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Ovulation Induction Techniques in Women with Polycystic Ovary Syndrome: A Review of literature

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ABSTRACT

Background: Amenorrhea, oligomenorrhea, and irregular uterine bleeding are a few of the many clinical signs of anovulation, which is fairly prevalent. Anovulation can result from a number of mechanisms. Polycystic ovarian syndrome (PCOS), which has clinical repercussions and is the most prevalent chronic anovulatory illness, affects 6 to 10% of people worldwide. While a variety of factors may eventually lead to PCOS, a number of therapeutic strategies have been documented in the literature, frequently without addressing the underlying reason. Ovulation Induction (OI) is a series of methods used by PCOS-afflicted women who want to get pregnant but are unable to do so naturally.

Aim: The current review discusses OI in PCOS-affected women, with an emphasis on their effectiveness and application. **Development:** Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, and EMBASE, up to November 2022, search by keyword of "Polycystic Ovarian Syndrome" and "Ovulation Induction".

Conclusion: The likelihood of a good pregnancy outcome in PCOS patients receiving OI should be able to be determined by clinicians, taking into account age, body weight, the various protocols employed, and the length of infertility. A recommendation to a specialised fertility clinic for in vitro fertilisation would be a good backup plan if the aforementioned therapies don't succeed in conceiving a child. Future research should evaluate the results of the various OI techniques outlined above and stratify the efficiency of laparoscopic ovarian drilling in comparison to current medical therapy.

Keywords: Ovulation, Anovulation, Induction, Clomiphene, Letrezole, PCOS, laparoscopic ovarian drilling, Review.

INTRODUCTION

The inability to get pregnant after six months for women over 35 and after a year for women under 35 who are not using contraception is referred to as infertility. Epidemiological data show that 10% to 15% of all couples will struggle to conceive the optimal number of children (secondary infertility) or have primary infertility [(1)].

Over 70 million couples experience infertility globally, with most of them living in underdeveloped nations. When compared to Western society, emerging nations endure the negative effects of childlessness to a greater extent. The most frequent cause of infertility in poor nations is bilateral tubal blockage brought on by sexually transmitted diseases and infections contracted during pregnancy, a condition that may be treated by assisted reproductive technology (ART). In developing nations, new reproductive technologies are either unavailable or extremely expensive [(2)]. The World Health Organization (WHO) reports that female infertility accounts for 37% of reasons for infertile couples, male infertility for 18%, and both male and female for 35%, according to a survey conducted in wealthy countries. 5% of couples experience unrecognised infertility. Ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (11%), tubal obstruction (11%), other tubal abnormalities (11%), and hyperprolactinemia (7%) were the most often discovered contributing variables. According to certain studies, ovulatory abnormalities account for more than half of the causes [(3)].

Women with PCOS who are seeking fertility treatment should first consider changing their lifestyles and losing weight. Up to 70% of obese women fit the criteria for PCOS, compared to 9–18% of all women of reproductive age [(4)].

When compared to PCOS patients who are not obese, obese PCOS patients have an increased risk of the disease's metabolic and psychological side effects in addition to its impact on fertility. With a delivery rate per initiated cycle of about 22%, intracytoplasmic sperm injection (ICSI) is becoming more widely used worldwide. Data from almost 2,500 ART clinics from 58 to 61 countries between the years 2008, 2009, and 2010 are included in the report. More than 4,461,300 ART cycles were performed over the course of the three years, leading to an estimated 1,144,858 births globally [(5)].

The aim of this study is to review the ICSI outcome among PCOS patients treated with letrozole-gonadotropins, clomiphene citrate-gonadotropins, or gonadotropins only for controlled ovarian super-stimulation.

INFERTILITY

A healthy preovulatory oocyte is released, sufficient spermatozoa are produced, the gametes are transported normally to the ampullary region of the fallopian tube (where fertilisation takes place), and the cleaving embryo is then transported into the endometrial cavity for implantation and development. These events are all necessary for reproduction to occur [(6)]. The causes of infertility might be either male or female. Aproximately

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35% of instances involve male or female variables. Infertility is frequently caused by a combination of variables, with male and female causes accounting for 20% of cases. The cause of the remaining 10% of cases is uncertain [(7)].

