The effect of medication on serum anti-müllerian hormone (AMH) levels in women of reproductive age: a meta-analysis

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Research Article

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Abstract

Objective: The study aims to address whether serum anti-müllerian hormone (AMH) levels fluctuate in the short term after medication application, including oral contraceptives (OCs), metformin, GnRH analogues (GnRH-a), dehydroepiandrosterone (DHEA), vitamin D (VD), clomiphene citrate (CC), and letrozole.

Methods: Published literature from PubMed, Embase, and Cochrane central was retrieved up until 19 September 2021. A total of 51 self-control studies with an average Newcastle-Ottawa quality assessment scale (NOS) score of 6.90 were analyzed. Data collection and analysis: the extracted data were entered into Stata software, and the weighted mean difference/standardized mean difference (WMD/SMD) and 95% confidence interval (CI) were used for data analysis.

Results: After OCs treatment the AMH level showed a significant decline in women with normal ovarian function, which was significant within 3 months (WMD=-1.43, 95% CI: -2.05 to -0.80, P<0.00001). After metformin treatment the serum AMH decreased in polycystic ovary syndrome (PCOS) patients (WMD=-1.79, 95% CI: -2.32 to -1.26, P<0.00001), in both obese and non-obese patients. GnRH-a treatment in endometriosis patients led to dynamic changes in the serum AMH levels. that is, ascent at 1 month(P=0.05), and descent at 3 months (P=0.02). After DHEA treatment the serum AMH increased in diminished ovarian reserve (DOR) / poor ovarian response (POR) patients (WMD=0.18, 95% CI: 0.09 to 0.27, P<0.0001). After VD treatment the serum AMH increased, and it was obvious in non-PCOS patients (WMD=0.78, 95% CI: 0.34 to 1.21, P=0.0004). After CC treatment the serum AMH decreased significantly in PCOS patients, specifically in non-obese patients (WMD=-1.24, 95% CI: -1.87 to -0.61, P=0.0001).

Conclusions: Serum AMH levels may be affected in the short term after drug application. Specifically, OC, metformin and CC leads to decreased AMH level, DHEA and VD leads to increased AMH level, and GnRH-a leads to dynamic variation, which is correlated with PCOS, obesity, age, and duration of medication. The impacts of these medication should be taken into consideration when AMH is used as a marker of ovarian reserve.

1 Introduction

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein that belongs to the transforming growth factor-β (TGF-β) family [1, 2], and a female baby in the fetal period begins to produce AMH from the 9th month [3]. AMH is secreted by the antral follicles and small antral follicles in the ovary. The greater the number of these follicles, the higher the serum AMH concentration. Because of this feature that AMH was considered to be a marker for the process of ovarian ageing[4]. The objectivity and potential standardization of AMH levels, as well as their readily detectable convenience throughout the menstrual cycle, make AMH levels the gold standard biomarker for assessing ovarian reserve and predicting ovarian response to stimulation [5]. It is currently one of the best indicators for assessing ovarian function, guiding assisted reproduction, and indicate iatrogenic damage (such as chemotherapy, radiotherapy or surgery) to the ovarian follicle reserve. it has a broader application in assisted reproduction field [6, 7].

Therefore, the accurate measurement of AMH will guide the dosage of ovarian stimulation related programs, and it has important reference significance to improve the outcome of assisted reproduction technol [8].

Previous studies believe that AMH is stable and not affected by the menstrual cycle, or hormone drug use. However, more and more clinical studies have shown that drug use may interfere with serum AMH levels in the short term, which may lead to the risk of clinical misinterpretation of AMH values [9]. However, the sample size of relevant research reports is mostly small, the research results often contradict each other, and there is a lack of evidence-based analysis on the subject. Therefore, we carried out a meta-analysis to accurately assess the impact of drug use on AMH levels. In the present study, evidence-based investigation was performed on seven kinds of medications, including oral contraceptives (OCs), metformin (MET), GnRH analogues (GnRH-a), dehydroepiandrosterone (DHEA), vitamin D (VD), clomiphene citrate (CC), and letrozole (LET), and the variation in serum AMH levels was recorded to guide the correct interpretation and effective application of AMH values in clinics. The findings will provide useful information for elucidating the relationship between the medicine application and the fluctuation of AMH.

2 Materials And Methods

2.1 | Literature search and study selection

This study was based on the PRISMA guidelines [10] for systemic review and meta-analysis. The authors searched PubMed, Cochrane, EMBASE, until September 19th, 2021 and without limitation of region, language, or publication type. Reference list of all selected articles were independently screened to identify additional studies left out in the initial search. Combinations of the following MeSH terms were used: (Anti-Müllerian hormone OR AMH) AND (Oral Contraceptives OR Oral Contraceptive OR OC OR COCS) AND (Metformin OR Dimethylbiguanidine OR Glucophage) AND (DHEA OR dehydroepiandrosterone) AND (Gonadotropin Releasing Hormone OR GnRH) AND (Vitamin D) AND (Clomifene OR Chloramiphene OR Clomifen OR Clomiphene Citrate) AND (Letrozole). All studies after the search were screened and analyzed by two authors independently (YWW and HCC), and any disagreement will be resolved by discussion until consensus were reached or by consulting the third author (CYR). This paper included prospective self-control studies. Studies were excluded if: (1) Clinical case report, review, meta-analysis or cell, animal model; (2) Evidence-based information comes from: books, conferences, notes, thesis, case series, letters or unpublished articles; (3) unreliable extracted data, overlapped data sets, and paragraphs only abstract available.

2.2 | Data Extraction

The following data was extracted from every study by two reviewers independently: (1) name of the first author, (2) year of publication, (3) country where the study was conducted, (4) study period, (5) total number of people included in in cases and controls, (6) doses of different drugs, (7) time of application,

(8) mean change of anti-Müllerian hormone. We contacted investigators for additional information when extra information was required.

2.3 | Assessment of Study Quality

We used the Newcastle-Ottawa scale (NOS) to assess the quality of the included literature [11]. The NOS scale was based on 3 indicator systems: suitable study object selection, inter-group comparability and intervention exposure. It consisted of 8 indicators, each with a score of 0 or 1, but the “inter-group comparability” can be given 0 or 1 or 2 points, so the overall quality assessment score for each article ranged from 0 to 9 points. Each study was evaluated independently by two authors. Any disagreement was resolved by discussion until consensus reached (TABLE S1-S7).

2.4 | Statistical Analysis

All data were entered into Stata(version14.0). Literature heterogeneity was assessed by Q test and quantified by I^2 index, If values of $I^2 \leq 25\%$, it meant that our results were of low heterogeneity. If $P > 0.10$ and $25\% < I^2 < 50\%$, then the heterogeneity was acceptable. The fixed effects model (FEM) [12] was used to calculate the parameters of the data pool. If $P < 0.10$ and $50\% < I^2 < 75\%$, then the heterogeneity could not be ignored, the random effects model (REM) was used to calculate the parameters of the data pool. We performed a subgroup analysis of results with high heterogeneity $I^2 \geq 75\%$. Since it was continuous data, the serum AMH variation over time was assessed by calculating the Weighted Mean Difference (WMD) or Standard Mean Difference (SMD) among the pooled data, and the statistical significance was calculated with Z test.

2.5 | Publication Bias

Publication bias was evaluated by examining the asymmetry of funnel plot. If the scatter points of the documents were symmetrical on both sides of the funnel chart, it indicated that the publication bias of the literature was small, and vice versa, it indicated that the publication bias was large. The literature used in this article was symmetrical on both sides of the funnel chart, indicating that there was no serious publication bias.

2.6 | Author Contributions

Chun Feng and Wei-Wei Yin designed the study and wrote the paper; Chang-Chang Huang, Yi-Ru Chen and Dan-Qing Yu performed the data curation; Wei-Wei Yin, Chang-Chang Huang, and Min Jin analyzed the data.

