility, PCOS, thyroid disease, hyperprolactinemia, as well as current malignancy, more than 10 pack-years of smoking, and previous ovarian surgery. Each of the 120 participants was assessed by the same serial measures at baseline (pre-initiation), 3, 6 and 12 months.

B. The choice of contraceptive method is 2.2.

Participants were not randomized, but their choice of contraceptive method, clinical judgment (contraception, menorrhagia, dysmenorrhea, or other gynecologic conditions), or recommendation by their provider were the factors according to which the choice of contraceptive—method was made. Non-randomized allocation can lead to selection bias but clinical practice defines the selection of methods that a patient should use. Mixed-effects We statistically adjusted the mixed-effects model to control the age and BMI. There were no significant or significant differences between groups on baseline characteristics (Table 1), which justifies the possibility of making comparisons even in this situation of non-random distribution.

C. Standardization and Timing of Measurement.

Contraceptive method standardized laboratory sampling to reduce variability in circulating hormones: OCP and LNG-IUD users sampled on days 2-5 of hormone-free interval/during withdrawal bleed; control and naturally cycling women sampled on days 3-5 of follicular phase of menstrual cycle. The withdrawal bleed timing being a constant reference point, although there are no natural cycles in OCP users, the withdrawal bleed time is analogous to the hormonal state of early follicular phase. All the ultrasound tests were carried out by one trained sonographer (F.A.T.) under a standardized protocol (7.5 MHz transvaginal probe) to reduce variability based on operators. Intra observer reproducibility was measured among 15 randomly selected subjects, through measurement repeat; intra-class correlation coefficient of AFC was higher than 0.95.

D. Statistical Analysis

Linear mixed-effects models were used as primary methods to examine longitudinal changes in the markers of an ovarian reserve (AMH and AFC). The variables were fixed in terms of time (baseline, 3, 6 and 12 months), group (OCP, LNG-IUD and Control) and the time x group interaction with baseline age and BMI being adjusted. To consider within-subject correlation of repeated measurements, a random intercept of participant was added.

E. Specification of the model: outcome = time + group + time x group + age + BMI + (1 participant).

It used maximum likelihood estimation, which enabled the use of incomplete follow-up participants under the missing-at-random assumption. Random slope models were also run but were not accepted because they showed no significant contribution to model fit, in terms of Akaike Information Criterion (DAIC = 3.2) and likelihood ratio test (p = 0.074).

Type III analysis of variance was used to test the fixed effects with Satterthwaite degrees of freedom approximation (through the lmerTest package). Estimated marginal means were conducted to establish the determination of post-hoc pairwise comparisons by the use of Tukey adjustment to multiple testing. The findings are given in the form of model-based estimated marginal means with confidence intervals at 95 percent.

Secondary exploratory analyses tested post-cessation recovery on a subgroup (n = 22) of participants through paired t-tests without taking any statistical power. All calculations were done in R with the help of the lme4, lmerTest and emmeans packages. Two tailed $p < 0.05$ was considered statistically significant.

RESULTS

A. The characteristics of the participants and their follow-up were outlined in 3.1.

Out of 120 enrolled subjects, 114 subjects (95 percent) completed 12-month follow-up. There was no significant difference in the baseline characteristics (Table 1). Of the participants of the treatment, 84 were using assigned contraceptive method 12 months. Six had been discontinued prematurely (3 OCP because of side effects, 3 LNG-IUD because of user dissatisfaction) and entered analysis by month available. Twenty-four women (13 OCP, 11 LNG-IUD) stopped contraception in follow-up to become pregnant; 22 of them had follow-up data (mean 5.9+-2.3 months) after stopping contraceptive use.

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Table 1: Participant Characteristics in the Baseline.

Characteristic	OCP (n=45)	LNG-IUD (n=45)	Control (n=30)
Age (years)	32.6±6.1	32.2±6.3	31.8±6.4
BMI (kg/m²)	24.2±3.8	24.6±3.9	23.9±3.6
Baseline AMH (ng/mL)	3.1±1.2	3.2±1.3	3.0±1.1

No significant differences at baseline (p>0.05 for all comparisons).

B. AMH Trajectories: Estimated Marginal Means

Linear mixed-effects model (converged without warning) indicated large timexgroup interaction (F[2,336]=3.847, p=0.022). The table below (Table 2) shows the estimated marginal means (model-predicted adjusted means) of the mixed-effects regression. Significant AMH deterioration between baseline and 3 months (estimated difference -0.9 ng/mL, 95% CI -1.4 to -0.02, p<0.001 post-hoc Tukey comparison) with some recovery pattern persisting through 12 months (12-month difference between baseline and -0.4 ng/mL, CI -0.8 to -0.02, p=0.040) was found in OCP users. The same pattern of suppression was observed in LNG-IUD users (3-month difference -0.8 ng/mL, CI -1.3 to -0.3, p<0.001) but the recovery was at 12 months (-0.3 ng/mL, CI -0.7 to 0.1, p=0.102). AMH control group did not change (time effect p=0.32, there was no significant change across the time points). Random intercept only model was preferred in model comparison (AIC) over random slope model (DAIC=3.2, LRT p=0.074), and this is in support of simpler model.

