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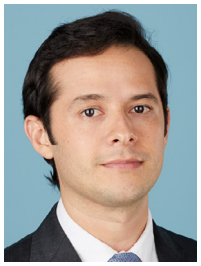
ARTICLE

Effect of various contraceptives on oocyte yield and maturation in patients undergoing planned oocyte cryopreservation



BIOGRAPHY

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KEY MESSAGE

Different common forms of contraception are not associated with a negative influence over the oocyte yield or maturation rate in patients undergoing planned oocyte cryopreservation. Patients using contraception should be reassured that their contraceptive preference will not result in a decreased number of oocytes or maturation rates during their treatment cycle.

ABSTRACT

Research question: Do the various forms of hormonal and non-hormonal contraceptives have any association with ovarian stimulation outcomes, such as oocyte yield and maturation, in patients undergoing planned oocyte cryopreservation (POC)?

Design: This retrospective cohort study included all patients who underwent POC cycles between 2011 and 2023. The use of types of contraception before a POC cycle was recorded. The study evaluated the median number of cumulus–oocyte complexes obtained after vaginal oocyte retrieval and the proportion of metaphase II oocytes that underwent vitrification among all the cohorts.

Results: A total of 4059 oocyte freezing cycles were included in the analysis. Eight types of contraceptive method were recognized in patients undergoing ovarian stimulation: intrauterine device (IUD), copper ($n = 84$); IUD, levonorgestrel low dose (<52 mg) ($n = 37$); IUD, levonorgestrel ($n = 192$); subdermal etonogestrel implant ($n = 14$); injectable medroxyprogesterone acetate ($n = 11$); etonogestrel vaginal ring ($n = 142$); combined oral contraceptive pills ($n = 2349$); and norelgestromin transdermal patch ($n = 10$). The control group included patients not using contraceptives or using barrier or calendar methods ($n = 1220$). Among all the cohorts the median number of cumulus–oocyte complexes retrieved during oocyte retrieval was comparable ($P = 0.054$), and a significant difference in oocyte maturity rate with median number of vitrified oocytes was found ($P = 0.03$, $P < 0.001$, respectively). After adjusting for confounders a multivariate analysis found no association between the type of contraceptive and proportion of metaphase II oocytes available for cryopreservation.

Conclusions: Among the various forms of contraception, none was shown to have an adverse association with oocyte yield or maturation rate in patients undergoing POC.

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KEY WORDS
Egg freezing
Fertility preservation
Oocyte freezing
Ovarian stimulation
Planned oocyte vitrification

INTRODUCTION

Delayed childbearing has become commonplace In contemporary society. Advances in hormonal contraceptives have enabled women to pursue personal and professional pursuits while managing the initiation of childbearing. Some of these women will face unforeseen fertility issues while trying to conceive at an advanced age due to a compromised ovarian reserve and/or other infertility-related causes. Consequently, these patients may require assisted reproductive technique (ART) treatments, with a suboptimal prognosis. In some cases, ART may result in costly and time-consuming therapies that ultimately require donor gametes or the abandonment of treatment.

Fertility preservation strategies may provide a flexible solution to the delayed childbearing enabled by modern contraceptive technologies. The most common strategy employed by reproductive-aged women is elective egg freezing. Planned oocyte cryopreservation (POC) has experienced significant improvements in reliability and availability since its inception in the 1980s (*Bernard et al., 1985*; *Chen, 1986*). POC is broadly offered to women who want to postpone motherhood, as a novel strategy aimed to mitigate the risk of age-related infertility (*Gil-Arribas et al., 2022*). This procedure has provided practitioners with the opportunity to offer an improvement in the autonomy of many women in their decision-making processes prior to undertaking motherhood (*Cobo et al., 2021*).

Oocyte vitrification initially targeted patients facing gonadotoxic chemotherapy treatments. In 2012, as outcomes improved and oocyte cryopreservation technology improved, oocyte vitrification was no longer classified as an experimental procedure by the American Society for Reproductive Medicine (*American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2013*). Soon thereafter, a rapid uptick in the use of vitrification was observed not only in patients facing oncological treatments, but also among patients with other medical conditions. The commercial adoption of oocyte cryopreservation soon followed, with a widespread availability of cryopreserved donor oocytes (*American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, 2021*). Since then, the technology of vitrification has markedly improved the efficacy of oocyte cryopreservation in terms of oocyte survival and pregnancy rates and has boosted women's options for fertility preservation (*Rienzi, 2017*).

