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Review

# Steroids pretreatment in assisted reproduction cycles

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ABSTRACT

The objective is to present an overview of trials and appreciate the relevant data on the effect of steroids pretreatment (oral contraceptives, 17β-estradiol and estradiol valerate) in assisted reproduction cycles.

The subject of the study is to evaluate the clinical characteristics during steroids pretreatment cycles focused on the prevention of ovarian cysts, the positive contraceptive effect on the onset of regular period during long gonadotropin releasing hormone agonist protocol. In gonadotropin releasing hormone antagonist protocol the review is interested in supporting ovarian stimulation in low responders, the idea of cycle scheduling and improving treatment outcomes. The method is a review from MEDLINE/Pubmed database between 1994 and July 2012.

We identified 15 randomised controlled trials ($n = 3069$ patients). One trail ($n = 83$ patients) assessed GnRH agonist protocol with or without steroids pretreatment, 8 trials ($n = 1884$ patients) assessed GnRH antagonist protocols with or without steroids pretreatment and 6 trials ($n = 1102$ patients) assessed GnRH antagonist protocols versus agonist ones with steroid pretreatment.

Data demonstrates that oral contraceptives offer the effective prevention of functional ovarian cysts, the predictable onset of period during desensitisation. Existing data suggest that pretreatment with oral contraceptive pills or estradiol valerate give no advantage concerning number of oocytes or pregnancy rate. Pretreatment with oral contraceptive pills aiming to avoid weekend oocytes retrievals has to be more elucidated. In low responders oral contraceptive pill pretreatment may be beneficial in improving ovarian responses by reducing the amount of gonadotropins and the number of days required for ovarian stimulation. Current research indicates that also 17β-estradiol may be encouraging pretreatment in low responders and in cycle scheduling.

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**Contents**



*Abbreviations:* 2PN, two pronucleate stage; AMH, anti Mullerian hormone; FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; IVF, in vitro fertilisation; ICSI, intracytoplasmic sperm injection; LH, luteinising hormone; MII, metaphase of the second meiotic division; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; RCT, randomised controlled trial.

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## 1. Introduction

Infertility is defined as the failure to conceive after 1 year of unprotected intercourse. It is estimated that 1 in 6–10 couples worldwide have experienced difficulty with becoming pregnant [1]. Infertility is caused by anovulatory disorders, male or tubal factors, endometriosis, congenital anomalies of the female genital tract or genetic diseases. Assisted reproductive techniques comprise all clinical and laboratory techniques offering treatment of all kinds of causes of infertility, namely ovarian stimulation, intrauterine insemination, in vitro fertilisation and intracytoplasmic sperm injection, embryo transfer, preimplantation diagnosis and so on. Treatment of infertility during assisted reproduction cycles may be accompanied with several risks and complications. Most often risks are multiple pregnancy, ectopic (tubal) pregnancy or ovarian hyperstimulation syndrome (OHSS), but functional abnormalities during treatment (for example functional ovarian cyst) may cancel treatment cycle before collecting eggs, diminish number of collected oocytes, decreased quality of oocytes and diminish expected pregnancy rate after embryo transfer [2]. This should be minimised to result into safer treatment or improved outcomes (higher pregnancy rate or increased take home baby rate) [3].

Steroid contraception was introduced during the 1950s and approved for use during 1960s. It contains oestrogen, usually 20–35 μg ethinyl estradiol, and synthetic progesterone (levonorgestrel, gestodene, desogestrel etc.). These steroids provide contraception primarily by inhibiting ovulation [4,5]. Exogenous oestrogen inhibits follicle stimulating hormone (FSH) secretion (follicle growth is not initiated) and progesterone inhibits the development of the luteinising hormone (LH) surge (ovulation does not occur). The pills also change cervical mucus and cause endometrial atrophy. In addition to contraceptive effect the benefits of pills are regular, lighter and less painful withdrawal bleeding, decreased incidence of functional ovarian cysts, benign breast disease, ovarian and endometrial cancer. Oral contraceptives also offers the effective treatment for hirsutism by suppressing ovarian androgen production and stimulation of hepatic production of sex hormone binding globulin [6]. The pills are safe and the fertility is restored after their withdrawal [5]. Steroid contraception was introduced into ovarian stimulation protocols during 1980s. Oral contraceptives may be considered in healthy, nonsmoking women older than 35 years if there are no other contraindications to combined hormonal contraceptives [7,8]. Steroids pretreatment have been demonstrated to be associated with beneficial effects during assisted reproductive cycles.