OVARIAN FACTOR INFERTILITY

From the first trimester of embryonic development until 28–30 weeks of gestation, oogenesis takes place in the ovary. Around 7 million oocytes are present by that point. At the prophase stage of the first meiosis division, they are stopped. As a result of an ongoing atresia process, the quantity of oocytes declines. The number of oocytes in the pool is lowered to about 2 million at birth. Approximately 500,000 oocytes are present by menarche. Those oocytes are utilised up until menopause during the reproductive years [(8)].

When the hypothalamus-pituitary-ovarian axis is fully developed and follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are controlled by gonadotropin-releasing hormone (GnRH), acquire their typical secretory patterns, the ovulatory process begins. Only one oocyte is chosen from the cohort of follicles that are accessible each month, achieves dominance, and matures to the preovulatory stage. The granulosa cells secrete increasing levels of estradiol (E2) during follicular development, initially suppressing the release of FSH. The LH surge that initiates the ovulatory process causes the oocyte to resume meiosis, and drives the development of the corpus luteum and subsequent progesterone production is later produced by E2 through a positive feedback loop [(9)].

EPIDEMIOLOGY AND PREVALENCE (ETHNIC VARIATIONS)

With a prevalence of 10% to 15%, it is the most common endocrine condition affecting women. 20–30% of the general population has polycystic ovaries, according to ultrasonography alone. PCOS is 26% frequent in the UK, and 33% of women between the ages of 18 and 25 have polycystic ovaries. Anti-mullerian hormone (AMH) may be a precise marker to identify PCO with a threshold serum concentration of >35 pmol/l, however it should not yet be used as a replacement for PCOM detection or as the only test to identify PCOS [(10)].

DIAGNOSIS OF OVARIAN FACTOR OF INFERTILITY

OVARIAN RESERVE

Physiology of Ovarian Aging:

A woman's OR development from prenatal life through menopause: At about 24 weeks of intrauterine life, the ovaries have over 7.0 million follicles, which is the highest amount ever recorded. They then rapidly decline, reaching 3.5 million at the time of birth during the period of greatest follicle loss, before falling to 1.0 million by adolescence. Ironically, there are only a few hundred left by menopause because the rate of decline is slowest during the reproductive years [(11)].