Commonly, patients who are planning oocyte cryopreservation include healthy young women who do not have an infertility diagnosis (*Letorneau et al., 2017*). A significant proportion of these women are actively using some form of contraception, and some forms of oral contraception alter serum anti-Müllerian hormone (AMH) and other ovarian reserve markers depending on the type and duration of use (*Letorneau et al., 2017*; *Nelson et al., 2023*). Fluctuations in serum AMH are attributed to the suppressive effects of hormonal contraceptives on the hypothalamic–pituitary–ovarian axis, which negatively affects follicular development and ovulation. Furthermore, some studies have shown that hormonal contraceptive use is linked to suboptimal outcomes in infertile patients undergoing ovarian stimulation and/or embryo transfers (*Farquar et al., 2017*).

Besides the widely recognized temporary effect of hormonal contraceptives on ovarian reserve markers, along with a few controversial findings on IVF outcomes, there is, to date, limited research on the use of hormonal contraceptives in patients undergoing POC. The clinical repercussions of these contraceptives, the relationship to suppression of the ovarian–hypothalamic axis and the influence on oocyte quality after ovarian stimulation require further elucidation. Therefore, the objective of this study was to evaluate the possible association of various forms of hormonal and non-hormonal contraceptive on oocyte yield and maturation in patients undergoing POC treatment cycles.

MATERIAL AND METHODS

Study design and participants

A retrospective cohort analysis was performed at a single, private-academic ART centre, including all patients who underwent POC cycles via vitrification between January 2011 and July 2023. Only patients who underwent gonadotrophin-releasing hormone (GnRH) antagonist protocol stimulation were included in the analysis. All ovarian stimulation protocols and laboratory methods used in the study have previously been described (*Hernandez-Nieto et al., 2019*; *Hernandez-Nieto et al., 2020a*).

The oocytes were vitrified using a vitrification technique following a standardized laboratory protocol. Vaginal oocyte retrieval was performed 36 h after the trigger injection, and during oocyte searching and manipulation, Enhance WG (modified human tubal fluid [HTF] with Human Serum Albumin (HSA) and gentamicin for sperm washing; Vitrolife, USA) was used. Following retrieval, the oocytes were immediately cultured in low-oxygen conditions (5% oxygen, 5.8% carbon dioxide, 89.2% nitrogen) in equilibrated Sage Quinn's Advantage Cleavage Medium (SAGE In Vitro Fertilization, CooperSurgical, USA) supplemented with 5% Sage Human Albumin (100 mg/ml; SAGE In Vitro Fertilization, CooperSurgical, USA).

At 1 h after retrieval, oocyte cumulus cells were removed by washing them for 30 s in Sage Hyaluronidase (80 U/ml in HEPES-HTF; SAGE In Vitro Fertilization, CooperSurgical, USA), followed by oocyte denudation using three different internal diameter sizes of Stripper Tips (275, 175 and 135 μm; ORIGIO, USA). Following this, the maturity of the oocytes was assessed; after they had been classified as mature (metaphase II [MII]) or immature (metaphase I or germinal vesicle), the oocytes were cultured for a further hour.

Two hours after retrieval, MII oocytes were vitrified using the Cryotop method (Kitazato, Japan). During this vitrification technique, MII oocytes were initially placed in an equilibration solution containing 7.5% ethylene glycol, 7.5% dimethyl sulphoxide and 20% synthetic serum substitute/M199 solution for 12–15 min, followed by 60 s in a vitrification solution containing 15% ethylene glycol, 15% dimethyl sulphoxide, 0.5 mol/l sucrose and 20% synthetic serum substitute/M199. Following this washing, the oocytes were immediately loaded on a Cryotop strip with minimum volume and plunged into liquid nitrogen. Any remaining oocytes that were immature at time of denuding and assessment were cultured for another 4–6 h, and if they matured to late MII oocytes they were vitrified. Immature oocytes were cultured for up to 24 h after retrieval and vitrified if matured, using the same technique as previously described.

The study cohorts were stratified based on their history of prior contraceptive use. Demographic information, ovarian stimulation parameters and embryology laboratory data were recorded from the electronic medical record. Contraceptive use was mainly self-reported by the participants. Before the first consultation at the study site, all the enrolled participants completed an online questionnaire about their reproductive and gynaecological history, including contraceptive use and duration of use. During the first consultation for the fertility assessment and counselling, the women were also asked about their current contraceptive method. Finally, a manual chart review was conducted to confirm the type and duration of contraceptive use. Actual contraceptive use was considered if the patients had used any given method for at least 3 consecutive months before the initiation of ovarian stimulation. Patients who used an IUD maintained the device in place during ovarian stimulation. Use of the oral contraceptive pill (OCP) for scheduling purposes before ovarian stimulation was considered as a covariate in the multivariate analysis and was not considered towards the 3-month period of usage before stimulation started.

Participants with incomplete information regarding the use of contraceptives, those planning oocyte cryopreservation for other medical reasons and patients with polycystic ovary syndrome, a fragile X pre-mutation, a cancer diagnosis or a diagnosis of diminished ovarian reserve with AMH concentrations below 0.7 ng/dl were excluded from the analysis.

