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Assisted Reproductive Technologies for Women with Polycystic Ovarian Syndrome

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Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory fertility problems in women of reproductive age, with a prevalence as high as 40% to 75%. There are different treatment modalities for increasing the chance of pregnancy in PCOS patients. Since most of the PCOS patients suffer from ovulatory problems, therapeutic efforts are focused mainly towards restoring normal ovulation. However, even after pharmacological interventions to ameliorate ovulatory irregularities, women with polycystic ovary are still at high risk of fetal loss. Thus, assisted reproductive techniques (ARTs) have become popular approaches which significantly increase the chances of successful pregnancy in these women, bypassing the conditions of PCOS. The present mini-review 'pinpoints' on the suitability of ARTs for PCOS patients who fail to ovulate following the conventional infertility treatment. The article also briefly explains how intracytoplasmic sperm injection (ICSI), the most effective ART, correlates with better biological parameters, fertilization rate and better quality of embryos in PCOS women.

Keywords: Assisted reproductive techniques; intracytoplasmic sperm injection; polycystic ovarian syndrome.

Polycystic ovarian syndrome (PCOS) is the most common gynecological health issue and heterogenous endocrinopathy among reproductive-aged women[1, 2]. The first attempt in defining PCOS was made by the National Institute of Health (NIH) as a clinical disorder characterized by clinical and/or biochemical hyperandrogenism associated with a menstrual disorder, and that to make an accurate diagnosis, other conditions such as Cushing syndrome, congenital adrenal hyperplasia and hyperprolactinemia should be excluded[3]. In 2003, Rotterdam criteria defined PCOS as a condition in which the affected females should show at least two of three symptoms of (a) clinical or biochemical hyperandrogenism (oligomenorrhoea: cycles >35 days), (b) anovulation (cycles >180 days) and (c) polycystic ovarian morphology (one or both ovaries having volume of at least 10cm^3 and/or follicle of 2-9 mm size and one or both the ovaries bearing e"12 follicles)[4]. PCOS is the most common cause of anovulatory subfertility or infertility in reproductive-aged women[5] with the

prevalence of infertility ranging from 40% to 75%[6]. Women with PCOS usually fail to get pregnant spontaneously[7]. Numerous treatment modalities have been introduced to increase the chances of pregnancy[7], including, lifestyle modifications, pharmacological therapies, surgical interventions and assisted reproduction[1, 8, 9]. Followed by the treatments with ovulation-inducing agents[10] or insulin sensitizing drugs[11] or gonadotrophin treatment[12] or laparoscopic ovarian drilling[13], assisted reproductive technologies (ARTs) are one of the most suitable treatment options in PCOS women with variable success rates[14].

Assisted reproduction in PCOS

ARTs include different acronyms with a similar aims, *i.e.* facilitating sperms and eggs to interact in a close proximity to each other to enhance the probability of fertilization and achieve a successful conception[15]. ARTs like, intrauterine insemination (IUI), *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) must be proceeded by multiple sequential steps to obtain best results[16]. Pharmacological stimulation of both ovaries to produce adequate number of eggs and laboratory preparation of semen sample to yield progressively motile, morphologically normal sperms are prerequisites of successful ART procedure. Each procedure is performed for specific indications, like ICSI which is usually used for cases with severe impairment of semen quality[17, 18]. IUI, where female uterus is generally inseminated with the male sperms, is carried out in mild-to-moderate impairment in semen quality and failure of ejaculation e.g. retrograde or an ejaculation for males, cervical hostility, mild-moderate endometriosis for females and presence of anti-sperm antibodies (ASAs) and unexplained infertility for both[19, 20]. The success rate is for IUI is 15% to20%[21]. *In vitro* fertilization (IVF) is the procedure by which both sperms and eggs have been cultured in the laboratory to get fertilized eggs. Its main indications are female tubal obstruction and severe endometriosis in addition to the indications of IUI[22]. ICSI was introduced to ARTs in 1990 as a best ART option for severe male factor infertility treatment[23]. Since then, it has become the gold standard fertility treatment, and now-a-days it is generally recommended to a significant number of subfertile couples who are candidate for ARTs. This is due to the advantage that only single motile, morphologically normal sperm was needed to fertilize each oocyte[23]. The success rate for ICSI is about 25% to 30%. ARTs are not free from complications. The most significant indications are severe ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy (25% twins and 1% triplets)[24]. To a lesser extent are viral disease transmission (infection with human immunodeficiency virus, hepatitis B and C viruses), bleeding, severe pelvic infection, ectopic pregnancy and failure to get a pregnancy[24-26].