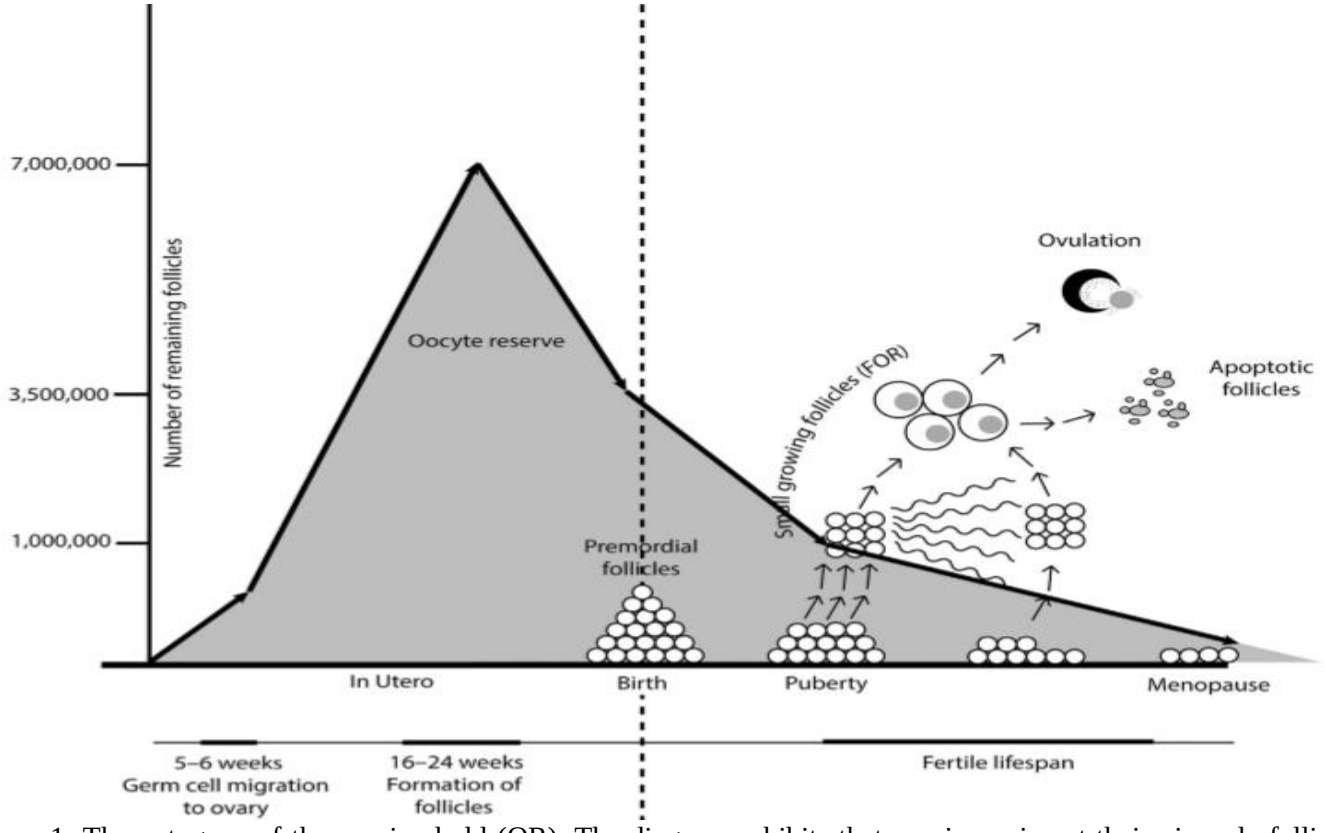

Figure 1: The ontogeny of the ovarian hold (OR). The diagram exhibits that ovaries arrive at their pinnacle follicle numbers at something like 24 weeks of intrauterine life, upon entering the world they arrive at around 3.5 million, at youth just 1.0 million, and at menopause only a couple hundred [(11)].

Around 90% of ladies of all races and identities follow the ovarian maturing bend displayed in **Figure 1**. Ovarian age is estimated by the quantity of enduring follicles and eggs in the ovaries. They are remembered to have standard OR/FOR. Be that as it may, assuming exorbitantly high-AMH values are found, OR/FOR is judged unreasonably high and reminiscent of a PCOS finding despite the fact that ongoing global indicative measures don't perceive unusually high age explicit AMH values as demonstrative of PCOS. Considering that they display signs of astoundingly low age-explicit follicle/egg counts, 10% of ladies are remembered to have LOR/LFOR. The essential ovarian disappointment (POF), otherwise called essential ovarian deficiency (POI), is recognized in around 1% of the ladies in this gathering, while the excess 9% just development past the phase of POA (otherwise called oPOI) [(11)].

MANAGEMENT OF ANOVULATORY INFERTILITY

Introduction:

About 15-20% of women seeking therapy for subfertility have ovulation issues as the underlying cause of their infertility. According to WHO categorization, subfertility brought on by ovulation abnormalities can be divided into groups based on the location of the hypothalamic-pituitary-ovarian axis insufficiency [(12)].

Treatment principles for the common causes:

PCOS accounts for the majority of these women with normo-gonadotrophic anovulation, albeit the typical full-blown picture may not always be present. This picture might potentially be impacted by additional reasons of androgen overproduction. In obese women with PCOS, losing weight should be the primary line of treatment. This may restart spontaneous ovulation and enhance the woman's responsiveness to ovulation induction if necessary. Aromatase inhibitors or clomiphene citrate can be used to induce ovulation. Gonadotrophins or ovarian drilling may be prescribed to patients who are unresponsive to oral therapy or who fail it. Other sources of androgen overproduction should be addressed appropriately [(13)].

MEDICAL OPTIONS FOR OVULATION INDUCTION ANTI-OESTROGENS

Clomiphene citrate:

The standard first-line treatment for WHO group II anovulation is clomiphene citrate. It is a non-steroidal drug that predominantly exerts its anti-oestrogenic effect when taken orally [(14)]. Clomiphene citrate is often well accepted despite the uncommon occurrence of adverse symptoms such hot flushes, breast discomfort, abdominal distension, nausea, vomiting, anxiety, mood changes, dizziness, hair loss, and blurred vision [(15)]. Tamoxifen: Clomiphene citrate and tamoxifen, a derivative of triphenylethylene, are similar structurally. 20–40 mg per day for five days is the recommended dosage for ovulation induction following a spontaneous menstruation or withdrawal bleed [(16)]. Substance susceptible to insulin: Insulin resistance is a recognised metabolic problem in PCOS women.

