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Clomiphene versus Clomiphene plus Tamoxifen in Ovulation Induction in Women with PCOS: Randomized Controlled Trial

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List of Abbreviations

Abb.	Meaning
17-B-HSD	17 βhydroxysteroid dehydrogenase.
3B-HSD	3 βhydroxysteroid dehydrogenase.
AIDS	Aquired immune deficiency syndrome.
ASRM	American society for reproductive medicine.
B.M.I	Body mass index.
CC	Clomiphene citrate.
CRP	C- reactive protein.
DHEAS	Dehyrdoepiandrosterone sulfate.
ESHRE	European society of human reproduction and embryology.
F.A.I	Free androgen index.
F.D.A	Food and drug administration.
FSH	Follicular stimulating hormone.
FSH-GC	Follicular stimulating hormone granulosa cell.
GDM	Gestational diabetes mellitus.
GnRH	Gonadotropins releasing hormone.
HCA	Hyperandrogenism and chronic anovulation.

Abb.	Meaning
HCA-PCO	Hyperandrogenism chronic anovulation and polycystic ovary.
HDL	High density lipoprotein
HPCO	Hyperandrogenism and polycystic ovary.
IGF	Insulin like growth factor.
LH	Luteinizing hormone.
LHTIC	Luteinizing hormone theca interstitial cell.
NICH	National institute of child health and human development.
O.H.S.S.	Ovarian hyperstimulation syndrome.
OCP	Oral contraceptive pills.
PCO-CA	Polycystic ovary and chronic anovulation.
PCOS	Polycystic ovary syndrome.
SCC	Side chain cleavage enzyme.
SHBG	Sex hormone binding globulin.
STAR	Steroidogenic acute regulatory protein.
T.S.H.	Thyroid stimulating hormone.
TIC	Theca interstitial cell.

Protocol

Introduction:

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine condition that affects approximately 5% to 10% of women in the reproductive age group. Depending on the population being examined, however, prevalence rates as high as 26%have been reported. Although debate on what constitutes PCOS continues, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition ***(Knochenhauer et al., 1998).***

According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria: oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (> 12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome ***(Asuncionet et al., 2000).***

Patients who fulfill these criteria are often plagued by infertility secondary to both ovulatory dysfunction and the effects of hyperandrogenism. Several methods have been effective for ovulation induction and fertility treatment in women with PCOS:

- Weight loss, exercise, and lifestyle modifications.
- Clomiphene citrate.
- Metformin.
- Gonadotropins.
- Ovarian drilling.
- IVF (in vitro fertilization).

Clomiphene citrate has been used for induction of ovulation since 1966, It is accepted as first- line therapy because of its low cost, easy administration and safety, with no need for close monitoring. It is also effective for superovulation in the empirical treatment of unexplained infertility, especially in conjunction with intrauterine insemination ***(Topipat et al., 2008)*.**

Clomiphene citrate is an estrogen- receptor modulator, has mixed estrogen agonist and antagonist properties, exhibiting its effects throughout the hypothalamic, pituitary, gonadal and uterine axis. Many of side effects of (CC) are related to its estrogenic antagonist properties, particularly the hot flushes and endometrial thinkness ***(Reynolds et al., 2010)*.**

Over the years, evidence has accumulated indicating that CC is successful at inducing ovulation in 50-75% of patients, but the pregnancy rate achieved after ovulation induction is much lower than expected. The discrepancy has

been attributed to CC's prolonged peripheral anti-estrogenic effects on cervical mucus and the endometrium, this effect on the endometrium may explain a larger part of the lower pregnancy rate in assisted reproduction cycles ***(Chia et al., 2008)*.**

The elevated concentrations may persist during the mid and late follicular phases of the cycle. It is unclear whether the increase in LH influences outcome in patients being treated with clomiphene citrate and whether basal endogenous LH secretion affect outcome. ***(Hull et al., 1985)***, in a large population study, reported that among 708 couples who needed specialist help for infertility, failure of ovulation occurred in 21% of cases. ***(Polson et al., 1989)***

The starting dose of clomiphene citrate is 50 mg per day for 5 days, commencing between day 2 and 5 of menses. Menses may be induced with a progestin if required. If this dose produces multiple follicular development, the dose can be lowered to 25 mg. If ovulation is not achieved using 50 mg per day, the dose can be increased in increments of 50 mg. The manufacturer does not recommend exceeding 100 mg per day; however, many clinicians use doses up to 150 mg and some even up to 250 mg per day for 5 days, taking into account that alternatives treatments such as gonadotropins are more costly and have greater risk ***(Winkel et al., 1983)***.

Tamoxifen is a nonsteroidal selective estrogen receptor modulator that has been advocated as an ovulation-inducing agent. Unlike clomiphene, tamoxifen acts as an agonist on the estrogen receptors of the endometrium. Tamoxifen is not widely used. This could be explained by the results of a recent meta-analysis that found there was no difference in the ovulation rate between tamoxifen and clomiphene. The pregnancy rate was also similar. Despite the theoretical benefits of tamoxifen, this meta-analysis failed to find a significant benefit of tamoxifen over clomiphene ***(Buckley et al., 2000).***

Agents like clomiphene and tamoxifen". These drugs occupy the estrogenic receptors in hypotalamus which then cause the increase in gonadotropin secretion. Previous studies reported 80% ovulation rate and 40% pregnancy rate after the prescription of clomiphene (50 mg oral) from day 5 to 9 of the menstruation cycle ***(Hull et al., 1999).***

There is no record of serious effects from tamoxifen after acute overdosage, adverse effects in therapeutic use are usually mild. They include effects caused by antagonism of endogenous oestrogens: hot flushes, non-specific gastrointestinal effects (nausea and vomiting), central nervous system effects, and rare ocular effects. Adverse haematological effects have been reported, also isolated cases of death from peliosis hepatis and from hyperlipidaemia, anti-oestrogenic effects in women treated with tamoxifen include vasomotor