The primary outcome of the study was to compare the total and median number of retrieved cumulus–oocyte complexes (COC) during each stimulation cycle and the percentage of MII or mature oocytes yielded per cycle, more commonly termed the oocyte maturity rate.

This retrospective analysis was approved by the academic Institutional Review Board of Mount Sinai School of Medicine (HS number STUDY-18–00441, dated 8 December 2023). All patient information was de-identified before data analysis.

Statistical analysis

Demographic and ovarian stimulation and embryology laboratory data were obtained for all the participants. Medians, interquartile ranges (IQR) and frequencies were calculated for all the variables.

Descriptive and univariate analysis were performed using a Mann–Whitney *U*-test, Kruskal–Wallis test, Fisher's exact test or chi-squared test, as appropriate. A multivariate logistic regression analysis fitted with a generalized estimating equation (GEE) was used to account for participants who underwent multiple oocyte retrieval cycles. Adjusted odds ratios (aOR) with 95% confidence intervals (95% CI) were calculated. All variables that showed significance on the univariate analysis and/or variables that were thought to be clinically relevant were encompassed and adjusted for as covariates in the final model. The final model was adjusted for oocyte age, body mass index (BMI), AMH concentrations, previous oocyte retrievals, oestradiol concentrations on the day of the ovulation trigger, gonadotrophin dosage used, year of treatment and use of oral contraceptives for scheduling purposes. All *P*-values were two sided with a clinical significance level set at $P < 0.05$.

A sample size calculation and power analysis showed that 296 cycles per group were needed to provide an 80% power to detect a 10% difference in oocyte maturity rate among groups with a value of $\alpha = 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, USA).

RESULTS

During the study period, 4059 oocyte freezing cycles were included in the analysis. Different compositions and contraceptive methods were recognized in participants undergoing ovarian stimulation for oocyte cryopreservation: intrauterine device (IUD), copper ($n = 84$); IUD, levonorgestrel low dose (<52 mg) ($n = 37$); IUD, levonorgestrel 52 mg ($n = 192$); subdermal etonogestrel 68 mg implant ($n = 14$); injectable medroxyprogesterone acetate ($n = 11$); etonogestrel vaginal ring ($n = 142$); combined OCP ($n = 2349$); and norelgestromin transdermal patch ($n = 10$). In addition, there was a control group of patients not using contraceptives or using barrier or calendar methods ($n = 1220$). All the demographic and stimulation parameters are depicted in TABLE 1.

On analysis of the patients' demographic characteristics, the cohorts differed significantly in terms of age ($P < 0.0001$), BMI ($P = 0.01$), baseline FSH ($P = 0.01$), antral follicle count (AFC) ($P < 0.0001$), serum AMH ($P = 0.02$), day of the ovulation trigger ($P < 0.0001$), total gonadotrophin dose used ($P < 0.0001$) and number of follicles larger than 18 mm on the day of ovulation triggering ($P = 0.0003$). Significant differences ($P < 0.001$) were also found in the use of OCP for scheduling purposes among the cohorts, the oral contraceptive group being the largest one (45.64%) (TABLE 1).

The median number of COC retrieved was comparable among all the cohorts ($P = 0.054$). A significant difference in the median number of oocytes vitrified ($P = 0.03$) and the oocyte maturity rate ($P < 0.0001$) was found between the cohorts. FIGURE 1 depicts the median number of COC retrieved and the percentage of vitrified MII oocytes in each contraceptive group.

In the multivariate analysis after adjusting for age, BMI, AMH, previous oocyte retrievals, oestradiol concentration on the ovulation trigger day, gonadotrophin use, use of OCP for scheduling and year of treatment, and using control patients as the reference group, no association was found between all the distinct types of contraceptive and the proportion of MII oocytes vitrified. All the calculated aOR are shown in TABLE 2. A sensitivity analysis was performed analysing a simpler model avoiding potential collinearity, and adjusting only for AMH, oocyte age, BMI, previous oocyte retrievals, OCP for scheduling and year of treatment showed comparable estimates (Supplementary Table 1).