3 Results

3.1 | Study selection and characteristics of included studies

A total of 2620 articles were recognized by database searching and 21 through other sources. 600 of records duplicated removed, and 1934 studies were excluded based on information from titles and

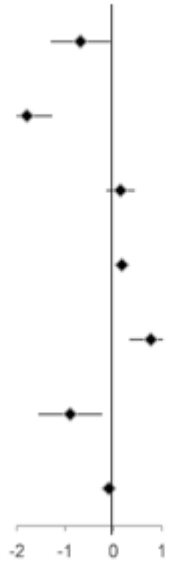
abstracts. Due to the exclusion reasons listed in the flow chart, 51 studies remained for the qualitative synthesis. Figure 1 shows the study flow diagram of the searching process of these records.

3.2 | Meta-Analysis Results

META analysis showed the trend of serum AMH changes after the application of 7 drugs as shown in the table below (Table 1).

TABLE 1 Overall meta-analysis of the effects of 7 different drugs.

Medications	No. trails	Samples	I^2 (%)	P	95% CI
OC	8	579	91	0.03	-0.68(-1.30, -0.06)
MET	12	362	68	<0.01	-1.79(-2.32, -1.26)
GnRH-a	10	1099	78	0.32	0.15(-0.14, 0.44)
DHEA	8	431	85	<0.01	0.18(0.09, 0.27)
VD	9	316	61	<0.01	0.78(0.34, 1.21)
CC	8	869	76	<0.01	-0.89(-1.55, -0.23)
LET	3	397	14	0.16	-0.09(-0.22, 0.04)



Negative values in forest plot: AMH value decreased after medication; positive values in the forest plot: AMH value increased after medication.

3.2.1 Variation of serum AMH levels in women with normal ovarian function after taking oral contraceptives

Women with normal ovarian function taking OC (conventional artificial cycle medication: 1 capsule per day for 21 days, repeated 7 days after stopping the drug; or continuous medication: 1 capsule per day, uninterrupted; the same below) 3 ~ 6 cycles or more than 6 cycles, a total of 9 articles [13–20] were included (the total number of sample cases n = 579, 8 groups self-control studies) used for the analysis of this topic. (Table S1)

All 8 sets of data (n = 579) random effects model meta-analysis showed that women with normal ovarian function taking oral contraceptive (3–6 cycles or more than 6 cycles) have a significant downward trend in serum AMH (WMD: -0.68,95%CI: -1.30 to -0.06; P = 0.03); The decrease in serum AMH level was statistically significant.

Perform subgroup analysis on 8 sets of data according to the length of OCs use showed that: serum AMH level decreased in two groups of use time ≤ 3 months (n = 165), and the decrease was statistically significant(WMD: -1.43, 95%CI: -2.05 to -0.80; P<0.00001). With use for more than 3 months or even longer, there is little effect on serum AMH levels (WMD: -0.09, 95%CI: -0.37 to 0.19; P = 0.45) see Fig. 2.

3.2.2 Variation of serum AMH levels in PCOS patients with metformin pretreatment

Regarding PCOS patients with MET pretreatment (conventional medication 1500 ~ 2250mg, 2 ~ 3 times a day orally, continuous medication for 2 ~ 12 months, the same below), a total of 12 articles [21–32] were included (total number of sample cases n = 362, 12 groups of self-control studies) used for the analysis of this topic. (Table S2)

All 12 sets of data (n = 362) random effects model meta-analysis showed that: PCOS patients taking metformin (2–12 months) can cause a significant decrease in serum AMH. (WMD: -1.79, 95%CI: -2.32 to -1.26,P<0.00001)

The above mentioned 12 groups of research data were highly heterogeneous (I2 = 68%, P = 0.0003). The meta subgroup analysis of a random effect model based on whether they were obese (BMI≥30 Kg/m2) showed that: obese patients MET pretreatment (n = 151, 5 sets of data) caused a significant decrease in serum AMH levels (WMD: -1.34, 95%CI: -1.62 to -1.05, P<0.00001). The decrease in serum AMH level was statistically significant. Corresponding non-obese patients MET pretreatment (n = 126, 5 sets of data) could also cause a significant decrease in serum AMH levels (WMD: -1.87, 95%CI: -2.75 to -1.00; P < 0.0001), see Fig. 3. which was statistically significant.

3.2.3 Variation of serum AMH levels in endometriosis patients GnRH-a (gonadotropin releasing hormone agonist) pretreatment

Regarding endometriosis patients GnRH-a pretreatment (conventional medication: One injection of long-acting (3.75 mg per tube) leuprolide for 7–21 days during menstruation, or short-acting leuprolide (0.1mg per tube) daily from 7–21 days of menstruation to the day of ovulation induction, the same below), a total of 5 articles [33–37] were included, and 10 sets of data (the total number of sample cases n = 1099, 10 groups of self-control studies) were used for the analysis of this topic. (Table S3)

All 10 sets of data (n = 1099) random effects model meta-analysis showed that GnRH-a pretreatment (7 days to 6 cycles) in endometriosis patients can cause dynamic changes in serum AMH levels.

The analysis based on the blood collection time of the subjects after GnRH-a pretreatment (≤ 14 days, 1 month, 3 months) showed that: The use of GnRH-a for a short period of time(≤ 14 days) has little effect on the serum AMH levels. After 1 month, there was a transient increase (WMD: 0.87; 95%CI: 0.00 to 1.73; P = 0.05), and the serum AMH decreased after 3 months (WMD: -0.26; 95%CI: -0.48 to -0.04; P = 0.02).

3.2.4 Variation of serum AMH levels in DOR/POR patients DHEA (dehydroepiandrosterone) pretreatment

About DOR/POR patients DHEA pretreatment (conventional medication 75mg, 3 times a day, the same below) A total of 8 articles[38–45] (total number of sample cases n = 431, 8 groups of self-control studies) were used for the analysis of this topic. (Table S4)

All 8 sets of data (n = 431) random effects model meta-analysis showed that: DOR/POR patients taking DHEA can cause an increase in serum AMH (WMD: 0.18, 95% CI :0.09 to 0.27; P<0.0001= See Fig. 4; The increase in serum AMH level was statistically significant.

3.2.5 Variation of serum AMH levels in women with VD pretreatment

Regarding VD pretreatment (conventional medication 2000IU-5000IU/week, continuous medication for 2 weeks to 6 months, the same below), a total of 7 articles [46–52] were included (total number of sample cases n = 316, 9 groups of self-controlled studies) used for the analysis of this topic. (Table S5)

All 9 sets of data (n = 316) random effects model meta-analysis showed that VD pretreatment (2 weeks to 6 months) in patients can cause an increase in serum AMH (WMD: 0.78, 95%CI: 0.34 to 1.21; P = 0.0004) the increase in serum AMH level was statistically significant. see Fig. 5.

Among them, according to whether they were PCOS patients, the meta subgroup analysis showed that: PCOS patients before and after VD supplementation could cause the fluctuate of serum AMH levels (WMD: 1.16, 95% CI: -1.58 to 3.89; P = 0.41), but this fluctuation was not statistically significant, Correspondingly, non-PCOS patients before and after VD supplementation could cause a statistically significant increase in serum AMH. (WMD: 0.77, 95%CI: 0.33 to 1.21; P = 0.0007),

3.2.6 Variation of serum AMH levels PCOS patients with clomiphene (CC) pretreatment

Regarding PCOS patients CC pretreatment (conventional medication 50mg/day, continuous medication for 1 to 3 cycles, the same below), a total of 8 articles [53–60] were included (total number of sample cases n = 869, 8 groups of self-control studies) for the analysis of this topic. (Table S6)

All 8 sets of data (n = 869) random effects model meta-analysis showed that: PCOS patients taking CC pretreatment (1 ~ 3 cycles) can cause a significant decrease in serum AMH levels (WMD: -0.89, 95%CI: -1.55 to -0.23; P = 0.008)

According to whether the study subjects were obese, a random-effects model META subgroup analysis showed: non-obese(BMI<25Kg/m^2) patients CC pretreatment (n = 376, 2 sets of data) have caused a significant reduction in serum AMH levels(WMD: -1.24, 95%CI: -1.87 to -0.61; P = 0.0001)as shown in Fig.

