



Clinical Gynecologic Endocrinology and Infertility: A Literature Review

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ABSTRACT

Objective Polycystic ovary syndrome (PCOS) is the most common cause of an ovulatory subfertility and affects up to 10% of the female population. Moreover, throughout the years, its definition remains controversial. *Method:* Electronic search in PubMed, science direct, google scholar, up-to-date, Wiley online library with keywords for Anovulation in PCOS, PCOS, Ovulation, Polycystic ovary syndrome, infertility between 2017 and 2018, and selected articles that are more relevant to the subject. *Conclusions:* the various factors, help us understand the ovulatory disturbance and provide parameters upon which to make treatment decisions.

Key words: Endocrinology, infertility, PCOS

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a very heterogeneous and complex disorder characterized by oligo-anovulation, hyperandrogenism and/or hyperandrogenemia, and polycystic ovarian morphology (PCOM) [1]. Polycystic ovary syndrome (PCOS) is the most common cause of an ovulatory subfertility and affects up to 10% of the female population [2]. Moreover, throughout the years, its definition remains controversial. An expert panel from the NIH Evidence-Based Methodology Workshop on PCOS [3] recommended that clinicians use the Rotterdam criteria for diagnosis of PCOS [4]; the same recommendation was also given subsequently in the practical guidelines of the Endocrine Society [5].

Most people will have the strong desire to conceive a child at some point during their lifetime. Understanding what defines normal fertility is crucial to helping a person, or couple, know when it is time to seek help [6]. Most

couples (approximately 85%) will achieve pregnancy within one year of trying, with the greatest likelihood of conception occurring during the earlier months. Only an additional 7% of couples will conceive in the second year [7]. As a result, infertility has come to be defined as the inability to conceive within 12 months. This diagnosis is therefore shared by 15% of couples attempting to conceive. Some medical conditions can affect fertility. Ovulation disorders appear to be the most common cause of infertility in women. Ovulation is the monthly release of an egg. The eggs may never be released or they may only be released in some cycles. There are various features of PCOS which could contribute to the disruption of ovulation and these will be discussed in this study [8].

MATERIALS AND METHODS

Electronic Search was conducted in a direct scientific article, Google Scholar, uptodate, wiley online library with keywords for Anovulation in PCOS, PCOS, Ovulation, Polycystic ovary syndrome, infertility between 2017 and 2018, and selected articles that are more relevant to the subject.

RESULTS AND DISCUSSION

Ovulation

To report a case series of in vitro fertilization patients with premature ovarian insufficiency, who were treated with oral contraceptives to reduce follicle stimulating hormone levels. In this study, refractory POI was defined as amenorrhea and/or oligoamenorrhea for at least 4 months, FSH >40 IU/l on two occasions more than 4 weeks apart, without visible antral follicle count on two occasions more than 4 weeks apart. Idiopathic POI was defined as cause unexplained. None of the patients had chromosomal/genetic disorders, iatrogenic injury or autoimmune diseases. The results indicated no oral contraceptive-related adverse event was detected. There were total 106 oral contraceptive treatment cycles in the 22 women (median 5, range 2–8). There were 53 oocyte retrieval cycles in 20 patients, but in two cases there was no follicular development. The total number of oocytes retrieved was 48 in 17 patients; the total number of 2-pronucleus was 34 in 16 patients. The normal fertilization rate was 70.8% (34/48). The total number of embryos frozen was 33 in 16 patients.