On the contrary with oral contraceptives natural oestrogen (17β-estradiol) was introduced into reproductive medicine a decade later by Fanchin et al. [9] and currently studied by Cedrin-Durnerin et al. [10]. Numerous animal models have been originated to demonstrate the importance of natural oestrogen's multiple signalling systems in follicle development. These animal models provide a basis for understanding human infertility and disease. Combined with studies concerning genes for mutational analysis, these models may improve our understanding of the physiology and pathology of oocyte development [11]. Based on the fact that in natural luteal phase was observed follicle size discrepancies, the luteal phase pretreatment with 17β-estradiol in the assisted reproduction cycles may improve the coordination of follicular development and increase the number and quality of embryos achieved in poor responders. Thus it is highly expected to improve cycle and pregnancy outcomes in these patients. Moreover, some experiments in delayed-implanting recipient mice gave us evidence that although the primary oestrogen, 17β-estradiol, initiates uterine events for implantation, its catechol metabolite, 4-hydroxy-estradiol-17β (4-OH-E2), plays the role in activation of blastocysts. These results provide evidence that both hormones are required for embryo–uterine interactions for successful implantation [11].

Estradiol valerate is a synthetic estradiol that has been described in ovarian stimulation protocols with just the anecdotal evidence.

The objective of the review is to present the trials and evaluate the relevant data on the effect of steroids pretreatment (oral contraceptives, 17β-estradiol and estradiol valerate) in assisted reproduction cycles.

## 2. Methods

The subject of the study is to evaluate the clinical characteristics of trials focused on the prevention of ovarian cysts, the positive contraceptive effect and the onset of regular period during long gonadotropin releasing hormone (GnRH) agonist protocol. During GnRH antagonist protocol the review is interested in the aim of supporting ovarian stimulation at low responders and the idea of cycle scheduling at egg donation cycles. The secondary subject is to compare the in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) outcomes of the long GnRH agonist and the fixed GnRH antagonist protocol in women with polycystic ovary syndrome (PCOS).

We have carried out a systematic review of evidence that was published in the MEDLINE/Pubmed database from 1994 to July 2012. We focused on randomised controlled trials. Other important prospective and retrospective studies are mentioned in discussion.

To retrieve publications relevant for this review, we searched the MEDLINE/Pubmed database using query both "oral contraceptives" or "oral contraceptive pill", "17β-estradiol" and "estradiol valerate" and "GnRH protocol" as of July 31, 2012.

## 3. Results and discussion

Table 1 summarises 15 randomised controlled trials relevant for the review.

### 3.1. Long GnRH protocol with oral contraceptive pills pretreatment

Long GnRH protocol with a GnRH agonist (Fig. 1) is still the most often prescribed stimulation protocol in assisted reproductive treatment. Meta-analysis of 26 randomised controlled trials [12] and 29 trials [13] indicate the superiority of the long protocol over the short and ultrashort protocols for GnRH agonist use in IVF. GnRH is naturally the hypothalamic hormone. GnRH agonist (GnRH analogue) has been synthesised by substitution of amino acid sequence to assure more potent and longer activity on GnRH receptor. GnRH agonist causes rapid desensitisation of the pituitary gland leading to decreased serum gonadotropin levels and inhibits ovarian steroidogenesis and follicular growth. The biggest advantage is to abolish the spontaneous LH surge and to preserve oocyte quality during ovarian stimulation [14].

The unwanted side effect of the GnRH agonist in the luteal or follicular phase in the long GnRH agonist protocol is the induction of the formation of functional ovarian cysts. Keltz et al. [15] described a poor stimulation outcome and a reduction in pregnancy rate in a cycle with presence of the ovarian cyst.

Table 2 shows clinical characteristics of long GnRH agonist protocol with oral contraceptive pills' pretreatment.

Biljan et al. [16] enrolled in the unique randomised trial patients into group with oral contraceptive pills pretreatment for 14 days and into group with no pretreatment. A cyst developed in 27 patients in the control group (52.9%) versus no patients in the study group. Authors proved, that pretreatment with oral contraceptive pills abolishes ovarian cyst formation.

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