REVIEW ARTICLE

Fertility Supplements and Their Impact on Reproductive Health in Women with Poor Ovarian Response (POR): A Scoping Review

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ABSTRACT

Background: Occasionally, infertile women undergoing fertility treatment, particularly those affected by factors such as poor-quality oocytes and poor ovarian response (POR), turn to supplements to enhance their chances of conceiving. However, women with POR represent approximately 10% of this group, making them a minority and limiting their available treatment options. Therefore, this study aims to investigate the most commonly used fertility supplements for women with POR and evaluate their potential effects on reproductive health.. **Methods:** Relevant keywords were used to search three major online databases: PubMed, Scopus, and ScienceDirect. Article selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, considering all articles published between 2012 and 2022 that met the inclusion and exclusion criteria. **Results:** A total of 11 articles were selected, demonstrating that fertility supplements have an effect on POR and reproductive health. The findings identified several fertility supplements as effective and suitable for women with poor ovarian response, including dehydroepiandrosterone (DHEA), vitamin D, myo-inositol, and the Ding-Kun Pill (DKP). These supplements have been linked to positive effects on reproductive health, such as increased insulin-like growth factor 1 (IGF-1) levels, healthy follicular growth, and improved oocyte quality and development, which may enhance fertility outcomes. **Conclusion:** This review is significant as it enhances our understanding of the effectiveness fertility supplements for women with impaired ovarian reserves. By offering suitable treatment options, it also fulfills the need for evidence-based knowledge about the reproductive impacts of these supplements.

INTRODUCTION

Fertility supplements, according to Forbes Health (2023), are manufactured products that exist in the form of a capsule, sachet, pill, or tablet. They may contain a range of substances and are frequently mentioned as serving a significant contribution to improving both male and female fertility. Examples include selenium, folic acid, coenzyme Q10, dehydroepiandrosterone (DHEA), and many others. Female fertility supplements assist in conception by providing extra micronutrients into the body, where they aid in the production of high-quality oocytes and the reduction of oxidative stress. The majority of women may benefit from consuming supplements, especially the older population who are more prone to oxidative cell damage as well as those with limited ovarian reserve or poor responses.

According to the United Nations (2015), infertility is a pressing global health issue that affects 20 to 30% of the female reproductive age population in society today. However, the most varying explanations are mostly rooted in the decrease of reproductive potential among females. A multitude of systemic and ovarian diseases, such as polycystic ovarian syndrome (PCOS), endometriosis, premature failure of the ovary, and pelvic inflammatory disease, can also influence the female reproductive system and potentially lead to infertility (Deshpande and Gupta, 2019). Fertility supplements should be addressed as one of the options for restoring fertility and normal reproduction as it can be seen that the reproductive health of poor ovarian responders are significantly compromised.

Approximately 10% of women pursuing fertility treatments have an impaired ovarian reserve where it can affect people of all ages (Greene et al., 2014). Jirge (2016) mentioned that poor ovarian reserve (POR) is a significant limiting element for the effectiveness of any infertility method of treatment. This suggests that women of reproductive age have fewer oocytes of lower quality and quantity. Moreover, the fertility rate of women with POR is also relatively low compared to a control group study, especially for women above 40 who have driven ovarian aging (Zhen et al., 2008). Although POR is a rare condition affecting a minority of women, some cases still involve low ovarian reserves and infertility complications. Consequently, fertility supplements that are suitable, effective, and safe to consume are few and minimal. It is also critical for women to comprehend the implications of fertility supplements on their reproductive health, particularly if they struggle with ovarian reserve issues. Thus, by compiling the available information based on

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scientific results, this study provides evidence of various fertility supplements effective for women with POR.

MATERIALS AND METHODS

Study Design

A scoping review study design was chosen to comprehensively examine the available evidence on fertility supplements for infertile females with ovarian reserve complications and their effects on reproductive health. The framework included the development of research objectives aligned with the research problems, the selection of articles that met the review's goals, and a screening process to ensure compliance with the inclusion and exclusion criteria, along with the availability of full-text articles.

