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Hormonal Pretreatment for Ovarian Stimulation: A Narrative Review

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ABSTRACT

Introduction: Assisted reproductive technologies are necessary and important for the management of infertility and can be applied with and without the use of strategies such as hormonal pretreatment. However, there is a discussion in the literature on whether hormonal pretreatment in ovarian stimulation protocols can improve the outcome of oocytes and embryos. This study aimed to conduct an integrative review of hormonal pretreatment and its impact on women undergoing assisted reproduction procedures.

Methods: We made searches in the PubMed and the Cochrane Library databases. The inclusion criteria were articles published in peer-reviewed journals in English, Portuguese, or Spanish from January 1, 2010 to December 31, 2021 and available as free full texts. We excluded gray literature works, including term papers, theses, and dissertations. We used a narrative synthesis for data analysis.

Results: The 189 articles retrieved from the two databases (2010-2021) were narrowed down to eight articles. In most studies, pretreatment seems to play a role beyond stimulation that includes an early inhibition of the FSH peak, a more homogeneous cohort, and better results.

Conclusions: Using a pretreatment with combined oral contraceptives (COC) produces conflicting results in assisted reproduction. The COC improves the quantity and quality of eggs, but it neither benefits nor harms reproductive outcomes. Also, the use of COC has contradictory results regarding clinical pregnancy.

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Introduction

Infertility is a condition emerging as a public health priority, particularly in developed countries, and it affects up to 15% of reproductive age couples [1]. It is defined as a failure to conceive after 12 months of unprotected sexual intercourse. This definition, however, may vary based on significant factors in the patient's medical history, clinical presentation, and age [2]. The most common female cause of infertility is ovulatory dysfunction, which is secondary to factors such as obesity, polycystic ovary syndrome (PCOS), hypothalamic and pituitary dysfunction, thyroid disease, and hyperprolactinemia [3, 4]. Thus, the use of assisted reproductive technology (ART) treatments is considered an important alternative to help couples trying to overcome the challenge of infertility [3]. In more developed countries, ART is responsible for 1% to 5% of conceptions, and this number is expected to increase even more as more countries expand access to this type of treatment in their health systems [5].

In recent years the gonadotropin-releasing hormone (GnRH) antagonist protocol has been widely used for the treatment of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) owing to the several features that improve its reproductive outcomes, such as simplicity, safety, and efficacy. Combined oral contraceptives (COCs), which contain both estrogen and progesterone, have been shown to be effective especially for endometriosis and poor ovarian response to IVF treatments [6-8]. They can be justified because they make it easier to plan the moment of ovarian stimulation and to obtain mature and homogeneous eggs. The use of COCs is important because it does not allow the FSH level to rise at the beginning of the menstrual cycle, thus delaying the arrival of the oocytes until the collection phase, during assisted reproduction with an artificial cycle, a homogeneous ovarian follicular cohort, and a decreased follicular asynchrony on the trigger day [9, 10].

Given the above, the importance of this review is to show the benefits and risks of pretreatment, as well as of follicular synchronization before ovarian stimulation, in obtaining a greater number of captured oocytes and making it possible to schedule the cycle of ovarian stimulation [10, 11].

This study aims to carry out an integrative review of pretreatment and its impacts on women undergoing assisted reproduction procedures.

Methods

Study Design

This research is characterized as an integrative, documentary review, focusing on the specialized literature of pretreatment with combined oral contraceptives and its impacts on assisted reproduction. This type of study is used to synthesize clinical findings from scientific studies of a specific topic. It provides updated knowledge for possible application in medical practice. Using research databases, information is identified, selected, analyzed, and synthesized. The knowledge imparted by the general conclusion of the study enables enhancement of patient care and improvement in the professional routine [12].

Eligibility Criteria

For this review, articles were included if published in peer-reviewed journals in English, Portuguese, or Spanish from January 1, 2010 to December 31, 2021 and if available as free full texts. Gray literature works were excluded, including term papers, dissertations, and theses. Seventy-four articles were identified in PubMed and 115 in the Cochrane Library, totaling 189 studies. These were narrowed down to 8 articles, which were selected for the narrative review. The selection process can be seen in figure 1.