6, the reduction of serum AMH level was statistically significant. Correspondingly, there was no significant difference in obese (BMI ≥ 25 Kg/m^2) patients (n = 261, 4 sets of data), as shown in Fig. 6.

3.2.7 Variation of serum AMH levels with letrozole (LET) pretreatment

Taking letrozole pretreatment (conventional artificial cycle medication: 2.5 mg, starts on menstrual cycle 3–5 days, once a day, continuous use for 5 days; the same below) for 3 to 6 cycles, a total of 3 articles [55, 56, 61] (total number of sample cases n = 397, 3 groups of self-controlled studies) were used for the analysis of this topic. (Table S7)

All 3 sets of data (n = 397) fixed-effect model meta-analysis showed that women pretreatment with letrozole (3–6 cycles) have little effect on AMH levels in the short term (WMD: -0.09, 95%CI: -0.22 to 0.04; P = 0.16).

3.3 | Sensitivity Analysis

Multi-group meta-analysis of literature sample data in this study showed significant heterogeneity (I^2>50%), so the sensitivity analysis was performed by removing one study at one time, for the above 7 different drug sample data, we found that removing any study in the analysis did not impact the overall results, indicated that the META analysis results of the corresponding group are stable.

4 Discussion

In assisted reproduction clinics, OCs is often used as a pretreatment medication before ovarian stimulation. OCs can negatively inhibit the secretion of FSH and LH, adjust the menstrual cycle, improve women's ovarian response and assisted reproduction outcomes. Traditional studies believed that after OCs application there have no significant effect on serum AMH levels in the short term [17, 20, 62], but some recent research results did not support the conclusion [14, 15], the influence of AMH level was related to the dosage, type of contraceptives and time of administration, female age, self-condition and so on.

The results of this study supported that OCs pretreatment in women with normal ovarian function will have a downregulation effect on serum AMH, and this effect was obvious in the short term of medication. This was because AMH is secreted by prefollicles and antral follicular granulosa cells which are sensitive to FSH. The down-regulation of FSH caused by OCs reduce the stimulation of granulosa cells, which will have a down-regulating effect on the secretion of AMH [17, 63]. However, with the extension of use time, the decrease of serum AMH decreases. This may due to the granule cells adaptation to the down-regulation of FSH to a certain degree, or the concentration of AMH may differ greatly from different experiments, so statistical uncertainty increase. In clinical practice, some PCOS patients who used oral contraceptives can ovulate spontaneously within a short time after stopping the drug, which may be related to the down-regulation of AMH by OC, reduced the inhibition of follicular development. This meta-analysis further confirmed that the serum AMH concentration in women who use hormonal contraception would be

negatively affected by exogenous sex hormones, and may not be able to maintain its value as a predictor of ovarian reserve, therefore, we recommend women who use oral contraceptives to measure their serum AMH levels at least 3 months after stopping the drug.

Polycystic ovary syndrome (PCOS) is one of the most common causes of female infertility, affecting about 8% of women in childbearing age, the increase in serum AMH in women with hyperandrogenism and/or oligoovulation may indicate the presence of PCOS, serum AMH is a useful prognostic biochemical marker for metformin treatment in PCOS.

As a first-line treatment for insulin resistance, metformin can improve insulin sensitivity and regulate blood sugar levels, thereby alleviating insulin resistance, which also reducing androgen levels and improving ovulation [64]. Currently, metformin has become a commonly used drug before assisted reproduction in women with PCOS.

In this article, a meta-analysis of 12 groups of PCOS patients taking metformin suggested that: the use of MET in PCOS patients will cause a decrease in serum AMH levels, both obese (BMI ≥ 30Kg/m2) and non-obese (BMI < 30Kg/m2) patients can occur, which suggested that even patients who are not obese can use MET to reduce the level of AMH, reduce the inhibition of follicular development, and increase the chance of spontaneous ovulation.

Endometriosis is a chronic estrogen-dependent disease. Common symptoms include secondary dysmenorrhea, dyspareunia, chronic pelvic pain and infertility. Although the exact mechanism leading to infertility is still unclear, some studies predicted that the excessive production of inflammatory cytokines, growth factors, and chemokines in endometriosis will cause the inflammation process to damage the ovaries, fallopian tubes and endometrial functions [65, 66]. Gonadotropin-releasing hormone agonists (GnRH-a) are common treatments for endometriosis. They inhibit the production of hypothalamic-ovarian axis and ovarian steroids, leading to a decrease in estrogen levels. In addition, they also reduce the expression of growth factors which participate in endometriosis tissue development, such as vascular endothelial growth factor (VEGF), and minimizes the macrophage infiltration and micro vessel density of endometriosis lesions [67, 68]. Studies have shown that in women with infertility related to endometriosis, given GnRH-a 3–6 months before in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) can significantly improve assisted reproduction outcomes [69], but the effect of GnRH-a on serum AMH levels was still controversial.

In this study, the dynamic observation of serum AMH after GnRH-a use emphasized the complexity of AMH levels after GnRH-a use. Serum AMH levels did not change much within 14 days, but some studies pointed out that there was a brief drop in serum AMH levels due to the up-regulation of GnRH receptors, and the anti-proliferation and apoptosis effects of GnRH-a short-term exposure on granulosa cells [70]. At the same time, the short term decrease in AMH may have led to the enlargement of the follicular pools of the anterior and small sinuses that secrete AMH, leading to an increase in AMH levels on the 1 month [33, 71]. Our study emphasized that after using GnRH-a, AMH levels follow a predictable two-way trajectory,

which also limited the application of AMH as a marker of ovarian reserve in the past 3 months after treatment, so it is recommended to perform AMH measuring after stopping the drug for more than 3 months to determine the ovarian reserve function.

DOR/POR (Diminished Ovarian Reserve/Poor Ovary Reserve) is a recognized state of ovarian failure [72], and is one of the most challenging problems in artificial reproductive medicine. DHEA is not only a food supplement, naturally found in wild yam and soy products, but also a steroid with both androgenic and weak estrogenic activity, which can improve ovarian response, reduce miscarriage and aneuploidy, and increase the chance of live birth [43, 73–75]. The reason is that oocytes are in a resting phase in unrecruited primordial follicles, once recruited, they enter an age-dependent ovarian environment where the follicles mature. The quality of this environment deteriorates evenly as women aged, and affects the separation process of meiosis, leading to aneuploidy. DHEA may change and restore the ovarian environment to prevent the aging of follicles [76]. Other studies have shown that DHEA can increase insulin-like growth factor-1 (IGF-1), promote follicle formation, enhance the effect of gonadotropin and reduce follicular atresia [72, 77–79], and make the outcome of assisted pregnancy significantly improve.

In this article, the meta-analysis of 8 groups of DOR/POR patients taking DHEA suggested that: the use of DHEA in DOR/POR patients will cause an increase in serum AMH levels, and this rising effect was obvious in the short term. With the high incidence and severity of DOR/POR in aged patients, whether DHEA pretreatment can achieve the same effect for this type of patients was another aspect. Previous studies have shown that patients less than 35 years old after pretreatment with DHEA, whether the number of follicles obtained, the fertilized eggs, or the serum E2, FSH, LH, or AMH level, all better than women more than 35 years old [80, 81]. In this study, a subgroup analysis of DOR/POR patients based on age showed that DHEA pretreatment in advanced reproductive age women(≥38 years old) can also cause a significant increase in serum AMH levels ($P < 0.00001$), which suggested that it is also necessary to supplement DHEA for such patients.