Search Method

Relevant research articles were retrieved from three medically and scientifically credible online databases: PubMed, Scopus, and ScienceDirect. The following keywords were used to identify relevant publications: 'fertility supplements', 'poor ovarian response', 'POR', 'diminished ovarian reserve', 'DOR', 'poor ovarian responders', 'women', 'females'. Additionally, in order to further clarify and broaden the search parameters while using databases, Boolean operators (AND, OR) and asterisks (*) were utilized in combination with the search keywords.

Inclusion and Exclusion Criteria

Several criteria were established and considered during the selection of relevant papers for this scoping review. Articles that failed to meet the inclusion criteria outlined in Table 1 were excluded from the analysis

Selection of Studies

The research papers were selected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) standards. These standards provide guidelines for choosing, evaluating, and synthesizing studies in scoping reviews, and the most recent statement incorporates improvements in these approaches (Page et al., 2021). Articles published between 2012 and 2022 were extracted from online databases and screened. After eliminating duplicates from various sources, the remaining articles underwent title and abstract screening to filter out irrelevant studies. Subsequently, the full-text versions of the selected papers were retrieved. Next, the information in those articles was thoroughly examined to analyze the data on fertility supplements for women with POR and their impact on reproductive health. During the screening process, articles that did not meet the inclusion criteria or conformed to the exclusion criteria were excluded. The PRISMA extension for scoping reviews, retrieved from Tricco et al. (2018), is presented in Figure 1.

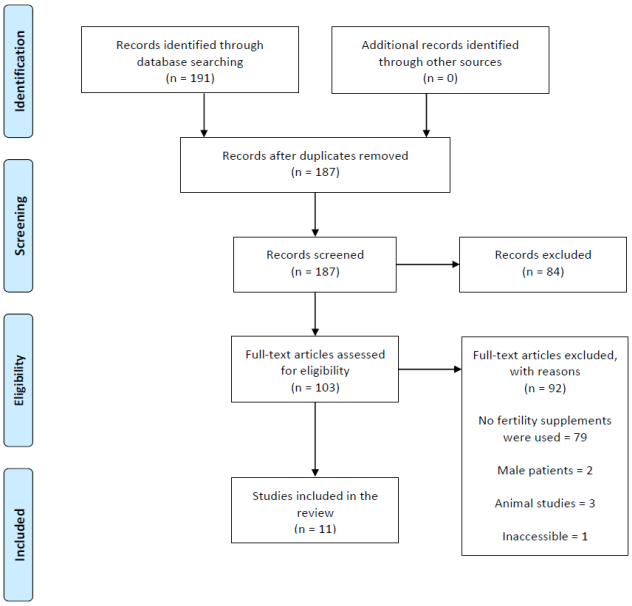

Figure 1: PRISMA flow diagram

Data Extraction

The final phase for methodology is data retrieval from the chosen articles. The findings from the final selection of research articles were extracted, examined, and are presented in Table 3 and Table 4. Here, the characteristics of each study is clearly identified and examined for further discussion.

RESULTS

The selection of articles is summarised in Figure 1. Initially, 191 references were retrieved from the databases (Table 2). After removing duplicates, 187 references remained. These references were screened based on predetermined criteria (Table 1), focusing on infertile women with POR and the use of fertility supplements. A total of 103 articles were eligible for inclusion after excluding conference papers, review articles, case reports, and inaccessible publications. Among the eligible articles, 11 publications specifically mentioned the type of fertility supplements used. Table 3 presents data on the characteristics of the research articles, including the author, title, year of publication, study type, country of origin, participant data, and type of fertility supplements used. Table 4 illustrates the reproductive outcomes associated with fertility supplements in women with POR, providing information on the author, supplement type, ovarian markers, fertilization rate, and pregnancy rate. Out of 11 selected studies, six investigated the use of DHEA in women with POR, two focused on myo-inositol, two on vitamin D, and one study examined the effects of the Ding-Kun Pill (DKP).