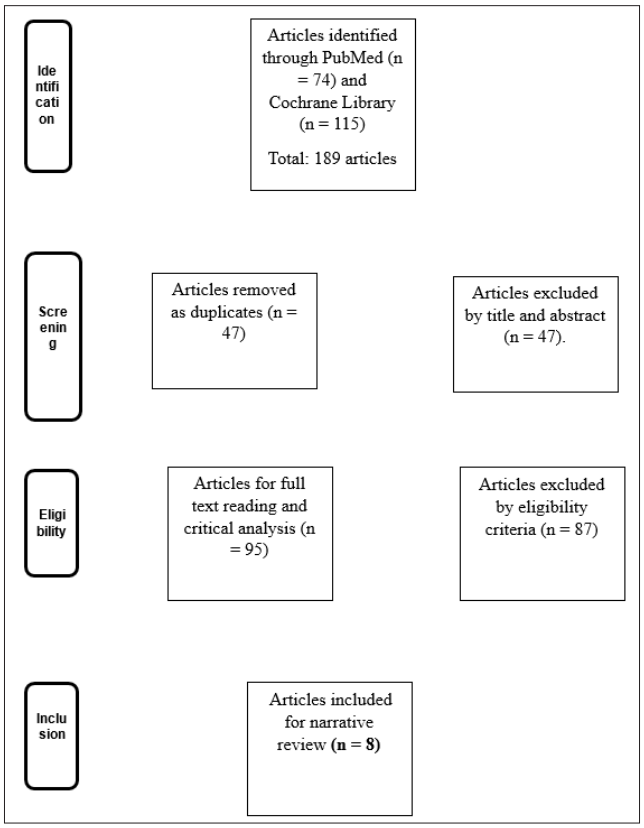

Figure 1: Flow chart with steps for selecting studies for the literature review

Data Sources and Search Strategy

Searches were conducted in the bibliographic databases PubMed and Cochrane Library. The MeSH terms were the following: (Female Infertility) OR (Female Subfertility) AND (Fertility Agents, Female) OR (Infertility Drugs, Female) OR (Fertility Agents, Female, Hormonal) AND (Contraceptives, Oral) OR (Oral Contraceptive) OR (Oral Contraceptive Pill) OR (Combined oral contraceptives). (Female Infertility) OR (Female Subfertility) AND (Fertility Agents, Female) OR (Infertility Drugs, Female) OR (Fertility Agents, Female, Hormonal) AND (Oral Contraceptives) OR (Oral Contraceptives) OR (Oral Contraceptive Pill) OR (Combined Oral Contraceptives). The final search results were exported to Mendeley, and duplicates were removed.

The search strategy consisted of the selection of evidence sources, data mapping to evaluate results, and extraction of the following information: 1) identification of the article (authors, year, title, and objective(s)); 2) study population; 3) method (a form of evaluation and statistical analysis), and 4) main findings.

The reviewers independently assessed the titles, abstracts, and full texts of the selected articles. Disagreements over article selection and data extraction were resolved by general consensus. At the end, the reviewers checked all the previously extracted information. Microsoft® Excel 2016 was used to create the data extraction form and summarize the findings. The articles selected for the narrative review were the following: A randomized controlled trial conducted in Spain, A proof-of-concept study also carried out in Spain, An updated meta-analysis carried out in Germany, A randomized controlled trial conducted in China, A randomized control trial conducted in Iran, A meta-analysis conducted in the Republic of Korea, A retrospective study carried out in Spain, A cohort study carried out in Brazil [13-20].

Stakeholders outside the study review team were invited to provide insights and to inform and validate the results of this scoping review, as well as to review the final version of the manuscript.

Results

A total of 189 articles were retrieved from the databases (2010-2021), 74 from PubMed, and 115 from the Cochrane Library (Figure 1). Of the total, 47 were excluded for being duplicate files and 47 for not having in their titles or abstracts any of the descriptors used in the search. The remaining 95 articles were read in full, and after applying the eligibility criteria, 87 were screened out, leaving 8 articles, which were included in this literature review (Figure 1).