It is typical of idiopathic POI patients that spontaneous ovulation may occur in 20% of patients, and spontaneous pregnancies in 5–10%^{12,13}. Although it is generally accepted that there are no reliable interventions for infertility except oocyte donation for POI women, there has always been a hope that pituitary suppression could arouse ovarian activity. It was thought that prolonged supraphysiologic FSH levels could down-regulate FSH receptors in follicles, resulting in poor ovarian response to any endogenous or exogenous stimulation¹⁴. Pituitary suppression treatments, including oral contraceptives, estrogen, progestogen, androgen, and GnRH_a, might restore the ovarian sensitivity in some patients¹⁴. Ovulation induction has been reported to occur even in women without follicles at ovarian biopsy². In our study, the POI patients did not have any visible follicles; the treatment with oral contraceptives reduced FSH levels of all 22 patients within 3 weeks, and follicular reappearance and growth were observed in most women (91%, 20/22). We reduced the oral contraceptive dose to increase the FSH levels as endogenous stimulation, or gave gonadotropins as exogenous stimulation, and oocyte retrievals and embryos frozen were achieved in more than half of the patients. However, two cases failed to

produce any follicles after five oral contraceptive treatment cycles per patient. The reason for this remains unknown but may represent a more advanced stage of POI [9].

In the study of ovulation, with the level of mid-luteal progesterone and ultrasound follicles, in patients with CC resistant PCOS undergoing transvaginal hydro-parosomal ovarian surgery. Before the surgical procedure, all patients underwent clinical examination, routine preoperative biochemical testing and a transvaginal pelvic ultrasound examination. Each participant after surgical treatment underwent blood sampling on days 20–24 of the cycle to measure serum Pg levels. Progesterone level 43 ng/mL was considered as ovulation (13–15). The endometrial thickness and follicle size were monitored on days 10, 12 and 14 of the cycle and the subsequent surveillance timepoint was adjusted according to the individual situation until ovulation. The presence of ovulation was found only in those cycles in which the follicle reached at least 16 mm in diameter. Ovulation frequency and the highest mean follicular diameters during the monitoring were recorded. Both tests were repeated each month for 6 months after surgery. The serum hCG concentration was measured in case of amenorrhea longer than 45 days. Biochemical pregnancy was considered when hCG was 42.5 mIU/ml in the absence of menstruation, and clinical pregnancy was defined by a fetal heart beat monitored by ultrasound at 6 weeks of gestation. In conclusion, in this study shows that THLOD improve ovulation and pregnancy rate in women with CC-resistant PCOS [10].

In the study of Acupuncture for Infertility in Women with Polycystic Ovary Syndrome, result showed : Clomiphene was twice as effective at achieving live birth, with no effect of acupuncture alone or in combination with clomiphene. Thus, the findings from the recent RCT do not support acupuncture as an infertility treatment, alone or in combination, in women with PCOS. However, the ovulation rates in the active and control acupuncture groups were higher than rates in trials with no intervention control group. Thus, a woman with irregular cycles may use acupuncture to get more regular cycles and to improve PCOS-related symptoms, including health-related quality of life, mood, and insulin sensitivity, as there were few negative side effects of acupuncture. The recent RCT¹⁸ has important clinical implications not only for women with PCOS with an active wish

for pregnancy but also for those women with no active wish for pregnancy, as acupuncture induced ovulation to a higher degree than no treatment and also relieved other PCOS-related symptoms [11].

Infertility in Women with Polycystic Ovary Syndrome

Compare the clinical outcome of laparoscopic ovarian drilling with gonadotropin ovulation induction in patients with clomiphene resistant Polycystic Ovarian Syndrome. In this study women between age group 20-35 years with complaints of infertility due to PCOS not responding to clomiphene citrate were recruited for present study following Rotterdam's criteria to diagnose PCOS. The subjects included in the study were randomly divided into two equal groups of 20 each after written informed consents. Detailed history was taken, and physical examination was done, which included anthropometric measurements like height (m), weight (kg), body mass index. This was followed by local examination (per-speculum and paravaginal examination) including cervix, uterine size, position and mobility of uterus, tenderness on uterine motion and in fornices. Pre-defined Performa was filled for all the patients. Baseline investigations like Complete Blood Count, hematocrit, blood sugar profile, HbA1c, urine analysis, liver and kidney function tests, thyroid function tests, Chest X-Ray, viral markers were done for all patients. Husband semen analysis (HSA) was done to rule out male factor of infertility. Ultrasonography was done for all patients at time of presentation to measure the volume and calculate number of antral follicles in ovaries. USG criteria included presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 ml) regardless of follicle distribution or ovarian stromal echogenicity. Hystero salpingo graphy (HSG) was done to rule out any uterine/tubal cause of infertility. The results of this study showed in present study, we found that the ovulation rates were comparable in both the groups; that is 80% in laparoscopic ovarian drilling (LOD) group and 90% in gonadotropins induction group. The pregnancy rates in the gonadotropins group were although numerically higher than LOD group, (20% in LOD group and 45% in gonadotropins group) there was no statistically significant difference found. Gonadotropins group had the advantage of being a nonsurgical technique with good results but the