Additionally, a secondary sensitivity analysis was performed by excluding contraceptive groups that included small sample sizes in order to diminish the potential heterogeneity created by the small sample size among the groups. After excluding etonogestrel implants, injectable medroxyprogesterone acetate and norelgestromin transdermal patches, and comparing the other contraceptive groups, the findings were similar to those of the main analysis. Significant differences were observed in the univariate analysis between the remaining cohorts: age ($P < 0.0001$), baseline oestradiol ($P < 0.0001$), baseline progesterone ($P < 0.0001$), AMH ($P = 0.007$), previous oocyte retrievals ($P = 0.009$), baseline AFC ($P < 0.0001$), gonadotrophin cumulative dose ($P < 0.0001$), day of ovulation triggering ($P < 0.0001$) and follicles measuring over 18 mm on the trigger day ($P < 0.0001$) (Supplementary Table 2). The

TABLE 1 DEMOGRAPHIC, OVARIAN STIMULATION AND EMBRYOLOGICAL LABORATORY DATA FOR THE STUDY COHORTS BASED ON THE TYPE OF CONTRACEPTION USED

Variable	None – control group	IUD, copper	IUD, levonorgestrel <52 mg	IUD, levonorgestrel 52 mg	Etonogestrel implant 68 mg	Injectable medroxyprogesterone acetate	Etonogestrel vaginal ring	Oral contraceptive pills	Norelgestromin transdermal patch	*P*-value
	(*n* = 1220)	(*n* = 84)	(*n* = 37)	(*n* = 192)	(*n* = 14)	(*n* = 11)	(*n* = 142)	(*n* = 2349)	(*n* = 10)	
Age (years)	36.6 (4.2)	35.1 (3.5)	33.1 (4.0)	33.8 (3.8)	32.9 (2.5)	37.4 (4.2)	35.9 (4.1)	35.8 (4.1)	35.5 (2.9)	<0.0001[a]
Body mass index (kg/m^2)	22.7 (4.6)	22.4 (4.0)	23.0 (4.3)	22.9 (4.2)	21.8 (5.4)	21.5 (4.3)	23.6 (5.6)	22.6 (4.8)	25.5 (8.5)	0.01[a]
Baseline oestradiol (pg/ml)	42.3 (22.5)	45.0 (22.0)	44.0 (24.5)	48.0 (33.2)	42.0 (26.0)	43.4 (15.0)	45.0 (26.3)	38.0 (30.0)	36.5 (37.8)	<0.0001[a]
Baseline FSH (mIU/ml)	6.5 (2.7)	6.0 (2.3)	6.3 (2.2)	6.5 (2.7)	6.2 (2.4)	5.5 (2.3)	6.6 (2.8)	6.5 (3.4)	4.6 (1.4)	0.01[a]
Baseline progesterone (ng/ml)	0.5 (0.2)	0.6 (0.4)	0.5 (0.5)	0.5 (0.4)	0.4 (0.3)	0.5 (0.2)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	<0.0001[a]
Anti-Müllerian hormone (ng/ml)	2.3 (2.2)	2.6 (2.3)	2.3 (2.1)	2.4 (2.0)	2.4 (0.5)	1.9 (3.0)	2.0 (2.1)	2.2 (2.2)	3.2 (2.4)	0.02[a]
Baseline antral follicular count	13.0 (9.0)	16.0 (8.0)	18.0 (11.0)	16.0 (11.0)	13.0 (10.0)	13.0 (7.0)	13.0 (9.0)	13.0 (9.0)	16.5 (19.0)	<0.0001 [a]
Previous oocyte retrieval cycles	0 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.5)	<0.0001[a]
Days of OCP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (15)	0 (0)	<0.0001[a]
Gonadotrophin cumulative dose (IU)	3600.0 (1650.0)	3400.0 (1925.0)	3450.0 (2025.0)	3487.5 (1762.5)	3975.0 (1725.0)	3525.0 (1375.0)	3900.0 (1875.0)	3900.0 (1725.0)	3525.0 (2325.0)	<0.0001[a]
Day of ovulation trigger	11.0 (1.0)	12.0 (2.0)	12.0 (1.0)	12.0 (1.0)	12.0 (2.0)	11.0 (0.0)	12.0 (1.0)	12.0 (2.0)	11.0 (3.0)	<0.0001[a]
Oestradiol on trigger day (pg/ml)	2444.0 (1647.0)	2657.5 (1389.5)	2787.0 (1155.0)	2420.0 (1698.0)	2718.0 (1461.0)	2749.0 (2669.0)	2619.5 (1637.0)	2549.0 (1637.0)	2353.5 (1641.0)	0.13[a]
Progesterone on trigger day (ng/ml)	1.0 (0.6)	1.0 (0.7)	0.9 (0.5)	1.1 (0.7)	1.2 (1.0)	1.1 (0.6)	1.1 (0.6)	1.0 (0.7)	1.0 (0.7)	<0.0001[a]
Follicles >18 mm on trigger day	4.0 (3.0)	4.0 (3.5)	6.0 (3.0)	4.0 (3.0)	4.0 (3.0)	5.0 (2.0)	4.0 (3.0)	4.0 (3.0)	4.0 (3.0)	0.0003[a]
Cumulus–oocyte complexes retrieved	15.0 (10.0)	15.0 (10.0)	18.0 (10.0)	16.0 (12.0)	16.5 (12.0)	15.0 (12.0)	15.0 (11.0)	14.0 (13.0)	16.0 (11.0)	0.054[a]
Oocytes vitrified	11.0 (8.0)	13.0 (8.5)	14.0 (10.0)	12.0 (10.0)	13.0 (7.0)	12.0 (7.0)	11.0 (8.0)	11.0 (10.0)	13.0 (8.0)	0.03[a]
Used OCP for scheduling, *n* (%)	9 (0.74%)	1 (1.19%)	0 (0)	1 (0.52%)	0 (0)	0 (0)	0 (0)	1072 (45.64%)	0 (0)	<0.000[b]
MII oocyte proportion, *n* (%)	1567/19630 (79.83%)	1149/1436 (80.0%)	561/688 (81.54%)	2876/3633 (79.16%)	206/262 (78.63%)	140/193 (72.54%)	1812/2307 (78.54%)	31,735/39,023 (81.32%)	151/183 (82.51%)	<0.0001 [b]