The study objectives were mostly centered on the differences in embryo quality and pregnancy rates between estradiol valerate (E2V) and IVF cycles of GnRH antagonists programmed with COCs used alone and/or in combination (n=7). A few studies sought to assess the outcomes of endometrial gene expression and live birth rate (n=3). Results from systematic reviews (n=3) were also included. These sought to evaluate the effect of pretreatment with COC: there was one study of women without PCOS and two of women with PCOS. The results are summarized in table 1.

Table 1: Characteristics of studies on pretreatment and its impacts on assisted reproduction, 2010-2021

Author and year	Objective	Population of study	Méthods	Main findings
Hauzman et al., 2013	Finding differences in ongoing pregnancy rates between IVF cycles of gonadotropin-releasing hormone (GnRH) antagonists scheduled with combined oral contraceptives (COCs) or E2 valerate	100 women between 18 and 38 years old, non-obese, with a regular cycle and normal hormone levels on day 3 and <3 previous IVF/ICSI attempts, undergoing IVF with the GnRH antagonist protocol, residing in Madrid, Spain.	These patients were randomly divided into two pretreatment groups (COC or E2), and restrictions such as blocking or stratification were not considered. The COC group (n=50) received 30μg of ethinyl E2/150μg of levonorgestrel for 12 to 16 days from day 1 or 2, and stimulation was started 5 days after COC discontinuation. Likewise, the E2 group (n=50) received 4mg/day of oral E2 valerate from day 20 for 5 to 12 days, until the day before the start of stimulation.	Pretreatment with COC (mean±SD, 14.5±1.7 days) was significantly longer than with E2 (7.8±1.9 days). The groups showed differences in ongoing pregnancy rates (46.0% vs. 44.0%; risk difference, -2.0% [95% CI - 21.2% to 17.3%]), as well as implantation (43.5% vs. 47.4%), clinical pregnancy (50.0% vs. 8.0%), clinical abortion (7.1% vs. 7.7%) and live births (42.0% vs. 40.0%), but not significant.
Bermejo et al, 2014	To compare endometrial gene expression between women treated with the combined oral contraceptive pill (COC) and those who had spontaneous menses without PAOC.	10 young, healthy oocyte donors undergoing controlled ovarian stimulation (COS) with GnRH antagonists and recombinant FSH, from a university-affiliated private infertility clinic.	In group A (n=5), PAOC pretreatment was used for 12 to 16 days and stimulation started after a 5-day pill-free interval. Stimulation in group B (n=5) was started on day 3 of the cycle after spontaneous menses. Endometrial biopsies were taken 7 days after the challenge with concentrations of chorionic gonadotropin (hCG).	No individual gene with increased or decreased expression (fold shift (MD) .2) was observed in pretreated PAOC patients (group A) compared to controls (group B). However, the results of the functional analysis showed a total of 11 biological processes that were significantly enriched in group A compared to group B (non-PAOC).
Griesinger et al., 2015	Discuss the results of Garcia-Velasco and Fatemi (2015), on the topic of pretreatment with COC in ovarian stimulation using GnRH.	Commentary article on the results of pooling data from six RCTs covering 1343 patients, with and without pretreatment with the combined oral contraceptive pill.	----	The pregnancy rate was significantly lower in PAO pretreatment patients (relative risk [RR]: 0.80, 95% confidence interval [CI]: 0.66–0.97; rate difference [RD]:-5%, 95%CI: -10% to -1%). This finding remained robust in multiple sensitivity analyses: exclusion of one low-quality study, exclusion of the three smaller studies, or exclusion of studies with a pill-free interval of fewer than 5 days, resulting in an RR of 0.78 (95%CI: 0.64–0.94), 0.80 (95%CI: 0.65–0.98) and 0.79, (95%CI: 0.64–0.99), respectively.