Insulin-sensitizing medications might minimise the detrimental effects of insulin on ovulatory function by increasing the responsiveness of target tissues to insulin and lowering compensatory hyperinsulinemia. Contrary to live birth rates (OR 1.05; 95% CI 0.75 to 1.47), co-treatment with metformin and clomiphene increases ovulation rates (OR 1.76; 95% CI 1.51 to 2.06) and clinical pregnancy rates (OR 1.48; 95% CI 1.12 to 1.95) [(17)]. Aromatase blockers Androstenedione and testosterone are changed into oestrone and oestradiol, respectively, by the enzyme aromatase. By decreasing the negative feedback to the hypothalamic-pituitary axis by preventing the synthesis of oestrogen, aromatase inhibitors increase endogenous FSH secretion [(18)]. Patients with PCOS who were clomiphene citrate resistant responded favourably to letrozole, ovulating at a rate of 70–84% and became pregnant at a rate of 20–27% each cycle. Letrozole and clomiphene citrate had similar rates of ovulation, pregnancies per cycle, and pregnancies per patient, according to a meta-analysis [(19)]. Gonadotrophin-releasing hormone: When given in a pulsatile form, gonadotrophin-releasing hormone restores the typical pattern of gonadotrophin production found in naturally occurring menstrual cycles, leading to the establishment of a single dominant follicle [(20)].

After six and twelve rounds of therapy, respectively, cumulative pregnancy rates of 80% and 90% have been observed. The percentage of multiple births varied from 3.8 to 13.5%. Inconvenience from leaving the needle in place for an extended amount of time, needle site reactions and infections, displacement, and pump failure are further downsides [(21)]. Exogenous gonadotrophins are used to reduce the FSH threshold necessary for follicular development. The primary gonadotrophic hormone required for follicular development is follicle-stimulating hormone. Luteinizing hormone is necessary for ovarian steroidogenesis in order to achieve optimal endometrial proliferation; hence a preparation with both FSH and luteinizing hormone works better in women with hypogonadotrophic hypogonadism than one with only FSH51. Support during the luteal phase is required in these women [(22)].

Surgical induction of ovulation:

Ovarian drilling may be a possibility for women who have failed or are resistant to clomiphene. The ideal surgical technique for inducing ovulation is laparoscopic ovarian drilling (LOD), as opposed to standard laparoscopic ovarian wedge excision, as the latter carries a higher risk of postoperative adhesion development. Although the precise mechanism of

LOD's effect is uncertain, it might be related to the ovary's elimination of androgen-producing tissue [23].

IN VITRO FERTILIZATION (IVF) & INTRA-CYTOPLASMIC SPERM INJECTION (ICSI)

The two most common assisted reproductive techniques for successful fertilisation are intracytoplasmic sperm injection (ICSI) and in vitro fertilisation (IVF). The method the egg is fertilised is the only distinction between the two. In contrast to ICSI, which physically inserts the sperm into the egg, IVF allows the sperm to enter the egg on its own. Qualified technicians manipulate the samples with extremely fine tools under a microscope. When the sperm is unable to break through the egg wall, the method is utilised. The embryo is placed inside the uterus in the same manner as with IVF if the egg is fertilised.

The stages of IVF & ICSI: The basic steps of the IVF process are described in detail here. Typically, it takes six to eight weeks to complete the process up to the embryo transfer stage.

Stage 1: Ovarian stimulation and monitoring:

The brain region of the hypothalamus, which regulates a number of biological processes, releases a hormone known as gonadtrophin-releasing hormone during the start of your menstrual cycle (GnRH). To prepare one egg for release, GnRH stimulates the pituitary gland to generate a hormone known as follicle stimulating hormone (FSH). The pituitary gland releases luteinizing hormone (LH) after the egg is fully developed [24]. Agonists of gonadotrophin-releasing hormone (GnRH) The pituitary gland at the base of the brain is stimulated to produce more FSH and LH when a GnRH agonist (or GnRH analogue) is administered daily, but these hormones then diminish immediately afterward [25].