Data are presented as median and interquartile range unless stated otherwise. The proportion of MII oocytes was calculated as the number of MII oocytes divided by the total number of oocytes retrieved.

Unadjusted analysis was performed using a [a]Kruskal–Wallis test or [b]chi-squared test. Statistical significance was set at $P < 0.05$.

IUD, intrauterine device; MII, metaphase II; OCP, oral contraceptive pill.

median number of COC retrieved ($P = 0.02$) and the percentage of MII preserved oocytes were different among the cohorts ($P = 0.01$) (Supplementary Figure 1). The adjusted multivariate GEE analysis showed that there was no association between the type of contraceptive and a lower odds of cryopreserving fewer MII oocytes per group (Supplementary Table 3).

Finally, a sub-analysis was performed by grouping all types of hormonal contraception ($n = 2755$) and comparing this group versus a control group with no hormonal contraception ($n = 1293$). Copper IUD users ($n = 84$) and barrier or non-users ($n = 1209$), as well as control participants who used OCP for scheduling ($n = 11$), were excluded from the analysis. The demographics of the two groups and the ovarian stimulation parameters are depicted in TABLE 3.

In a univariate analysis, significant differences were found in terms of age ($P < 0.0001$), AMH ($P = 0.007$), number of previous oocyte retrieval cycles ($P = 0.0007$) and baseline oestradiol ($P < 0.0001$) and baseline progesterone ($P < 0.0001$) concentrations among patients using hormonal contraception compared with the control group. Furthermore, other significant differences in cumulative gonadotrophin dosage ($P < 0.0001$), day of ovulation triggering ($P < 0.0001$) and oestradiol ($P = 0.006$) and progesterone ($P < 0.0001$) concentrations on the day of ovulation triggering were found (TABLE 3). No significant differences were found in the median number of oocytes retrieved (hormone group, 15 oocytes, IQR 13; controls, 15 oocytes, IQR 10; $P = 0.69$) and median number of MII oocytes vitrified (hormone group, 12 oocytes, IQR 10; controls, 11 oocytes, IQR 9; $P = 0.35$). There was a significant difference in the oocyte maturity rate (hormone group, 81.0%; controls, 79.8%; $P = 0.0002$) between the two groups. In a multivariate analysis, after adjusting for confounders, there was no association between the use of hormonal contraception and the proportion of vitrified MII oocytes (aOR 1.01, 95% CI 0.939–1.087).

DISCUSSION

Through POC, women can actively manage their reproductive lifespan, and align family planning with their personal