Wei et al., 2016	To verify whether the primary outcome of live birth was affected by oral contraceptives (COC) or pretreatment with progestins before ovarian stimulation.	1508 women from 14 health centers in China.	The variable Live birth rates after fresh embryo transfer (FET) versus frozen embryo transfer (ECT) in women with PCOS were compared. The GnRH antagonist protocol was started on day 2 or 3 of the induced or spontaneous menstrual cycle. Women were divided into groups to wait for spontaneous menses (control group, n=323), or to be prescribed progestogens (P group, n=283) or OC (CO group, n=902) to induce menses before the start of menses. of ovarian stimulation.	With fresh embryo transfer, women with CO-induced menses had lower rates of clinical pregnancy (48.8% vs 63.6%, RR 0.77, 95% CI: 0.66–0.89) and births live (36.1% vs 48.1%, RR 0.75, 95%CI: 0.61–0.92). With delayed and frozen ECT, the OC group had a higher pregnancy loss rate (27.7% vs 13.0%, RR: 2.13, 95% CI: 1.28–3.52) after ECT than women with spontaneous pregnancy. The live birth rate after FET in the OC, progestin-induced menstruation, and spontaneous menstruation group was 49.4%, 50.7%, and 60.2%, respectively (p=0.06).
Nejad et al., 2018	Comparison of pre-treatment with COCs or estradiol valerate vs. no pre-treatment before GnRH antagonist used for IVF cycles: An RCT.	Determining the number of mature oocytes and pregnancy rate of three pretreatment methods for fresh embryo transfer cycles.	225 women (18-35 years and less than 2 previous IVF attempts) undergoing IVF with GnRH antagonist protocol, attending the infertility center of Vali Asr hospital, Iran.	Women were randomized into 3 groups. The COC group (n=53) received PAO (ethinyl estradiol 30μg and levonorgestrel 150μg), the E2 group (n=63) received 4mg/ day of oral E2 (17β-E2) for 10 days from day 20 of the previous cycle and GnRH antagonist stimulation was started 6 days after stopping COC and E2. The control group (n=70) received no pretreatment.
Song et al., 2019	To evaluate the effect of pretreatment with combined oral contraceptives (COC) on outcomes in women with polycystic ovary syndrome (PCOS) undergoing assisted reproductive technology for subfertility.	Searches were conducted in MEDLINE, Cochrane Library, and EMBASE electronic databases in December 2018; ongoing trials and gray literature were also reviewed.	Electronic databases were searched to identify and review articles published from October 1995 to December 2018 according to the selection criteria. Results are expressed as mean difference and Odds Ratio (OR) in a meta-analysis model.	A meta-analysis of 7 studies showed that COC pretreatment did not affect the clinical pregnancy rate (OR 0.93, 95% CI 0.65-1.34, I2 = 76%) or ovarian hyperstimulation syndrome (OR 0.90, 95%CI 0.57-1.44, I2 0%). However, the miscarriage rate in the COC group was significantly higher (OR 1.33, 95%CI 1.02-1.72, I2 9%), and the cumulative live birth rate was significantly lower compared to the control group (OR 0.72, 95%CI 0.54–0.98, I2 55%). Subgroup analysis showed higher rates of miscarriage and lower rates of live births in studies using the GnRH protocol (OR 1.69, 95%CI 1.17-2.44, I2 0% and OR 0.38, 95%CI 0.29-0.50, respectively.