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
a) Research articles that are written in English b) Research articles that are published from year 2012 to 2022 c) Research articles that are related to fertility supplements for infertile women POR d) Full-text and peer-reviewed research articles e) Qualitative (eg. case study) and quantitative (eg. descriptive) studies f) The search consists of specific keywords	a) Research articles that are written in languages other than English b) Research articles that are published before year 2012 c) Research articles that are not related to fertility supplements for infertile women with POR d) Research articles that are not in full text e) Conference papers, case reports, grey literatures, review studies, editorials, letters f) Research articles that are irrelevant to the objectives of the study g) Research articles on female medications

Table 2: Total number of hit-searches based on keywords of PubMed, Scopus and ScienceDirect

Online Database	Keywords	Total of References
PubMed	("fertility supplement" AND (women OR female) AND ("poor ovarian response" OR POR OR "diminished ovarian reserve" OR DOR OR "poor ovarian responder") AND infertil*	20
Scopus	"fertility supplement" AND (women OR female) AND ("poor ovarian response" OR "diminished ovarian reserve" OR "poor ovarian responder") AND infertil*	42
ScienceDirect	"fertility supplement" AND (women OR female) AND ("poor ovarian response" OR "diminished ovarian reserve") OR "poor ovarian responder") AND infertility	129
	Total	191

Table 3: Data Extraction on the Common Types of Fertility Supplements for Infertile Women with POR

Author	Title	Year of Publication	Specific of Study Design	Country of Origin	Type of Fertility Supplement	Dose of Supplement	Duration of Supplement
Moawad & Shaeer	Long-term androgen priming by use of dehydroepiandrosterone (DHEA) improves IVF outcome in poor-responder patients. A randomized controlled study	2012	Randomized controlled trial (RCT)	United Arab Emirates	DHEA	25mg	12 weeks
Yeung et al.	A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and *in vitro* fertilization outcomes in poor responders	2014	RCT	Hong Kong	DHEA	25mg	12 weeks
Zhang et al.	Dehydroepiandrosterone plus climen supplementation shows better effects than dehydroepiandrosterone alone on infertility patients with diminished ovarian reserve of low-FSH level undergoing in-vitro fertilization cycles: a randomized controlled trial	2016	RCT	China	DHEA	25mg	12 weeks
Hu et al.	The effect of dehydroepiandrosterone supplementation on ovarian response is associated with androgen receptor in diminished ovarian reserve women	2017	Prospective chort study	China	DHEA	25mg	8 weeks
Ozcil	Dehydroepiandrosterone supplementation improves ovarian reserve and pregnancy rates in poor responders	2020	Prospective chort study	Turkey	DHEA	50mg	5 months
Nazari et al.	Effect of myo-inositol supplementation on ICSI outcomes among poor ovarian responder patients: A randomized controlled trial	2020	RCT	Iran	Myo-inositol	4g	1 month
Mohammadi et al.	The effect of Myo-inositol on fertility rates in poor ovarian responder in women undergoing assisted reproductive technique: a randomized clinical trial	2021	RCT	Iran	Myo-inositol	4g	12 weeks
Aramesh et al.	Does vitamin D supplementation improve ovarian reserve in women with diminished ovarian reserve and vitamin D deficiency: a before-and-after intervention study	2021	Pre-post intervention study	Iran	Vitamin D	50,000IU	3 months
Song et al.	The Role of Traditional Chinese Formula Ding-Kun Pill (DKP) in Expected Poor Ovarian Response Women (POSEIDON Group 4) Undergoing *In Vitro* Fertilization-Embryo Transfer: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial	2021	RCT	Mainland China	Ding-Kun Pill (DKP)	7g	5-6 weeks
Bacanakgil et al.	Effects of vitamin D supplementation on ovarian reserve markers in infertile women with diminished ovarian reserve	2022	prospective, non-randomized, cross-	Turkey	Vitamin D	300,000IU	2 months

			sectional study				
Hou et al.	DHEA restores mitochondrial dynamics of cumulus cells by regulating PGAM5 expression in poor ovarian responders	2022	nested case-control study	Taiwan	DHEA	25mg	2 months