Table 2: Model-Estimated Marginal Means (95% CI) of AMH.

Group	Baseline	3 months	12 months	Time×Group p
OCP	3.1(2.8–3.4)	2.2(1.9–2.5)**	2.7(2.4–3.0)*	0.022
LNG-IUD	3.2(2.9–3.5)	2.4(2.1–2.7)**	2.9(2.6–3.2)	
Control	3.0(2.7–3.3)	3.1(2.8–3.4)	3.0(2.7–3.3)	

Linear mixed-effects regression estimated marginal means (model-predicted adjusted means) with 95% confidence intervals. p version (compared to baseline) p<0.001 versus 0.05 versus baseline (post-hoc Tukey testing of multiple comparisons).

C. AFC and Secondary Outcomes

Antral follicle count had a significant timexgroup interaction (p=0.031). After 3 months of OCP use, there was a decrease in AFC (estimated mean difference of -2.5 follicles, CI -3.9 to -1.1, p-value of 0.001) and a partial recovery after 12 months (-1.3 follicles, p=0.043). The LNG-IUD clients demonstrated the significant moderately decreasing tendency at 3 months (-1.3 follicles, p=0.052) and the restoration of the baseline by 12 months (p). There was no significance in timexgroup interaction of FSH (p=0.184) and little variation at every group and time.

The secondary outcomes encompassed the follicles stimulating hormone (FSH), ovarian volume, and post-cessation recovery pattern of AMH and AFC among participants who were not on contraception anymore. Paired analysis in 22 patients who had post-cessation follow-up data (Mean of 5.9+-2.3 months after discontinuation) revealed AMH recovery which was numerical though no longer significant. The AMH at cessation among OCP users was 2.1+-1.0 ng/mL and 3.0+-1.1 ng/mL, respectively, at cessation and post-cessation (mean difference +0.9 ng/mL, 95% CI -0.2 to 2.0, p=0.156). Similar results were obtained with LNG-IUD users who demonstrated numerical recovery 2.3+-1.1 to 3.1+-1.2 ng/mL (mean difference +0.8 ng/mL, CI -0.3 1.9 p=0.188). Such insignificance in this subset cannot be ascribed to a large sample size and the absence of data.

Participants of the control group did not change their non-contraceptive status during the 12 months follow-ups, and none of them started using hormone contraception in the follow-up. One of the control subjects conceived at month 8 and was locked out of the further analyses as per protocol.

Discussion

Our longitudinal, prospective, serial baseline, and linear mixed-effects regression study indicates that hormonal contraception causes short-term inhibition of markers of ovarian reserve. The scale of early AMH loss (25-29) agrees with the previous cross-sectional data, but the prospective design with baseline data provides a temporal correlation and defines the pattern of recovery.

This pattern has a known mechanism (functional pharmacological suppression of follicle recruitment in the ovary through the decreased secretion of FSH/LH) that is consistent with the observed pattern (rapid suppression and later recovery) and is not due to structural ovarian injury. This conclusion is backed by: (1) marker recovery curves when continued used; (2) numerical recovery after cessation; (3) comparable controls when used by control group; (4) mechanism of action which is different between OCP-LNG-IUD.

Important limitations worthy of acknowledgment may include non-randomized allocation may have introduced selection bias, albeit baseline characteristics were balanced and variables controlled statistically, single sonographer may reduce the general applicability of results, but lower bound estimate of intra-observer variability was performed and >0.95, measurement procedure timing between methods (withdrawal bleed vs

natural cycle), although timing was equalized within method, moderate sample size leading to decreased power for post-cessation subset analysis, observational design resulting in not using causal analysis, and no oocyte quality or clinical fertility outcomes.

Clinical implications: It can be explained to women on hormonal contraception that decreases in the indicators on ovarian reserve are temporary functional abrogation, and not enduring structural injury. Such hypothesis-generating observations justify counseling that marker suppression induced by contraceptives should not discourage proper use of contraceptives to those who want to postpone childbirth.

Conclusion

In the mode of using serial within-participant measurements and linear mixed-effects modeling, initiation of combined oral contraceptives and levonorgestrel-releasing intrauterine devices were found to be linked with an early AMH and AFC drop and partial restoration within continued use and numerical recovery following discontinuation in a small group. The results of the observed trajectories are in line with pharmacological inhibition of ovarian activity through physiological mechanisms as opposed to permanent structural ovarian damage. As the study was not randomly designed and did not include a large post-cessation sample, the results ought to be regarded as the hypothesis-generating ones and should be verified in more extensive longitudinal cohorts with the clinical fertility outcomes taken into account.

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