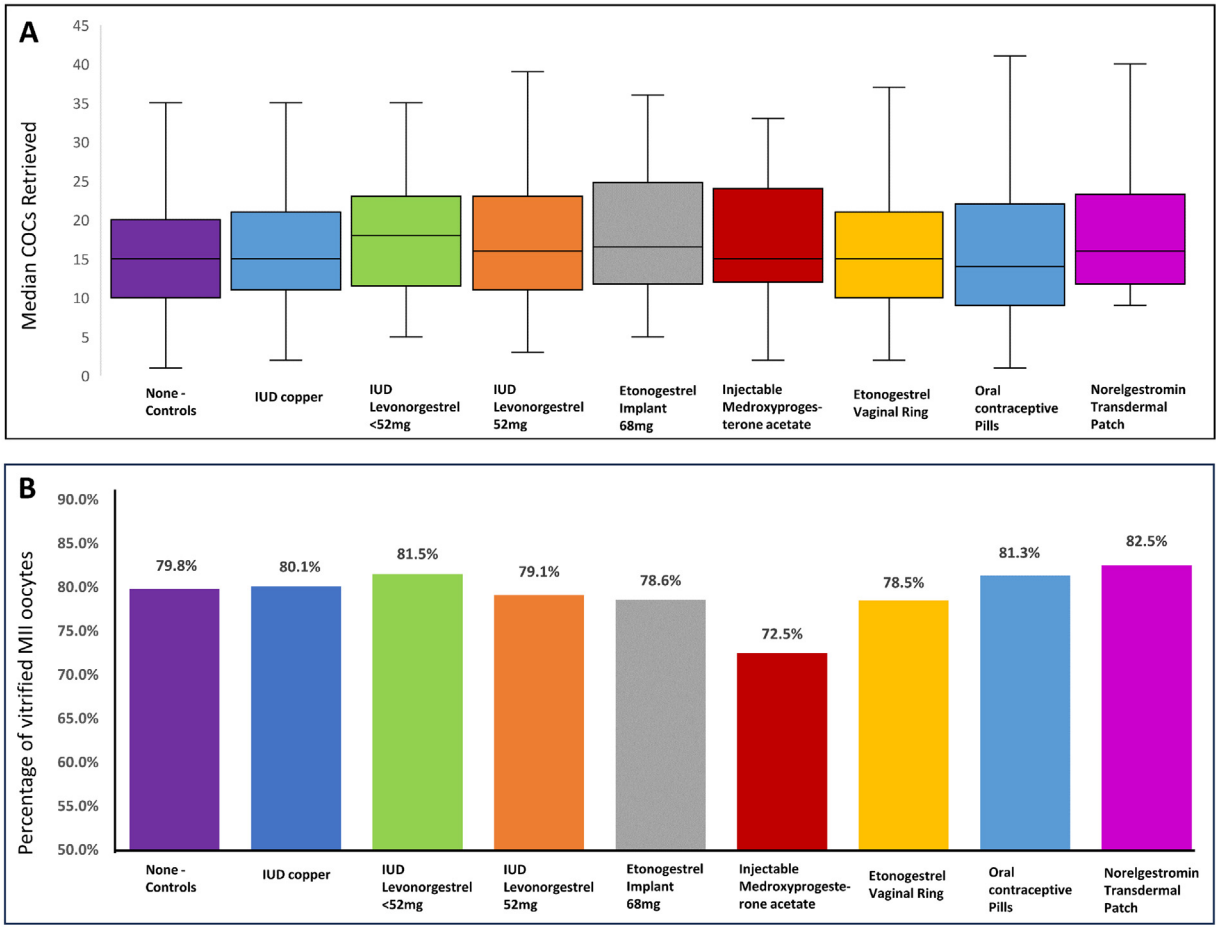

FIGURE 1 (A) Box plot graph showing medians, interquartile ranges and minimum and maximum values of retrieved cumulus–oocyte complexes (COCs) per cohort of contraceptive method. Univariate analysis, $P = 0.054$. (B) Percentage of vitrified metaphase II (MII) oocytes per total number of COC by cohort of contraceptive method. Univariate analysis, $P < 0.0001$. IUD, intrauterine device.

TABLE 2 MULTIVARIATE ANALYSIS ESTIMATES AND AOR FOR THE DIFFERENT TYPES OF CONTRACEPTIVE AND PROPORTIONS OF MII OOCYTES VITRIFIED

Contraceptive type	aOR (95% CI)	*P*-value
Controls	**1 (reference)**	
IUD, copper	1.08 (0.87–1.34)	0.43
IUD, levonorgestrel <52 mg	1.19 (0.83–1.72)	0.33
IUD, levonorgestrel 52 mg	1.06 (0.93–1.22)	0.33
Etonogestrel implant 68 mg	1.03 (0.70–1.52)	0.86
Injectable medroxyprogesterone acetate	0.76 (0.47–1.23)	0.27
Etonogestrel vaginal ring	0.97 (0.82–1.16)	0.81
Oral contraceptive pills	1.01 (0.93–1.09)	0.78
Norelgestromin transdermal patch	1.16 (0.76–1.78)	0.48

Model adjusted for oocyte age, body mass index, serum anti-Müllerian hormone concentrations, previous oocyte retrievals, serum oestradiol concentrations on the day of the ovulation trigger, gonadotrophin total dosage, year of treatment and use of oral contraceptives for scheduling purposes.

Statistical significance was set at $P < 0.05$.

aOR, adjusted odds ratio; IUD, intrauterine device; MII, metaphase II.

and professional aspirations. Contraceptive use plays a crucial role in this reproductive journey. This study evaluated POC cycle outcomes in women who used some form of contraception and found that the method of contraception was not associated with diminished oocyte yield or maturity.

The study population included the majority of contraceptives modalities currently used by reproductive-aged women. The most commonly used methods in the population were hormonal contraceptives, such as the OCP, followed by patients not using any contraception at all or employing other methods such as barrier methods, levonorgestrel IUD, etonogestrel vaginal rings or copper IUD. When comparing these cohorts, significant differences in the demographic variables of the populations were observed.