Vitamin D (VD) is a steroid hormone that has a well-known effect on calcium and bone metabolism. The current research has more and more evidence that the concentration of 25-hydroxyvitamin D (25(OH)D) is related to various conditions, including obesity, metabolic disorders [82, 83], cardiovascular disease [84], gonadal function decrease [85], polycystic ovary syndrome [86] and decreased female fertility [87]. Studies have shown that vitamin D deficiency was associated with various manifestations of polycystic ovary syndrome (PCOS), including anovulation, hyperandrogen and insulin resistance [88]. Vitamin D supplementation has been shown to improve menstrual cycles, hyperandrogen and metabolic disease in polycystic ovary syndrome [89, 90], which shows that vitamin D has a direct impact on female fertility.

The 9 sets of data in this article showed that in non-PCOS patients serum AMH level will increase in the short term after VD pretreatment, but in PCOS patients, this increase is not obvious. The results of this meta-analysis demonstrated that the relationship between vitamin D and AMH is complex, we encourage

non-PCOS patients to supplement VD appropriately. Meanwhile, there is no need to worry about the increase of AMH after VD administration for the patients with PCOS.

Similarly, as a common endocrine disease, polycystic ovary syndrome (PCOS) affects 6–10% of women of childbearing age [91]. Sparse ovulation or anovulation caused by PCOS is a common cause of infertility. Clomiphene (CC) as a first-line drug for inducing ovulation [91, 92] is widely used in ovulation therapy. It is a selective estrogen receptor modulator that can antagonize the negative feedback of endogenous estrogen on the hypothalamic-pituitary axis. Clomiphene treatment can restore luteinizing hormone to normal, increase the secretion of follicle stimulating hormone, thereby promoting follicular growth and ovulation [93], and increase the chance of ovulation and conception in PCOS patients. In addition, existing studies have shown that obesity is an important parameter, which will have a negative impact on the response of PCOS patients to CC [94].

The research results of CC pretreatment in 8 groups of PCOS patients in this article all indicated that: The AMH levels have a short-term reduction after using CC, and it was more obvious in non-obese patients, so we can assume that thinner people represent better sensitivity to CC responses.

As an ovulation-stimulating drug, letrozole was initially used in Clomiphene -resistant cases. In recent years, evidence has shown that compared with CC, LET stimulation has a higher ovulation rate, pregnancy rate, cumulative live birth rate, and lower multiple births [95–97]. The meta-analysis in this article shows that serum AMH levels are affected to some extent after letrozole use, but the trend was not obvious, and there was no statistical significance.

5 Conclusion

Medication application may affect serum AMH levels in the short term. Specifically, OC, metformin and CC leads to decreased AMH level, DHEA and VD leads to increased AMH level, and GnRH-a leads to dynamic variation, which is correlated with PCOS, obesity, age, and duration of medication. The impacts of these medication should be taken into consideration when AMH is used as a marker of ovarian reserve.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Data availability statement

All data analyzed during this study are included in the supplementary information tables (TABLE S1-TABLE S7).

Competing interests

All authors declare no conflict to declare.

Founding

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Authors' contributions

Chun Feng and Wei-Wei Yin designed the study and wrote the paper; Chang-Chang Huang, Yi-Ru Chen and Dan-Qing Yu performed the data curation; Wei-Wei Yin, Chang-Chang Huang, and Min Jin analyzed the data.

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Not Applicable.

References

1. Grootegoed JA, Baarends WM, Themmen AP. Welcome to the family: the anti-müllerian hormone receptor. Mol Cell Endocrinol. 1994. 100(1–2): 29–34.
2. Baarends WM, Uilenbroek JT, Kramer P, et al. Anti-müllerian hormone and anti-müllerian hormone type II receptor messenger ribonucleic acid expression in rat ovaries during postnatal development, the estrous cycle, and gonadotropin-induced follicle growth. Endocrinology. 1995. 136(11): 4951–4962.
3. Rajpert-De Meyts E, Jørgensen N, Graem N, Müller J, Cate RL, Skakkebaek NE. Expression of anti-Müllerian hormone during normal and pathological gonadal development: association with differentiation of Sertoli and granulosa cells. J Clin Endocrinol Metab. 1999. 84(10): 3836–3844.
4. Dewailly D, Andersen CY, Balen A, et al. The physiology and clinical utility of anti-Mullerian hormone in women. Hum Reprod Update. 2014. 20(3): 370–385.
5. Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Prediction of high ovarian response to controlled ovarian hyperstimulation: anti-Müllerian hormone versus small antral follicle count (2–6 mm). J ASSIST REPROD GEN. 2009. 26(6): 319–325.
6. Peluso C, Fonseca FL, Rodart IF, et al. AMH: An ovarian reserve biomarker in assisted reproduction. Clin Chim Acta. 2014. 437: 175–182.

7. Iliodromiti S, Nelson SM. Ovarian response biomarkers: physiology and performance. Curr Opin Obstet Gynecol. 2015. 27(3): 182–186.
8. Friis Petersen J, Løkkegaard E, Andersen LF, et al. A randomized controlled trial of AMH-based individualized FSH dosing in a GnRH antagonist protocol for IVF. Hum Reprod Open. 2019. 2019(1): hoz003.
9. Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. Hum Reprod Update. 2014. 20(5): 688–701.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009. 62(10): e1-34.
11. Luchini C, Veronese N, Nottegar A, et al. Assessing the quality of studies in meta-research: Review/guidelines on the most important quality assessment tools. Pharm Stat. 2021. 20(1): 185–195.
12. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med. 1997. 127(9): 820–826.
13. Kucera R, Ulcova-Gallova Z, Topolcan O. Effect of long-term using of hormonal contraception on anti-Müllerian hormone secretion. Gynecol Endocrinol. 2016. 32(5): 383–385.
14. Johnson LN, Sammel MD, Dillon KE, Lechtenberg L, Schanne A, Gracia CR. Antimüllerian hormone and antral follicle count are lower in female cancer survivors and healthy women taking hormonal contraception. Fertil Steril. 2014. 102(3): 774-U489.
15. Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. Antimüllerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril. 2013. 99(5): 1305–1310.
16. Bentzen JG, Forman JL, Pinborg A, et al. Ovarian reserve parameters: a comparison between users and non-users of hormonal contraception. Reprod Biomed Online. 2012. 25(6): 612–619.
17. Deb S, Campbell BK, Pincott-Allen C, Clewes JS, Cumberpatch G, Raine-Fenning NJ. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2012. 39(5): 574–580.
18. Li HW, Wong CY, Yeung WS, Ho PC, Ng EH. Serum anti-müllerian hormone level is not altered in women using hormonal contraceptives. Contraception. 2011. 83(6): 582–585.
19. Arbo E, Vetori DV, Jimenez MF, Freitas FM, Lemos N, Cunha-Filho JS. Serum anti-mullerian hormone levels and follicular cohort characteristics after pituitary suppression in the late luteal phase with oral contraceptive pills. Hum Reprod. 2007. 22(12): 3192–3196.
20. Somunkiran A, Yavuz T, Yucel O, Ozdemir I. Anti-Müllerian hormone levels during hormonal contraception in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2007. 134(2): 196–201.