risks of multiple pregnancies; ovarian hyper stimulation syndrome (OHSS) and cycle cancellation due to excessive number of dominant follicles formed were higher than LOD group. The cycle also required an intensive and complex monitoring. Laparoscopic ovarian drilling on the other hand had the advantages of providing an opportunity to assess the pelvic organs including evaluation of tubal patency, tub ovarian relations, to rule out any pelvic pathology and a cost effective one time treatment, but the disadvantage of being a surgical procedure with the associated risks and morbidity (Although no such complications were observed in present study group). To conclude, both laparoscopic ovarian drilling and gonadotropins are equally effective treatment options for clomiphene citrate resistant infertile polycystic ovarian syndrome women, each having their own advantages and disadvantages. The treatment option can be selected and tailored according to the individual needs and desires of the patient [12].

Anovulation in PCOS

At inositol treatment of anovulation in women with polycystic ovary syndrome, from 107 potential citations, included ten studies (601 women) in the review. The list of included and excluded studies is provided in the Supplementary material and also the search strategy. Inositol (myo-inositol or di-chiro-inositol) was compared with placebo in seven trials, 25-31 myo-inositol was compared with di-chiro-inositol and with placebo in a three-arm trial, 32 myo-inositol was compared with di-chiro-inositol in one trial, 33 and one trial compared myo-inositol with metformin 34. We found no RCTs that compared myo-inositol with clomiphene. In total, 362 women on inositol were included (257 on myo-inositol; 105 on di-chiro-inositol), 179 were on placebo and 60 were on metformin. In this study result showed Inositol appears to significantly improve the ovulation rate, and metabolic and hormonal profiles in women with PCOS compared with placebo. There is a need to assess its effect on pregnancy and live birth rates and on longer term metabolic health outcomes. This review shows promising but preliminary favourable results with myo-inositol in women with PCOS. A well-designed and well-conducted multicentre trial to address this issue to provide robust evidence of benefit is warranted before the widespread use of inositol can be recommended [13].

In this question, the Rotterdam criteria for polycystic ovary syndrome? Result showed, as with many other complex syndromes, PCOS does not have a single diagnostic marker to provide a gold standard for reference. The consensus-based diagnostic criteria for PCOS in the Rotterdam criteria have defined the disease and, as such, have been valuable both clinically and scientifically. Although the Rotterdam criteria were developed based on expert opinions, research evidence has shown their advantages in predicting reproductive outcomes. As a next step, they should be evaluated for their capacity to guide treatment. Then could revisit these criteria based on both prognostic characteristics and treatment selection markers [14].

Hyperandrogenism

A growing number of women looking for a mental and physical wellbeing, but at the same time they want to treat their own problems, in particular, those of an aesthetic nature with non-traditional therapies. In recent years, many studies was performed to clarify the involvement of inositol's in PCOS to improve the ovary function and oocyte quality; in fact a large amount of evidence exists to prove the positive effect of inositol in this way; inositol exert important actions in the glucose homeostasis and when incorporated into phospho glycans has been shown to serve as second messengers involved in the signalling-transduction cascade of insulin116 and in PCOS patients the metabolism of inositol is dysregulated; these data suggest the relationship between insulin resistance and inositol deficiency in PCOS women. As expressed in this review, can assert that exist a lot of natural association to help women to resolve primary insulin resistance but enough a lot of related problems. In particular, the use of MI or DCI exerts a reduction of metabolic and endocrine symptoms in PCOS women through the synergy between insulin sensitizer (inositol) and other product personalized on women request. Myo-inositol can reduce insulin blood levels to restore physiological menstrual cycle. Restoration of the ovulatory cycle can improve mild acne and hirsutism. The association between myo-inositol and monacolin K (3-10 mg/die) can improve moderate acne and hirsutism after 3, 6 months of therapy, in fact, monacolin interferes with the production of cholesterol and then with the androgen synthesis. Another relevant association is between myo-inositol and alpha lipoic acid; with this combination, we can restore ovulatory cycles, and we can interfere with