Table 4: Data Extraction on the Reproductive Impacts of Fertility Supplements on Infertile Women with POR

Author	Title	Type of Fertility Supplement	Ovarian Reserve Markers				Fertilization Rate	Pregnancy Rate
			FSH	AMH	AFC	Estradiol		
Moawad & Shaeer	Long-term androgen priming by use of dehydroepiandrosterone (DHEA) improves IVF outcome in poor-responder patients. A randomized controlled study	DHEA	Decreased	No change	Increased	Increased	Improved	Improved
Yeung et al.	A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and *in vitro* fertilization outcomes in poor responders	DHEA	Slightly increased	Slightly increased	No change	Slightly increased	Improved	No significant improve-ment
Zhang et al.	Dehydroepiandrosterone plus climen supplementation shows better effects than dehydroepiandrosterone alone on infertility patients with diminished ovarian reserve of low-FSH level undergoing in-vitro fertilization cycles: a randomized controlled trial	DHEA	Decreased	Increased	Increased	Increased	Improved	Improved
Hu et al.	The effect of dehydroepiandrosterone supplementation on ovarian response is associated with androgen receptor in diminished ovarian reserve women	DHEA	Decreased	Increased	Increased	Increased	Improved	Improved
Ozcil	Dehydroepiandrosterone supplementation improves ovarian reserve and pregnancy rates in poor responders	DHEA	Decreased	Slightly increased	Increased	Increased	Improved	Improved
Hou et al.	DHEA restores mitochondrial dynamics of cumulus cells by regulating PGAM5 expression in poor ovarian responders	DHEA	Decreased	Increased	N/A	Slightly increased	Improved	Improved
Nazari et al.	Effect of myo-inositol supplementation on ICSI outcomes among poor ovarian responder patients: A randomized controlled trial	Myo-inositol	Slightly increased	No change	No change	N/A	Improved	No significant improvement
Mohammadi et al.	The effect of Myo-inositol on fertility rates in poor ovarian responder in women undergoing assisted reproductive technique: a randomized clinical trial	Myo-inositol	Slightly increased	Slightly increased	Slightly increased	Slightly increased	Improved	Improved
Aramesh et al.	Does vitamin D supplementation improve ovarian reserve in women with diminished ovarian reserve and vitamin D deficiency: a before-and-after intervention study	Vitamin D	N/A	Increased	No change	N/A	Improved	Improved
Bacanakgil et al.	Effects of vitamin D supplementation on ovarian reserve markers in infertile women with diminished ovarian reserve	Vitamin D	Decreased	Increased	Increased	N/A	Improved	Improved
Song et al.	The Role of Traditional Chinese Formula Ding-Kun Pill (DKP) in Expected Poor Ovarian Response Women (POSEIDON Group 4) Undergoing In Vitro Fertilization-Embryo Transfer: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial	Ding-Kun Pill (DKP)	Slightly increased	Slightly increased	No change	Increased	Improved	No significant improvement

DISCUSSION

Numerous interventions have been explored to improve fertility outcomes in women with poor ovarian response (POR). Various supplements have shown potential in enhancing ovarian function and improving fertility in the management of POR. Among these, certain supplements have gained attention for their ability to support reproductive health. However, the effectiveness of these interventions may vary between individuals. Based on our the findings, the most common fertility supplementations for women with POR and their impacts on reproductive health are DHEA, Myo-inositol, Vitamin D and Ding-Kun Pill (DKP).