21. Saleh BO, Ibraheem WF, Ameen NS. The role of anti-Mullerian hormone and inhibin B in the assessment of metformin therapy in women with polycystic ovarian syndrome. Saudi Med J. 2015. 36(5): 562–567.
22. Madsen HN, Lauszus FF, Trolle B, Ingerslev HJ, Tørring N. Impact of metformin on anti-Müllerian hormone in women with polycystic ovary syndrome: a secondary analysis of a randomized controlled trial. Acta Obstet Gynecol Scand. 2015. 94(5): 547–551.
23. Neagu M, Cristescu C. Anti-Műllerian hormone–a prognostic marker for metformin therapy efficiency in the treatment of women with infertility and polycystic ovary syndrome. J Med Life. 2012. 5(4): 462–464.
24. Nascimento AD, Silva Lara LA, Japur de Sá Rosa-e-Silva AC, Ferriani RA, Reis RM. Effects of metformin on serum insulin and anti-Mullerian hormone levels and on hyperandrogenism in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2013. 29(3): 246–249.
25. Tomova A, Deepinder F, Robeva R, Kirilov G, Mechandjiev Z, Kumanov P. Anti-Müllerian hormone in women with polycystic ovary syndrome before and after therapy with metformin. Horm Metab Res. 2011. 43(10): 723–7.
26. Panidis D, Georgopoulos NA, Piouka A, et al. The impact of oral contraceptives and metformin on anti-Müllerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. Gynecol Endocrinol. 2011. 27(8): 587–592.
27. Carlsen SM, Vanky E, Fleming R. Anti-Müllerian hormone concentrations in androgen-suppressed women with polycystic ovary syndrome. Hum Reprod. 2009. 24(7): 1732–1738.
28. Piltonen T, Morin-Papunen L, Koivunen R, Perheentupa A, Ruokonen A, Tapanainen JS. Serum anti-Müllerian hormone levels remain high until late reproductive age and decrease during metformin therapy in women with polycystic ovary syndrome. Hum Reprod. 2005. 20(7): 1820–1826.
29. Chhabra N, Malik S. Effect of Insulin Sensitizers on Raised Serum Anti-mullerian Hormone Levels in Infertile Women with Polycystic Ovarian Syndrome. J Hum Reprod Sci. 2018. 11(4): 348–352.
30. Dawoud Z, Kamal M, Dahab S, Maged A, Aziz OA. The hormonal and biochemical effects of metformin in PCOS patients. European Journal of Contraception and Reproductive Health CareEur. J. Contracept. Reprod. Health Care. 2018. 23: 117.
31. Wiweko B, Susanto C. The Effect of Metformin and Cinnamon on Serum Anti-Mullerian Hormone in Women Having PCOS: A Double-Blind, Randomized, Controlled Trial. Journal of Human Reproductive SciencesJ. Hum. Reprod. Sci.. 2017. 10(1): 31–36.
32. Foroozanfard F, Samimi M, Sehhat M, Sadat Z, Hosseini K. Effect of metformin on anti-mullerian hormone (AMH) level in women with infertility and polycystic ovary syndrome. International Journal of Fertility and SterilityInt. J. Fertil. Steril.. 2017. 9(12): 5969–5973.
33. Su HI, Maas K, Sluss PM, Chang RJ, Hall JE, Joffe H. The impact of depot GnRH agonist on AMH levels in healthy reproductive-aged women. J Clin Endocrinol Metab. 2013. 98(12): E1961-E1966.
34. Drakopoulos P, van de Vijver A, Parra J, et al. Serum Anti-Müllerian Hormone Is Significantly Altered by Downregulation With Daily Gonadotropin-Releasing Hormone Agonist: A Prospective Cohort

Study. Front Endocrinol (Lausanne). 2019. 10: 115.

35. Cai J, Liu L, Zheng J, et al. Differential response of AMH to GnRH agonist among individuals: the effect on ovarian stimulation outcomes. J Assist Reprod Genet. 2018. 35(3): 467–473.
36. Mocciaro R, Venturella R, Lico D, et al. AMH levels variations during treatment with GnRh agonist: A prospective observational study. Human ReproductionHum. Reprod.. 2016. 31(1): 431.
37. Marschalek J, Ott J, Husslein H, et al. The impact of GnRH agonists in patients with endometriosis on prolactin and sex hormone levels: A pilot study. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2015. 195: 156–159.
38. Agarwal R, Shruthi R, Radhakrishnan G, Singh A. Evaluation of Dehydroepiandrosterone Supplementation on Diminished Ovarian Reserve: A Randomized, Double-Blinded, Placebo-Controlled Study. Journal of Obstetrics and Gynecology of IndiaJ. Obstet. Gynecol. India. 2017. 67(2): 137–142.
39. Tsui K-H, Lin L-T, Chang R, Huang B-S, Cheng J-T, Wang P-H. Effects of dehydroepiandrosterone supplementation on women with poor ovarian response: A preliminary report and review. Taiwanese Journal of Obstetrics and GynecologyTaiwanese J. Obstet. Gynecol.. 2015. 54(2): 131–136.
40. Vlahos N, Papalouka M, Triantafyllidou O, et al. Dehydroepiandrosterone administration before IVF in poor responders: a prospective cohort study. Reprod Biomed Online. 2015. 30(2): 191–196.
41. Yilmaz N, Uygur D, Inal H, Gorkem U, Cicek N, Mollamahmutoglu L. Dehydroepiandrosterone supplementation improves predictive markers for diminished ovarian reserve: serum AMH, inhibin B and antral follicle count. Eur J Obstet Gynecol Reprod Biol. 2013. 169(2): 257–260.
42. Gleicher N, Weghofer A, Barad DH. Improvement in diminished ovarian reserve after dehydroepiandrosterone supplementation. Reproductive BioMedicine OnlineReprod. BioMed. Online. 2010. 21(3): 360–365.
43. Kara M, Aydin T, Aran T, Turktekin N, Ozdemir B. Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve. Eur J Obstet Gynecol Reprod Biol. 2014. 173: 63–65.
44. Elprince M, Kishk EA, Metawie OM, Albiely MM. Ovarian stimulation after dehydroepiandrosterone supplementation in poor ovarian reserve: a randomized clinical trial. Arch Gynecol Obstet. 2020. 302(2): 529–534.
45. Hu Q, Hong L, Nie M, et al. The effect of dehydroepiandrosterone supplementation on ovarian response is associated with androgen receptor in diminished ovarian reserve women. J Ovarian Res. 2017. 10(1): 32.
46. Lerchbaum E, Theiler-Schwetz V, Kollmann M, et al. Effects of vitamin d supplementation on surrogate markers of fertility in pcos women: A randomized controlled trial. NutrientsNutrients. 2021. 13(2): 1.
47. Naderi Z, Kashanian M, Chenari L, Sheikhansari N. Evaluating the effects of administration of 25-hydroxyvitamin D supplement on serum anti-mullerian hormone (AMH) levels in infertile women. Gynecol Endocrinol. 2018. 34(5): 409–412.

48. Dennis NA, Houghton LA, Pankhurst MW, Harper MJ, McLennan IS. Acute Supplementation with High Dose Vitamin D3 Increases Serum Anti-Müllerian Hormone in Young Women. Nutrients. 2017. 9(7).
49. Taheri M, Modarres M, Abdollahi A. The effect of vitamin d supplementation on anti-mullerian hormone levels in reproductive-age women. Reproduction, Fertility and DevelopmentReprod. Fertil. Dev.. 2015. 27(1): 185.
50. Irani M, Seifer D, Minkoff H, Merhi Z. Vitamin D supplementation appears to normalize serum AMH levels in vitamin D deficient premenopausal women. Fertility and SterilityFertil. Steril.. 2013. 100(3): S338-S338.
51. Wong HYQ, Li HWR, Lam KSL, et al. Independent association of serum vitamin D with anti-Mullerian hormone levels in women with polycystic ovary syndrome. Clinical EndocrinologyClin. Endocrinol.. 2018. 89(5): 634–641.
52. Cappy H, Giacobini P, Pigny P, et al. Low vitamin D3 and high anti-Müllerian hormone serum levels in the polycystic ovary syndrome (PCOS): Is there a link. Ann Endocrinol (Paris). 2016. 77(5): 593–599.
53. Gaba A, Hörath S, Hager M, Marculescu R, Ott J. Basal Anti Mullerian hormone levels and endometrial thickness at midcycle can predict the outcome after clomiphene citrate stimulation in anovulatory women with PCOS, a retrospective study. Archives of Gynecology and ObstetricsArch. Gynecol. Obstet.. 2019. 300(6): 1751–1757.
54. Hager M, Hörath S, Frigo P, Koch M, Marculescu R, Ott J. Changes in serum markers of patients with PCOS during consecutive clomiphene stimulation cycles: a retrospective study. J Ovarian Res. 2019. 12(1): 91.
55. Vagios S, Sacha CR, Hammer KC, et al. Response to ovulation induction treatments in women with polycystic ovary syndrome as a function of serum anti-Müllerian hormone levels. J Assist Reprod Genet. 2021. 38(7): 1827–1833.
56. Vagios S, Sacha CR, Hsu JY, et al. Can anti-mullerian hormone (AMH) levels predict response to ovulation induction treatments in women with polycystic ovarian syndrome (PCOS). Fertility and SterilityFertil. Steril.. 2019. 112(3): e391-e392.
57. Gülşen MS, Ulu İ, Yıldırım Köpük Ş, Kıran G. The role of anti-Müllerian hormone in predicting clomiphene citrate resistance in women with polycystic ovarian syndrome. Gynecological EndocrinologyGynecol. Endocrinol.. 2019. 35(1): 86–89.
58. Xi W, Yang Y, Mao H, Zhao X, Liu M, Fu S. Circulating anti-mullerian hormone as predictor of ovarian response to clomiphene citrate in women with polycystic ovary syndrome. J Ovarian Res. 2016. 9: 3.
59. Mahran A, Abdelmeged A, El-Adawy A, et al. The predictive value of measuring circulating anti-müllerian hormone in women with polycystic ovary syndrome receiving clomiphene citrate. Human ReproductionHum. Reprod.. 2012. 27(2): p-493.
60. El-Halawaty S, Rizk A, Kamal M, et al. Clinical significance of serum concentration of anti-Müllerian hormone in obese women with polycystic ovary syndrome. Reprod Biomed Online. 2007. 15(5): 495–499.