inflammation that characterized the onset and maintenance of acne. In obese PCOS women, the association between inositol and glucomannan; glucomannan is a fibre that can induce a sense of satiety and reduce absorption of lipids and carbohydrates in the bowel with a consequent reduction of circulating insulin, weight reduction and improve hyperandrogenism in these women. In conclusion, MI and its metabolite DCI have been confirmed as a valid non-pharmacologic alternative to contrast insulin-resistance in PCOS women. Various choices between myo-inositol and other natural substances find specific indications depending on the predominant endocrine and metabolic symptom. It must be remembered that the first improvements of these symptoms are observed after long treatment (90-120) days. In fact, these therapies should be evaluated in medium and long-term associated with an adequate lifestyle. It is important to highlight that some studies we have cited are preliminary and conducted on a small population, larger sample sizes will also serve to strengthen future studies [15].

Hirsutism

It is the most obvious clinical indicator of androgen excess and is an important feature of PCOS. It is present in 70% of women with PCOS, and patients usually complain of cosmetically disturbing hirsutism.

At Combined Oral Contraception and Bicalutamide in Polycystic Ovary Syndrome and Severe Hirsutism, result showed that both OCP and anti-androgen BC in association with OCP were effective in reversing severe hirsutism in hyper androgenic women affected by PCOS. Performing the hair follicular count and establishing the VDI score, were able to demonstrate that when BC is given in association with OCP, the efficacy is significantly improved compared with OCP alone. Hirsutism is an important clinical sign of androgen excess (7), and its treatment is based on two major approaches that can also be used in combination. The first is cosmetic treatment (mainly the removal by laser of un wanted hair) and the second is hormonal treatment (OCP alone or in combination with antiandrogens), which, considering the time of cyclical hair growth renewal ,may take several months for positive effects to appear (31). The peripheral disruption of androgen pathways at the level of the pilosebaceous unit may represent a useful method of treatment of this symptom, assuming that the

activation of the AR is crucial for hair shaft growth through the differentiation of keratinocytes produced by the hair follicle [16].

At Prospective cohort evaluation of hirsutism and anthropometrics in a south east Asian PCOS population, The patients were evaluated via anthropometric data including height, weight, waist and hip circumference and AMH values. The diagnosis of polycystic ovary syndrome was made in 2/3 criteria (Rotterdam criteria). Mann Whitney U, age adjusted linear regression, Chi square, and Spearman correlation co-efficient were used to compare the cohorts. Result showed A total of 224 PCOS subjects and 212 infertile controls were prospectively evaluated. PCOS patients were younger than controls. AMH was three times higher in PCOS patients and this persisted in age adjusted regression analysis. PCOS patients had a greater waist circumference compared to non-PCOS patients, despite having similar height and weight. AMH negatively correlated with waist circumference in PCOS women (Spearman rho -0.15, P=0.02) but not in non-PCOS patients. Hirsutism was more common in PCOS women at any site (38% versus 6%, P=<0.001); however both groups of patients had minimal hair growth on the face and chin. Hirsutism in PCOS women was primarily concentrated on the arms, legs, and pubic region. In this prospective cohort, Vietnamese PCOS women demonstrate a greater waste circumference and a differing relationship between AMH and waste circumference compared to the general infertility population. Additionally, PCOS related hirsutism occurs primarily on non-facial sites [17].

CONCLUSION

The various factors outlined above, help us understand the ovulatory disturbance and provide parameters upon which to make treatment decisions.

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