GnRH blockers: Cetrorelix acetate and ganirelix acetate, members of the GnRH antagonist class of injectable medications, reduce FSH and LH levels without first raising them, unlike GnRH agonists [26]. Protocols A "Protocol" is a schedule or plan for how your IVF cycle will be carried out. Your doctor will pick the best standard protocol for you out of the few that are currently in use. The following are the top two: Long down regulation: During ovulation, a sudden spike of the hormone LH at mid-cycle causes the release of the egg. We do not want an LH surge to cause an early release of these eggs during an IVF round. In a process known as "pituitary suppression" or "down regulation," a GnRH agonist is used to momentarily stop your own LH and FSH output [27].

Stage 2. Egg (oocyte) retrieval: Just before the anticipated ovulation, an egg retrieval procedure, also called "egg pick up" is scheduled. Egg retrieval is often done 36 to 48 hours after the ovulation-inducing medications hCG or LH have been administered [28]. In order to guide a tube with a tiny camera to the ovarian follicles, a doctor will occasionally employ laparoscopy. The egg is then removed from the follicle using a mild suction via an aspiration device. The laparoscopic procedure, which necessitates general anaesthesia, is often only employed when the transvaginal technique fails to provide access to the ovaries (e.g. when large fibroids are present) [28].

Stage 3. Fertilization:

A sample of the male partner's semen is taken two hours before egg pickup. Prior to the sample collection day, it is preferable to abstain from intercourse or masturbation for two to three days. At the clinic, masturbation is typically used to produce the sperm sample. The strongest, most active sperm are chosen by processing of the sperm. It is known as "sperm washing." Sperm collection by surgery may be used if sperm are not present in the ejaculate [29].

If using IVF, the sperm and eggs are then put in an incubator that is set to a woman's body temperature. The eggs are examined the following day under a microscope to see if fertilisation has taken place, and you will be contacted by phone to find out how many of your eggs have been fertilised. The resultant embryos are either kept for a later transfer or are implanted to the uterus two to five days later. The eggs are ready for injection and their maturity is determined if ICSI is being used. A single sperm is injected into the cytoplasm (the centre) of the egg in a complex laboratory operation called an intra-cytoplasmic sperm injection. After roughly 20 to 24 hours, fertilisation can be detected similarly to IVF [30]. Studies suggest that the success rate of fertilization for ICSI and IVF are similar.

Stage 4: Embryo development:

'It is known as "embryo culture" to refer to the procedure that immediately follows egg collection. Your partner's sperm and eggs will be joined during the culturing phase to create a fertilised egg (also referred to as a zygote) [25].

Blastocyst transfers are preferred by some fertility doctors because it is simpler to select a viable embryo for transfer at this stage. According to the most recent figures from the Australian Institute of Health and Welfare, blastocyst transfers are becoming more popular than the conventional "3-day transfer." Blastocyst embryo transfers made up 59.8% of embryo transfer cycles in 2012, which is a considerable increase from the 33.7% of cycles that transferred blastocysts in 2007 [26].

Stage 5: Embryo transfer: Embryo transfer is a simple operation that can be carried out without the need for anaesthesia, much like a pap smear. The embryo is inserted in a catheter, a soft tube, and sent through the vaginal entrance to the uterus two to five days after the

egg is picked up. The quantity of embryos transferred is influenced by a woman's age, the reason for her infertility, previous pregnancies, and other factors. Typically, only one embryo, or possibly two, will be placed in the uterus [(31)].

Stage 6: Luteal phase support: The two-week interval between the embryo transfer and the pregnancy test is known as the luteal phase. It is typically advised that you rest up for a few days after the transfer. You can continue your regular activities after 48 hours; implantation won't be affected. You will visit the clinic or your doctor again in about 16 days to get a blood test to see if you are pregnant [(32)].

Success rates: Age of the woman, the reason for her infertility, how she responds to medicine and treatment, the calibre of her sperm, the quantity of embryos she transfers, and whether or not she uses cryopreserved (frozen) embryos all have a substantial impact on success rates [(33)].

DECLARATIONS

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