Montoya- Botero et al., 2020	To verify any differences in the fresh (LB) and cumulative (TCNV) live birth rates of women undergoing controlled ovarian stimulation (COS) for IVF/ICSI after pretreatment with different types of PAO pills for different durations compared to non-COC.	4116 patients aged between 18 and 45 years submitted to the first cycle of ovarian stimulation, in a gonadotropin-releasing hormone (GnRH) antagonist protocol, at the Department of Reproductive Medicine of the Dexeus University Hospital	Patients were categorized into two groups receiving COC (n=3517) and without COC (n=599). All patients with COC pretreatment started EOC 5 days after the pill. Overall, two types of COC were used at the study center: ethinylestradiol (EE) 30μg/desogestrel 150μg, a third-generation progesterone; or EE 30μg/drospirenone 3 mg, a fourth-generation progestin with mild antiandrogenic activity.	COC use was associated with a small increase in the number of oocytes retrieved after adjustment for age, BMI, COC use, cause of infertility, initial dose (ID), type of gonadotropin, days of stimulation, total units of stimulation (total ID) (β 0.22, 95%CI 0.12–0.31). Cumulative LBRs were comparable between PAO vs non-COC groups (32.4 vs 31.6%, p=0.712).
Samama et al., 2020	To verify whether pretreatment with a COC with natural estrogen, 17β-estradiol/nomegestrol, has effects on hormonal, embryological, and clinical outcomes of women undergoing assisted reproduction techniques.	130 patients followed by a group of researchers from the Graduate Program in Assisted Reproductive Techniques (ART) at an assisted reproduction center in São Paulo, Brazil.	3 groups were analyzed: (i) patients with no pretreatment, (ii) patients who received COC with natural estrogen, (iii) patients who received synthetic COC, whose data were analyzed retrospectively as a reference population. The patients underwent COC pretreatment before the GnRH antagonist ovarian stimulation protocol for in vitro fertilization (IVF)	Significant effects were observed on the mean number of embryos (no pretreatment=2.3; 17β-estradiol/ nomegestrol=3.41; p=0.006) and a number of high-quality embryos (day 3) (no pretreatment =1.3; 17β-estradiol/nomegestrol=2.64; p= 0.031). The mean number of mature oocytes was higher in the natural estrogen COC compared to the synthetic one, when the analysis was controlled by the duration of the COC treatment (17β-estradiol/ nomegestrol=6.28 and ethinylestradiol/gestodene=4.34; p= 0.014). Ethinylestradiol/ gestodene reduced the chances of biochemically positive pregnancy when compared to the group without pretreatment (OR=0.138, 95%CI=0.028–0.694).

Discussion

The main findings of this literature review were that hormone pretreatments with combined oral contraceptives harm neither in vitro fertilization techniques nor assisted reproduction techniques.

Hauzman et al. conducted the first randomized controlled trial (RCT) published in the literature comparing results of COCs and estradiol (E2) valerate as pretreatments in antagonist cycles (n = 100) [13]. Patients randomized to the COC group (n=50) started on the pill (30μg of ethinyl E2 plus 150μg of levonorgestrel on day 1 or day 2 of the menstrual cycle) prior to the scheduled IVF/ICSI procedure, spanning 12 to 16 days of pretreatment. In this group, ovarian stimulation was started 5 days after pill discontinuation, regardless of the specific day of the onset of menses, with a daily dose of recombinant FSH. From stimulation day 6 onwards, women's gonadotropin doses were adjusted according to serum E2 levels and ovarian response, which was assessed through vaginal ultrasonography every 2 days. For patients treated with E2 (n=50), doses of E2 valerate were started on day 20 of the menstrual cycle prior to the IVF/ICSI cycle at a daily dose of 4 mg (2 mg twice daily) orally for 5 to 12 days, until the day before the start of ovarian stimulation, regardless of the specific day of the onset of menstruation [12]. No significant differences were observed in the number of oocytes retrieved, fertilization rates, number of top-quality embryos or number of transferred embryos [13]. The proportion of oocyte collections performed on weekend days was similar between the groups: 8.5% (4/47) with the COC pretreatment and 10.4% (5/48) with the E2 pretreatment (p = 0.97). Both frequencies were significantly lower than 28.6%, which would be expected to occur by pure chance (i.e., 2 out of 7 days) (p = 0.03 for COC and p = 0.04 for E2) [13].

Bermejo et al. conducted an RCT to compare endometrial gene expression between women treated with a COC pill and those who had spontaneous menses without a COC pill [14]. Patients in group A received COC (Microgynon30, Bayer, Berlin, Germany) during the menstrual cycle prior to stimulation with a dose of 1 tablet per day from 12 to 16 days to program the cycle to start on day 1 of menstruation. In this group, stimulation began after a 5-day pill-free interval. Patients in group B started the stimulation directly on day 2 and 3 of the spontaneous menstrual cycle. Stimulation started with a single dose of 150 IU of recombinant FSH administered subcutaneously (Puregon, MSD, Madrid, Spain) for 4 days. After that the doses were adjusted according to the follicular response as seen on ultrasound. To prevent a premature LH surge, a daily dose of 0.25 mg of GnRH antagonist (Orgalutran, MSD, Madrid, Spain) was administered subcutaneously or orally (if the patient could not take the medication subcutaneously) on day 5 onwards until the day of challenge. The results of the endometrial receptivity array showed that 11 biological processes from the functional analyses were significantly enhanced by pretreatment with the combined oral contraceptive pill. This validates the method utilizing endometrial samples obtained in natural cycles after a hormone replacement therapy. The authors of this study concluded that it was not possible to classify the endometrial samples as receptive or nonreceptive [14].