TABLE 3 DEMOGRAPHIC, OVARIAN STIMULATION AND EMBRYOLOGICAL LABORATORY DATA OF THE STUDY COHORTS BASED ON THE USE OF HORMONAL VERSUS NON-HORMONAL CONTRACEPTION

Variable	Non-hormonal contraceptives	Hormonal contraceptives	*P*-value
	(*n* = 1293)	**(*n* = 2755)**	
Age (years)	36.5 (4.2)	35.6 (4.2)	<0.0001[a]
Body mass index (kg/m^2)	22.6 (4.5)	22.7 (4.8)	0.5[a]
Baseline oestradiol (pg/ml)	42.5 (22.8)	39.2 (29.7)	<0.0001[a]
Baseline FSH (mIU/ml)	6.5 (2.6)	6.5 (3.2)	0.06[a]
Baseline progesterone (ng/ml)	0.5 (0.2)	0.4 (0.3)	<0.0001[a]
Anti-Müllerian hormone (ng/ml)	2.3 (2.2)	2.2 (2.2)	0.007[a]
Previous oocyte retrieval cycles	0.0 (0.0)	0.0 (0.0)	0.0007[a]
Baseline antral follicular count	14.0 (9.0)	13.0 (9.0)	0.82[a]
Gonadotrophin cumulative dose (IU)	3600.0 (1650.0)	3900.0 (1800.0)	<0.0001[a]
Day of ovulation trigger	12.0 (1.0)	12.0 (2.0)	<0.0001[a]
Oestradiol on trigger day (pg/ml)	2464.0 (1637.0)	2549.0 (1622.0)	0.006[a]
Progesterone on trigger day (ng/ml)	1.0 (0.6)	1.0 (0.7)	<0.0001[a]
Days of OCP	0.0 (0.0)	16.0 (9.0)	<0.0001[a]
Follicles >18 mm on trigger day	4.0 (3.0)	4.0 (3.0)	0.93[a]
Cumulus–oocyte complexes retrieved	15.0 (10.0)	15.0 (13.0)	0.69[a]
Oocytes vitrified	11.0 (9.0)	12.0 (10.0)	0.35[a]
Use of OCP for scheduling, *n* (%)	0 (0%)	1073 (38.9%)	<0.0001[b]
MII oocyte proportion, *n* (%)	16,725/20,964 (79.8%)	37,470/46,274 (81.0%)	0.0002[b]

Data are presented as median and interquartile range or frequencies (%) unless stated otherwise. The proportion of MII oocytes was calculated as the number of MII oocytes divided by the total number of oocytes retrieved.

Unadjusted analysis was performed using an [a]Mann–Whitney *U*-test or [b]chi-squared test. Statistical significance was set at $P < 0.05$.

IUD, intrauterine device; MII, metaphase II; OCP, oral contraceptive pill.

A statistical difference was found among baseline AMH concentrations in all the study groups, as well as a statistically significant lower AMH concentration in patients using some type of hormonal contraception compared with non-hormonal contraceptives. Similar findings have previously been described in multiple studies with large cohorts of patients (*Amer et al., 2020*; *Bernardi et al., 2021*; *Letorneau et al., 2017*; *Nelson et al., 2023*). In addition, an effect of hormonal suppression of the gonadotrophin axis and lower AMH concentrations in OCP users has been broadly demonstrated (*Arbo et al., 2007*; *Bastianelli et al., 2018*). However, the true impact of lowered AMH and a diminished response to gonadotrophins is unclear, as an association between contraceptive-suppressed AMH concentrations and lower oocyte quality or quantity has been sparsely reported in the literature (*Cobo et al., 2011*; *Deb et al., 2012*; *Niederberger et al., 2018*; *Steiner et al., 2010*; *Streuli et al., 2008*). Most researchers propose that the most important predictor of efficiency is the age at time of oocyte cryopreservation and not solely the use of contraceptives *per se*.

Overall, the current study demonstrates that the type of contraception is not associated with the retrieval of a lower number of COC. Consequently, the mechanism of action of any contraceptive does not appear to adversely influence the number of oocytes that are available for cryopreservation. This finding is especially reassuring for patients, as current the literature is lacking in information on the relationship between contraceptive use and POC. Only an abstract report by Cascante and colleagues, which analysed a small group of patients intending to undergo fertility preservation, has evaluated the association with taking a break from oral contraceptives before ovarian stimulation (*Cascante et al., 2023*). In that study, the authors found that participants who used oral contraceptives had a similar MII oocyte yield to non-users. There was no correlation between the duration of OCP use and/or the interval between stopping OCP and ovarian stimulation cycle outcomes. To the authors' knowledge, no other studies have analysed multiple types of contraceptive, including non-hormonal contraceptives, on oocyte yield and quality in patients undergoing POC.