The most commonly used fertility supplement for POR is DHEA. DHEA, a common steroid in human blood, acts as a precursor for steroid hormone production in the follicle. Moawad and Shaeer (2012) found that DHEA supplementation improves oocyte yield and pregnancy rates in women with POR. Hou et al. (2022) confirmed that DHEA raises intrafollicular IGF-1 levels, enhancing follicle growth and oocyte quality. A study by Yeung et al. (2021) shows that DHEA boosts androgen levels, which are essential for follicular development and increased sensitivity to FSH. This mechanism, according to Hu et al. (2017), may promote follicle growth in women with diminished ovarian reserve (DOR). Ozcil (2020) also reported that DHEA improves ovarian reserve markers and pregnancy outcomes, particularly in women with secondary infertility. Similarly, Zhang et al. (2016) found that DHEA increases conception rates, boosts anti-Müllerian hormone (AMH) levels, and lowers FSH levels. Studies by Hou et al. (2022) and Hu et al. (2017) further show that DHEA enhances FSH effects and improves mitochondrial function, making it a potential treatment for improving clinical pregnancy rates. The majority of DHEA regimens involve a dose of 25 mg for a duration of 8–12 weeks, with the exception of Ozcil (2020), who utilized a dose of 50 mg over 5 months. Overall, these findings suggest that DHEA treatment has the potential to improve ovarian reserve markers, fertilization rates, and clinical pregnancy outcomes among poor responders.

Myo-inositol, part of the vitamin B complex, has been shown to improve oocyte maturation, reduce androgen production, and lower oxidative stress. Mohammadi et al. (2021) found that myo-inositol reduces the required gonadotropin dose, increases ovarian sensitivity, and improves fertilization rates. These effects may be due to myo-inositol's ability to enhance oocyte responsiveness to calcium oscillations during fertilization, contributing to higher embryo quality and pregnancy rates. Nazari et al. (2020) reported that administering myo-inositol for three months before ovulation in POR patients undergoing ICSI improved reproductive outcomes including fertilization, implantation, and embryo development. However, no statistically significant improvement was observed in the pregnancy rate. The studies utilized a Myo-inositol dose of 4 g, with treatment durations ranging from 4 to 12 weeks.

Vitamin D, a steroid hormone, is essential for bone and calcium metabolism, aiding calcium absorption and supporting bone growth. Studies have revealed an effective association between vitamin D levels in follicular fluid and embryo quality, as well as an increase in AMH and antral follicular count (AFC) levels which led to better treatment outcomes in terms of higher oocyte yield, higher fertilization rates, and increased chances of pregnancy (Aramesh et al., 2021; Bacanakgil et al., 2022). Bacanakgil et al. (2022) also linked vitamin D to reproductive conditions like PCOS and endometriosis, as well as improved outcomes in controlled ovarian stimulation during IVF. The doses of Vitamin D in these studies vary, ranging from 30,000 IU to 50,000 IU, with treatment durations of 2 to 3 months.

Ding-Kun Pill (DKP), a traditional Chinese medicine used since the Qing dynasty, contains ginseng, deer antler, safflower, scutellaria, and other herbs. A study by Song et al. (2021) found that 7g of DKP significantly increased estradiol, slightly increased FSH, and AMH but there is no changes in AFC in patients with reduced ovarian reserve. DKP also improved blastocyst quality and reduced follicle apoptosis by enhancing ovarian sensitivity to gonadotropins, leading to better oocyte development, increase in the fertilization rate along with higher qualities and quantities of blastocysts and endometrial receptivity. However, this supplement did not yield statistically significant improvements in the overall pregnancy rate.

This review has several limitations. Variations in dosages and durations of supplementation across studies make it difficult to determine the optimal regimen. The long-term safety and potential side effects of fertility supplements are not fully understood or adequately assessed. The findings are based on available evidence and may not reflect the most current research. Furthermore, the effectiveness of fertility supplements may vary depending on patient characteristics such as age, fertility status, and health conditions, limiting the applicability of this review to all women with POR. More research, including randomized controlled trials, is needed to establish the efficacy of these supplements.

CONCLUSION

In conclusion, this scoping review highlights the potential benefits of fertility supplementation in infertile women with POR. Fertility supplements such as DHEA, vitamin D, myo-inositol, and DKP have shown positive effects on reproductive health, including improved ovarian response, gonadotropin levels, embryo quality, endometrial receptivity, and fertility rates. These findings suggest that fertility supplementation may be a beneficial treatment option for women with POR.

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