Griesinger et al. published a meta-analysis on the topic of COC pretreatment in ovarian stimulation using antagonist GnRH [15]. The combinations of the oral contraceptive pills were the following: in one study, a combination of esogestrel (0.15 mg) with ethinyl estradiol (E2) (0.03 mg) was administered from 14 to 21 days; in another, the pill consisted of ethinyl E2 (0.03 mg) and levonorgestrel (0.15 mg), and it was administered for 21 days; and in the remaining studies, the hormonal combination was ethinyl E2 (30 mg) with gestogen (150 mg) (either desogestrel or levonorgestrel) The duration of the pill pretreatment ranged from 14 to 28 days. Griesinger et al. concluded that the available data from randomized trials to date suggest that oral contraceptive pretreatment in cycles of antagonist GnRH for IVF is associated with a significantly reduced chance of ongoing pregnancy. And they added that their results were inconsistent with the evidence in the literature. One such example of disagreement is a study carried out by Kim et al back in 2009 showing that pretreatment with COC in a GnRH antagonist using a multiple-dose protocol is effective in improving the ovarian response to controlled ovarian stimulation. The GnRH antagonists with COC pretreatment were at least as effective as low dose GnRH agonists in poor responders [21].

Wei et al. evaluated the variation in live birth as the primary outcome when using pretreatment with COC or progestins before ovarian stimulation for women with PCOS [16]. The three kinds of COCs used were ethinyl estradiol (0.03 mg) with desogestrel (0.15 mg), ethinyl estradiol (0.035 mg) with cyproterone acetate (2 mg), and ethinyl estradiol (0.03 mg) with drospirenone (3 mg). A total of 1508 women were evaluated and divided into the groups of spontaneous menstruation (n=323), progestin-induced menstruation (n=283), and COC-induced menstruation before ovarian stimulation (n=902). The live birth rate after the frozen embryo transfer in the three groups approached a significant difference (49.4% for COC-induced menstruation, 50.7% for progestin-induced menstruation, and 60.2% for spontaneous menstruation). Post hoc analyses showed that the live birth rate in women with COC-induced menstruation was lower than in women with spontaneous menstruation (RR 0.82, 95% CI, 0.70-0.96) (16). Wei et al. concluded that progestin was more effective than COC in both pregnancy and live birth rates.

Najed et al. carried out an RCT to determine the number of mature oocytes and the pregnancy rate [17]. They compared women undergoing pretreatment with COC, E2 valerate, or without pretreatment for fresh embryo transfer cycles. After evaluating the losses at the end of follow-up, 53, 63, and 70 patients were allocated to the COC, E2 valerate, and control groups, respectively. The combination of hormones was randomized to the COC, E2, and no pretreatment groups. The COC group (n=53) received ethinyl estradiol 30 µg and 17ß-levonorgestrel150 µg; the estradiol valerate (E2V) group (n=63) received oral E2 4 mg/day for 10 days from day 20 of the previous menstrual cycle. The GnRH antagonist stimulation was started 6 days after discontinuation of COC and E2. The control group (n =70) received no pretreatment. In their study, no significant differences were observed in average number of recovered or matured oocytes, embryo quality, and chemical and clinical pregnancies. Furthermore, pregnancy rates among the three groups (42.9% E2 valerate, 39.6% COC, and 34.3% control group) did not differ significantly ($p = 0.59$). The results showed there were no significant differences in the mean number of matured oocytes, embryo quality, and chemical and clinical pregnancies, demonstrating that pretreatment with COC or E2 valerate may not improve in vitro fertilization results [17].