61. Andersen CY, Lossl K. Increased intrafollicular androgen levels affect human granulosa cell secretion of anti-Müllerian hormone and inhibin-B. Fertil Steril. 2008. 89(6): 1760–1765.
62. van den Berg MH, Overbeek A, van Dulmen-den Broeder E, Lambalk CB. Comment on: Li HW, Wong CY, Yeung WS, Ho PC, Ng EH. Serum anti-Mullerian hormone level is not altered in women using hormonal contraceptives. Contraception 2011;83:582-5. Contraception. 2012. 85(5): 519–520; author reply 520–521.
63. Kristensen SL, Ramlau-Hansen CH, Andersen CY, et al. The association between circulating levels of antimüllerian hormone and follicle number, androgens, and menstrual cycle characteristics in young women. Fertil Steril. 2012. 97(3): 779–785.
64. Dunaif A. Drug insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome–a reappraisal. Nat Clin Pract Endocrinol Metab. 2008. 4(5): 272–283.
65. Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A. Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril. 2008. 90(2): 247–257.
66. Evans J, Salamonsen LA. Decidualized human endometrial stromal cells are sensors of hormone withdrawal in the menstrual inflammatory cascade. Biol Reprod. 2014. 90(1): 14.
67. Khan KN, Kitajima M, Hiraki K, et al. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod. 2010. 25(3): 642–653.
68. Marschalek J, Ott J, Husslein H, et al. The impact of GnRH agonists in patients with endometriosis on prolactin and sex hormone levels: a pilot study. Eur J Obstet Gynecol Reprod Biol. 2015. 195: 156–159.
69. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev. 2006. 2006(1): CD004635.
70. Joffe H, White DP, Crawford SL, et al. Adverse effects of induced hot flashes on objectively recorded and subjectively reported sleep: results of a gonadotropin-releasing hormone agonist experimental protocol. Menopause. 2013. 20(9): 905–914.
71. Fanchin R, Schonäuer LM, Righini C, Frydman N, Frydman R, Taieb J. Serum anti-Müllerian hormone dynamics during controlled ovarian hyperstimulation. Hum Reprod. 2003. 18(2): 328–332.
72. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011. 26(7): 1616–1624.
73. Qin JC, Fan L, Qin AP. The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: Evidence from a meta-analysis. J Gynecol Obstet Hum Reprod. 2017. 46(1): 1–7.
74. Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. Hum Reprod. 2010. 25(10): 2496–2500.

75. Yeung T, Chai J, Li R, Lee V, Ho PC, Ng E. A double-blind randomised controlled trial on the effect of dehydroepiandrosterone on ovarian reserve markers, ovarian response and number of oocytes in anticipated normal ovarian responders. BJOG. 2016. 123(7): 1097–1105.
76. Gleicher N, Barad DH. Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR). Reprod Biol Endocrinol. 2011. 9: 67.
77. Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet. 2007. 24(12): 629–634.
78. Barad DH, Gleicher N. Increased oocyte production after treatment with dehydroepiandrosterone. Fertil Steril. 2005. 84(3): 756.
79. Barad D, Gleicher N. Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum Reprod. 2006. 21(11): 2845–1849.
80. Singh N, Zangmo R, Kumar S, et al. A prospective study on role of dehydroepiandrosterone (DHEA) on improving the ovarian reserve markers in infertile patients with poor ovarian reserve. Gynecol Endocrinol. 2013. 29(11): 989–992.
81. Zangmo R, Singh N, Kumar S, Vanamail P, Tiwari A. Role of dehydroepiandrosterone in improving oocyte and embryo quality in IVF cycles. Reprod Biomed Online. 2014. 28(6): 743–747.
82. Wehr E, Pilz S, Schweighofer N, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. Eur J Endocrinol. 2009. 161(4): 575–582.
83. Trummer C, Pilz S, Schwetz V, Obermayer-Pietsch B, Lerchbaum E. Vitamin D, PCOS and androgens in men: a systematic review. Endocr Connect. 2018. 7(3): R95-R113.
84. Pilz S, März W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab. 2008. 93(10): 3927–3935.
85. Lerchbaum E, Pilz S, Trummer C, et al. Serum vitamin D levels and hypogonadism in men. Andrology. 2014. 2(5): 748–754.
86. Mu Y, Cheng D, Yin TL, Yang J. Vitamin D and Polycystic Ovary Syndrome: a Narrative Review. Reprod Sci. 2021. 28(8): 2110–2117.
87. Lerchbaum E, Rabe T. Vitamin D and female fertility. Curr Opin Obstet Gynecol. 2014. 26(3): 145–150.
88. He C, Lin Z, Robb SW, Ezeamama AE. Serum Vitamin D Levels and Polycystic Ovary syndrome: A Systematic Review and Meta-Analysis. Nutrients. 2015. 7(6): 4555–4577.
89. Xue Y, Xu P, Xue K, et al. Effect of vitamin D on biochemical parameters in polycystic ovary syndrome women: a meta-analysis. Arch Gynecol Obstet. 2017. 295(2): 487–496.
90. Irani M, Seifer DB, Grazi RV, et al. Vitamin D Supplementation Decreases TGF-β1 Bioavailability in PCOS: A Randomized Placebo-Controlled Trial. J Clin Endocrinol Metab. 2015. 100(11): 4307–4314.
91. McCartney CR, Marshall JC. CLINICAL PRACTICE. Polycystic Ovary Syndrome. N Engl J Med. 2016. 375(1): 54–64.

92. Conway G, Dewailly D, Diamanti-Kandarakis E, et al. European survey of diagnosis and management of the polycystic ovary syndrome: results of the ESE PCOS Special Interest Group's Questionnaire. Eur J Endocrinol. 2014. 171(4): 489–498.
93. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007. 370(9588): 685–697.
94. Douchi T, Oki T, Yamasaki H, Nakae M, Imabayashi A, Nagata Y. Body fat patterning in polycystic ovary syndrome women as a predictor of the response to clomiphene. Acta Obstet Gynecol Scand. 2004. 83(9): 838–841.
95. Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014. 371(2): 119–129.
96. Badawy A, Abdel Aal I, Abulatta M. RETRACTED: Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril. 2009. 92(3): 849–852.
97. Huang S, Du X, Wang R, et al. Ovulation induction and intrauterine insemination in infertile women with polycystic ovary syndrome: A comparison of drugs. Eur J Obstet Gynecol Reprod Biol. 2018. 231: 117–121.