As mentioned earlier, various treatment strategies are available to subfertile women with PCOS, but the optimal infertility treatment is still a controversy. As the majority of the patients suffer from ovulatory problems, efforts are predominantly centered towards restoring normal ovulation. In patients with insulin resistance (IR), ovulation rate can be improved by pharmacologic agents to increase insulin sensitivity[14]. Even after bypassing ovulatory dysfunctions by pharmacological interventions, women with polycystic ovary still remain at higher risk of fetal loss of about three-folds. This indicates that additional factors in the etiology might be implicated[27]. ARTs are the suitable treatment modality for PCOS patients who fail to ovulate following the conventional infertility treatment due to poor or no response or those who show a resistance to the conventional treatment[28]. In addition, it may be offered to couples with co-existing factors, such as severe male factor infertility, female tubal obstructions and endometriosis which necessitate ICSI[29]. It had been believed that the oocytes retrieved from polycystic ovary had an abnormality in the structure of zona pellucida (ZP) which leads to decrease fertilization rate in those patients and ICSI can overcome this problem by artificial injection of the sperm in to the oocyte and may increase the fertilization rate in PCOS women[30]. ICSI also can increase the chance of conception and successful pregnancy by choosing top quality embryos from all resulted embryos to be transferred to the uterus[31]. With IVF or ICSI, the number of transferred embryos can be determined, and thus multiple pregnancy can, therefore possibly, be reduced[25]. So, ICSI, as an ART, may correlate with better biological parameters, such as, fertilization rate and better embryo quality in PCOS women[32]. OHSS is a

potential complication of ARTs in PCOS patients due to an excessive response to gonadotropins during controlled ovarian hyper-stimulation which necessitates cancelling the cycle and freezes all embryos[33]. Different stimulation protocols have been offered for PCOS patients undergoing ARTs, which are mainly the GnRH agonist and antagonist protocols. There is no clear evidence for the advantage of one over the other. The GnRH agonist was initially considered to be the protocol of choice in PCOS women. Due to increased risk of mid-cycle gonadotrophin flares, multiple pregnancies and OHSS, its usage has been restricted to certain situations[34]. GnRH antagonist has been shown to have an advantage over the former protocol in form of quicker onset of action, short duration of treatment, lesser total dose of gonadotropins required, lower cost, higher tolerance, lower incidence of LH surge, lower incidence of OHSS and being more patient friendly[35]. Recent information obtained from systematic review and meta-analysis studies suggest that there is no significant difference in fertilization rate and pregnancy outcome between the two GnRH analogues: agonist versus antagonist in PCOS and normal women[36]. However, there is report that showed higher clinical pregnancy was attained via ultra-long agonist therapy instead of long agonist protocol[37]. The aim of every IVF or ICSI program is to achieve multi-follicular development and collection of several appropriately matured oocytes without causing OHSS and with a comparable pregnancy rate. This is especially important in women with PCOS as they usually exhibit greater sensitivity to exogenous gonadotropin stimulation than women with normal ovaries[38, 39].

CONCLUSION

Assisted reproduction, predominantly ICSI, can be considered as a good option to overcome the biological key events within polycystic ovary, increase the chance of oocyte fertilization, choosing best quality embryos to be transferred to the uterus and ultimately increase the chance of pregnancy.

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