Another meta-analysis, conducted by Song et al. also aimed to evaluate the effect of COC pretreatment on outcomes in women with PCOS undergoing assisted reproductive technology for subfertility [18]. The combination of COC types and doses are described in table 1. Among the 3179 studies retrieved, only seven were included in the review: one RCT, two prospective cohort studies, and four retrospective cohorts. In this meta-analysis, the clinical pregnancy rate was not altered by the COC treatment (OR 0.93, 95% CI, 0.65-1.34, I2 76%), but the cumulative pregnancy rate was higher in the COC group than in the control group (OR 0.72, 95% CI, 0.54-0.98, I2 55%). The use of a COC did not change the duration or the total dose of gonadotropin (OR 0.03, CI 95%, 0.70-0.76, I2 86%; OR -35.42, CI 95%, -97.18-26.34, I2 66%). The conclusion was that a COC pretreatment prior to ART in women with controlled ovarian stimulation (COS) may have an adverse effect on clinical outcomes with a GnRH antagonist protocol, suggesting the need for caution in using a GnRH antagonist protocol as part of a pretreatment. with COC for women with COS [18].

Montoya-Botero et al. found differences in live birth rates among women undergoing COS for IVF/ICSI after pretreatment with different COC types (two types of COC were used at the study's center: 1) ethinylestradiol (EE) 30 µg/desogestrel 150 µg, a third-generation progesterone, or 2) EE 30 µg/drospirenone 3 mg, a fourth-generation progestin with mild antiandrogenic activity.) for different durations compared with a non-COC pretreatment. This retrospective cohort study assessed data from 4116 patients (COC n=3517 and non-COC n=599) in their first cycle of ovarian stimulation on a GnRH antagonist protocol. Evaluation of the rates of clinical pregnancy, live births, and cumulative live births showed no significant differences between the groups. Also, the duration of COC use was not associated with the likelihood of achieving a live birth (OR 0.98, 95% CI, 0.95-1.02) [19]. The main conclusion was that, when comparing patients administered oral contraceptive pills with patients who did not take the pills, the study found that results did not differ in terms of the main reproductive outcome, i.e., the live birth rate. The results of this study give rise to serious questions regarding the ESHRE Guideline 2019 recommendation for ovarian stimulation, which discourages the use of COC. Such disincentive is corroborated by the meta-analyses conducted by Gresinger et al. and Farquhar et al. [6, 15].

Samama et al. carried out a longitudinal study to verify whether pretreatment with a COC with natural estrogen, 17β-estradiol/nomegestrol, exerted effects on the hormonal, embryological, and clinical outcomes of women undergoing ART [20]. The main analysis showed a higher mean number of embryos in the pretreatment group (3.41 vs 2.3; $p = 0.006$), as well as a higher number of top-quality embryos on day 3 (2.64 vs 1.3; $p = 0.031$). In addition, a higher number of mature oocytes was observed in the pretreatment group with natural E2 than in the group with the synthetic hormone when the analysis was controlled by the duration of COC use (6.28 vs 4.34; $p = 0.014$) [19]. The authors concluded that the natural estrogen in a COC, rather than being associated with deleterious embryological or clinical outcomes, significantly improved the number of embryos and top-quality embryos.

The juxtaposition of the main conclusions of the studies selected for this narrative review showed there was a conflict, for the administration of COCs in some studies failed to improve the outcomes in assisted reproduction, whereas in others, it led to positive results, such as better fertilization and pregnancy rates.

Our work was primarily limited by the fact that most studies with hormonal pretreatment for ovarian stimulation did not analyze the live birth rate [22].

Conclusion

The strategy of using a pretreatment with combined oral contraceptives has contradictory results in assisted reproduction. The COC improves the quantity and quality of eggs; however, it neither benefits nor harms reproductive outcomes. Also, the use of COC produced inconsistent results in terms of clinical pregnancy. As the articles in this study, some of which are systematic reviews, disagree in some points, there is an imperative need for more multicenter studies using randomized clinical trials with a prospective follow-up. Priming with androgens seems beneficial to poor responders, but this should be corroborated by future studies.

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