Figures

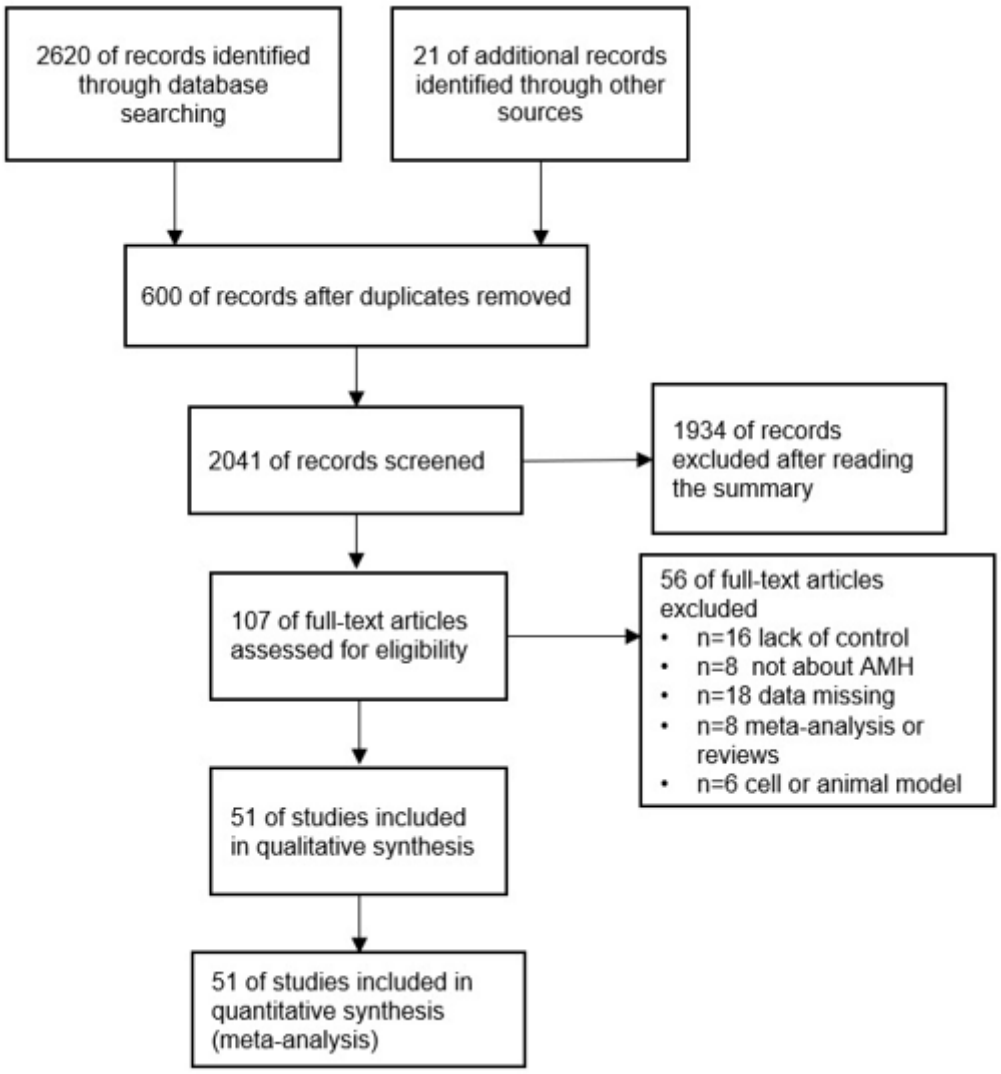

Figure 1

Flow chart for the selection of the retrieved articles.

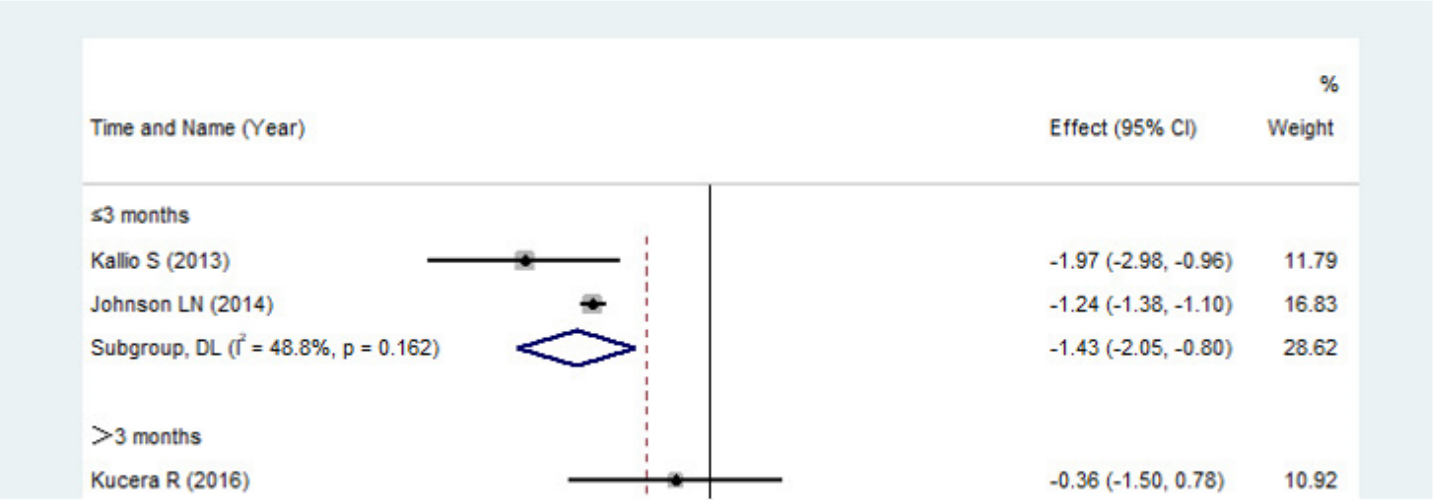

Figure 2

Forest plot of Meta subgroup analysis of serum AMH level changes in women with normal ovarian function taking oral contraceptives (≤3 months vs. >3 months).

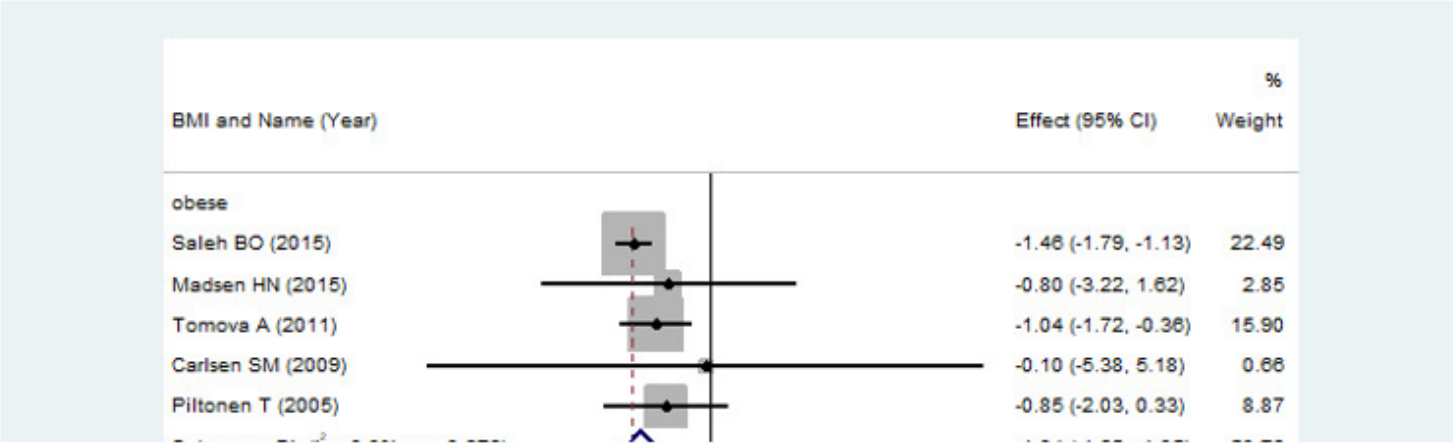

Figure 3

Forest plot of Meta subgroup analysis of changes in serum AMH levels of non-obese vs obese PCOS patients with MET pretreatment.