Other studies in diverse populations have shown controversial results related to the topic of OCP. Some have suggested that the use of long-term hormonal oral contraceptives could reduce the response to ovarian stimulation, producing lower than expected oocyte counts via an interruption of the normal synergism between androgenic preparations and FSH during the small follicle growth stage (*Barad et al., 2013*; *Farquar et al., 2017*).

In the current study, a small statistical difference was found in the univariate analysis when comparing oocyte maturity rates among all contraceptive users and controls. However, the same association was not found in the adjusted multivariate analysis, suggesting that the use of any type of contraception did not lower the

percentage of mature oocytes developing prior to oocyte cryopreservation. The findings remained consistent when excluding cohorts with very small sample sizes, as observed in the sensitivity analysis in order to adjust for the increased heterogeneity created by including the smaller sample size groups. Furthermore, in the adjusted multivariate analysis when analysing participants using hormonal contraception against control participants who were not using contraception or were using non-hormonal contraception, no association was found between the use of hormonal contraceptives and lower rates of oocyte maturity or a lower number of COC retrieved during POC cycles.

Similar to the current study, a larger number of studies analysing hormonal contraception including IUD (*Adeleye et al., 2018*; *Friedenthal et al., 2017*; *McQueen et al., 2017*; *Mikkelsen et al., 2013*) or OCP showed minimal to no effect on the outcome of ovarian stimulation (*Cohen et al., 1979*; *Hernandez-Nieto et al., 2020b*; *Tran et al., 2016*; *Yu Ng Eh et al., 2004*). Importantly, it should be mentioned that all the data available to date on this topic are limited in generalizability due to the highly heterogenic populations and different contraceptive preparations studied.

The current study has some important limitations, the most important being its retrospective design, which induces a selection bias associated with the type of data that are obtained during observational studies. Another important limitation is that all variables related to contraceptive use were self-reported or based on physician notes obtained during an electronic medical records review. The authors can confirm there was no feasible way to validate the participants' use of hormonal contraceptive using pharmacy records. In addition, exact information regarding the exact time of contraceptive use or information for different types of oral contraceptive formulation used is missing. Although the authors acknowledge the importance of this aspect as it represents a potential source of increased type 2 error, in this regard other researchers have anticipated misreporting of present hormonal contraceptive usage to be nondifferential (*Daniels et al., 2020*).

Finally, the smaller sample sizes of some of the individual types of contraceptive precluded evaluating these methods individually. Hence, the study was underpowered to detect subtle differences among all the cohorts analysed. Nevertheless, the study was powered to compare the two most common types of contraceptive category used in its population, yielding important clinical information that should be validated prospectively in future studies.

It should also be recognized that the study has several strengths. It includes one of the largest datasets of patients undergoing POC using state-of-the-art methods of oocyte vitrification and, furthermore, the inclusion of only one type of protocol for ovarian stimulation; this avoids the extra heterogeneity included in prior studies analysing multiple types of protocol or outdated cryopreservation techniques. In addition, the study includes the use of multiple types of contraceptive, yielding a more representative sample of the general population accessing this type of ART treatment than is seen in other smaller studies analysing only oral contraceptives or one type of contraceptive separately.

Rigorous prospective multicentre observational studies are imperative for accurately assessing the effects of various types of contraceptive on the outcomes of ovarian stimulation for POC. It is also essential to examine different subpopulations of patients, including those with diminished ovarian reserve, that were excluded from the current analysis. It has been previously demonstrated that, in these patients, the effects of contraception can differ from those in healthy populations (*Nelson et al., 2023*). This comprehensive approach will provide valuable insights into the nuanced effects of contraceptives on ovarian stimulation outcomes, enabling more informed decision making in clinical practice. Finally, the subsequent outcomes of these gametes once it is decided to thaw and fertilize them to create embryos should be investigated. An understanding of the relationship of OCP, oocyte cryopreservation and future embryo development must be addressed in order to discern the comprehensive benefits of these emerging treatments.

In conclusion, the various forms of contraception studied are not associated with a negative influence over the oocyte yield or maturation rate in patients undergoing POC. Healthy young patients using contraception should be reassured that their contraceptive preference will not result in a decreased number of oocytes or reduced oocyte maturation rate during their treatment cycle. This convergence of technological innovation and individual agency implies an archetype shift in fertility options, offering new opportunities for those navigating their family-building journey.

DATA AVAILABILITY

Data will be made available on request.

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ATTESTATION STATEMENT

The subjects in this trial have not concomitantly been involved in other randomized trials (if applicable). Data regarding any of the subjects in the study have not been previously published unless specified.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2024.104105.

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