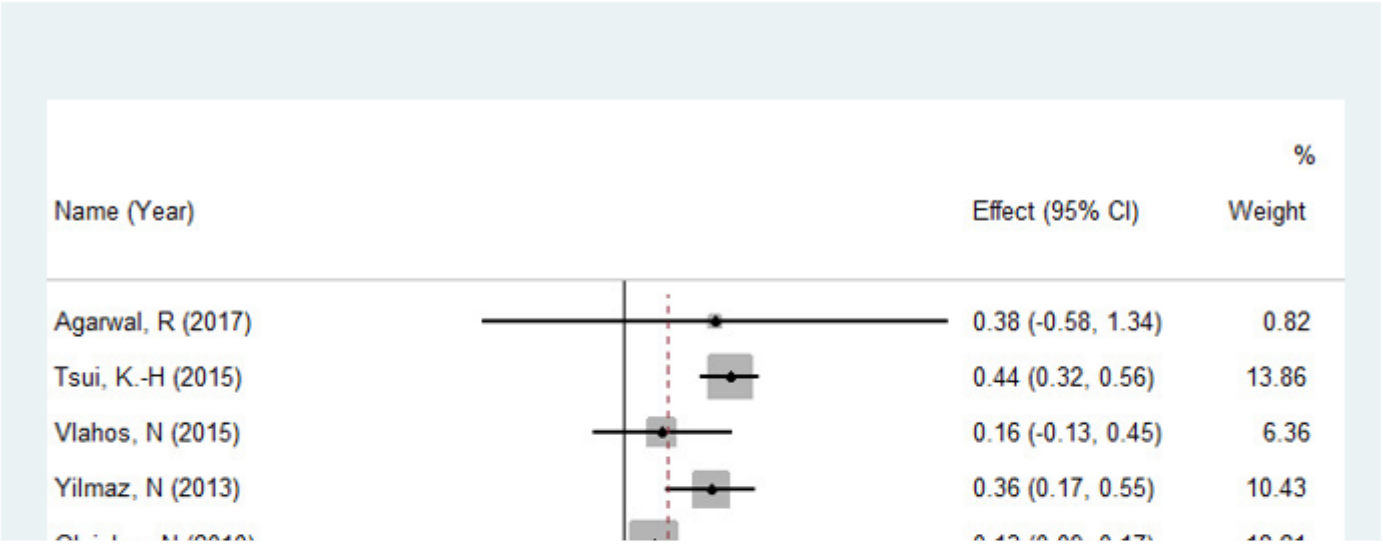

Figure 4

Changes in serum AMH levels in DOR/POR patients taking DHEA (dehydroepiandrosterone).

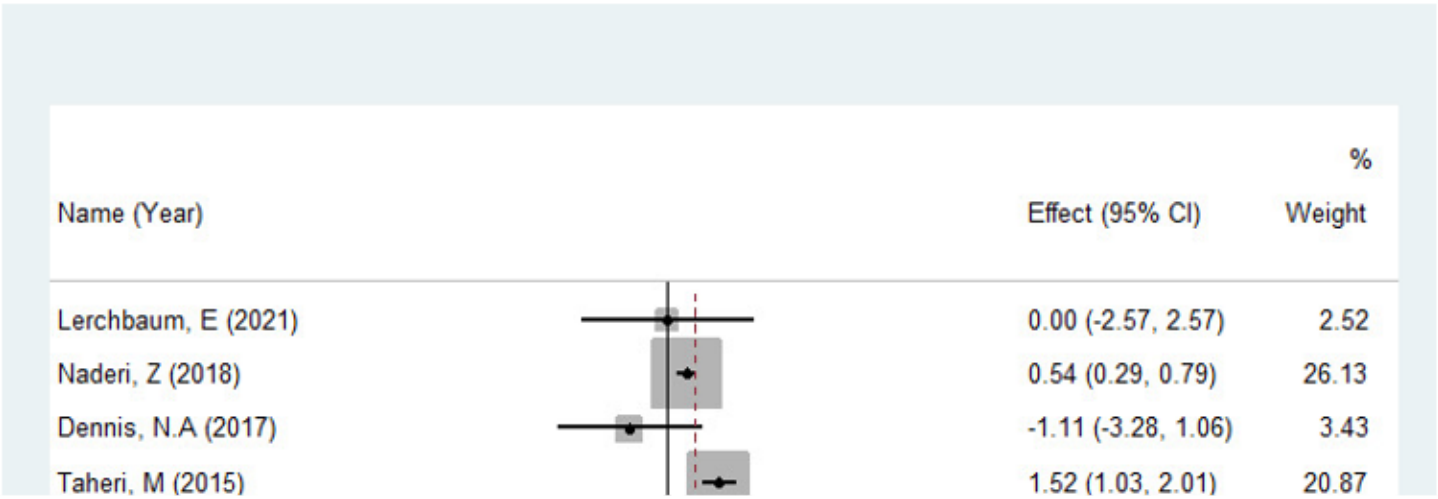

Figure 5

Forest plot of Meta analysis of changes in serum AMH levels after VD pretreatment.

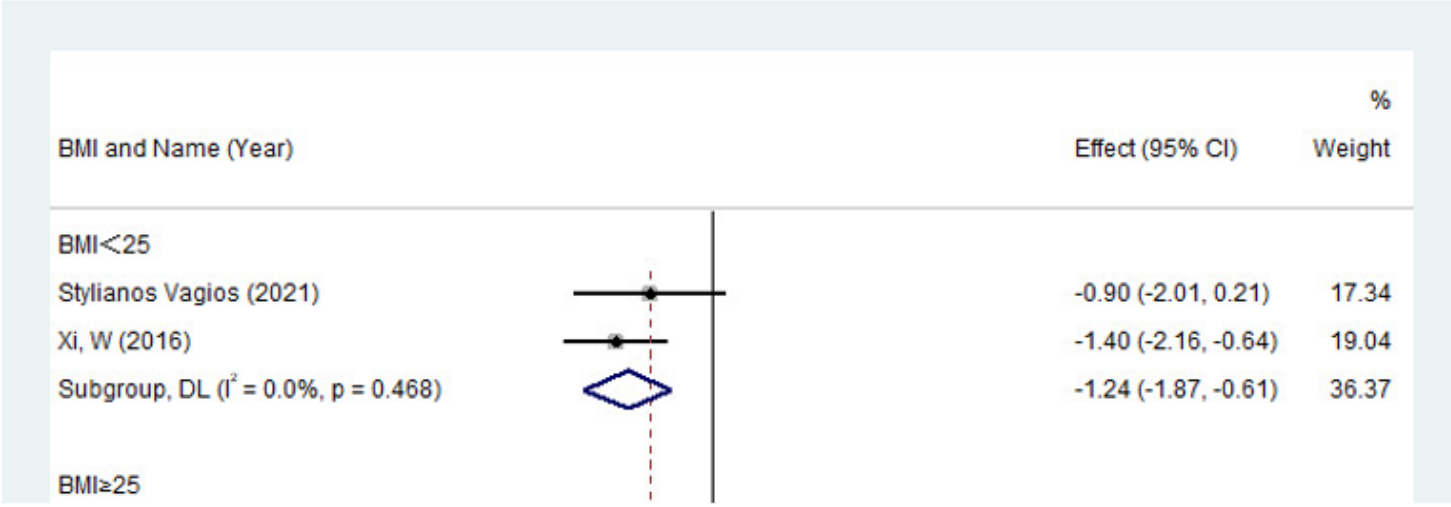

Figure 6

Forest plot of Meta subgroup analysis of changes in serum AMH levels of non-obese vs obese PCOS patients with CC pretreatment.

Supplementary Files

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