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THE REVIEW OF COMPARED PROGESTINS TYPE AND DOSE UTILITY AGAINST THE PITUITARY SUPPRESSION DURING OVARIAN STIMULATION FOR ASSISTED REPRODUCTIVE TECHNOLOGY

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Abstract: *We performed a literature review of studies comparing the effectiveness of progestins in preventing premature ovulation during ovarian stimulation for assisted reproductive technology (ART). Five randomized trials and cohort studies involving a total of 2404 women, which compared; i) two different progestins or ii) two different doses of the same progestin were included. The primary outcome was live birth rate (LBR) per woman. Secondary outcomes were live birth or ongoing pregnancy (LB/OP) per woman and per embryo transfer (ET), ongoing pregnancy, clinical pregnancy, positive pregnancy test, numbers of oocytes and metaphase-two oocytes, duration of stimulation and gonadotropin consumption. The primary outcome was not reported in most studies however there were no differences between progestins for secondary outcomes. All progestins seem to effectively prevent premature ovulation in ART cycles. Low-quality evidence suggests that progestins can effectively prevent premature ovulation in ART cycles.*

INTRODUCTION

Pituitary suppression is required to decrease the risk of ovulation before oocyte retrieval (OR) in assisted reproduction technology (ART) cycles. Currently, gonadotropin releasing hormone (GnRH) analogues are the standard of care for pituitary suppression.(1) However, progestins are also capable of suppressing endogenous luteinizing hormone (LH) secretion from the pituitary.(2,3,4,5) The advent of oocyte and embryo vitrification techniques coupled with increasing use of a freeze all strategy in assisted reproductive technology cycles led to increasing use of progestins for pituitary suppression.

Available evidence suggests progestins are as effective as GnRH analogues and may even yield more oocytes.(6) However, there is limited information about the effectiveness of different progestins or different dosages of the same progestin.

AIM

This narrative review proposed to explore the literature for studies comparing clinical outcomes of ART cycles using progestins for pituitary suppression.

MATERIALS AND METHODS

We searched for studies, which compared; i) two different progestins or ii) two different doses of the same progestin for pituitary suppression in ART. Only studies published in English as a full text article were included. Protocols of incoming studies, cross-over trials, case reports, comments, editorials, and letters were excluded.

The primary outcome was *live birth* of a fetus after 20 completed weeks of gestational age per woman starting a stimulation cycle.

Secondary outcomes were i) *live birth or ongoing pregnancy* beyond 12 weeks *per woman* starting a stimulation cycle, ii) *live birth rate per embryo transfer procedure, iii) live birth or ongoing pregnancy per embryo transfer procedure, iv) clinical pregnancy* (defined as evidence of a gestational sac at six weeks or later, confirmed with ultrasound*) rate per embryo transfer procedure*, v) *number of oocytes retrieved per OR, vi) number of metaphase two oocytes per OR, vii)* the duration of a stimulation cycle, viii) total gonadotropin consumption per stimulation cycle.

Adverse events included; i) *ectopic pregnancy per embryo transfer*, ii) *miscarriage per pregnancy*: defined as the number of spontaneous abortions (pregnancy loss before 20 completed weeks of gestation) and the number of stillbirths (pregnancy loss after 20 completed weeks of gestation)*, iii) multiple pregnancy rate per embryo transfer.*

We searched the public electronic resources as databases, trial registers and websites from the date of inception until June 1, 2019.

RESULTS

The electronic search returned 375 potential citations. After removing the duplicates 320 citations were screened and 305 were excluded by the title or abstract. Fifteen were assessed in full text. One of them was a protocol for an incoming RCT and two of the studies were irrelevant to this review. In total, one prospective cohort (7), one retrospective cohort (8) and three RCTs (2,9,13) were included.

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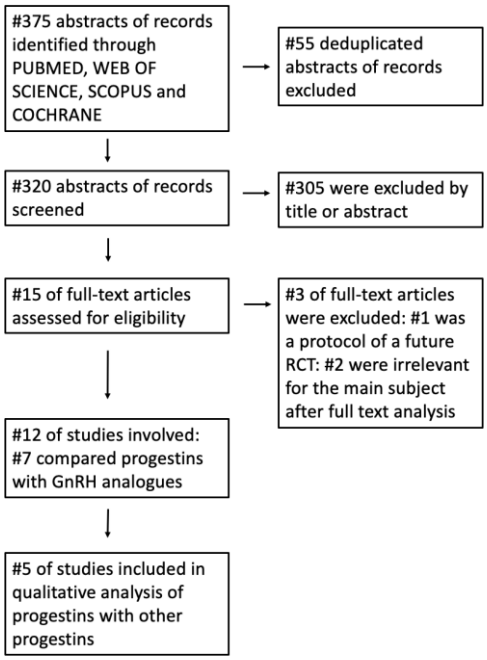
The five studies involved a total of 2404 patients.(2,7,8,9) Three studies compared two different progestins: medroxyprogesterone acetate (MPA) versus dydrogesterone (DYG) (9), DYG versus micronized progesterone (MIP) (7) and MPA versus MIP (8), two studies compared two different dosages of the same progestin (4 versus 10 mg of MPA (2), and 100 mg versus 200 mg of MIP (figure no. 1).(10)

Figure no. 1. Flowchart of the study



In all of the included studies, progestins were started simultaneously with gonadotropins (150 – 225 IU/day hMG or rFSH) on cycle day two or three. Comparisons included: 20 mg/day DYG with 100 mg/day MIP (7), 20 mg/day DYG with 10 mg/day MPA (9), 10 mg/day MPA with 200 mg MIP (8),100 mg with 200 mg/day MIP (10), 4 mg/day and 10 mg/day MPA (table no. 1).(2)

Table no. 1. Characteristics of included studies

Title	Type of study	Inclusion criteria	Exclusion criteria	Study group	Control group
Zhu 2017 b	RCT	• Age<40 years • AFC >4 • FSH <10 IU/L	• PCOS • Endometriosis ≥ Grade 3 • Hormonal treatments in the previous 3 months • Any functional ovarian cyst with E_2>100 pg/ml • Any contraindications to ovulation stimulation	DYG 20 mg Trigger: Triptorelin 0.1 mg n=125	MIP 100 mg Trigger: Triptorelin 0.1 mg n=125
Yu 2018	RCT	• Age<36 years • AMH>1 • First IVF/ICSI • Tubal factor • BMI 18-26 kg/m^2	• PCOS • Endometriosis ≥ Grade 3 • Major uterine or ovarian abnormalities • Endocrine or metabolic abnormalities	DYG 20 mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=260	MPA 10mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=256
Guo 2019	RC	• Women with regular menstrual cycles	• Adenomyosis • PCOS • Uterine cavity abnormalities • Untreated hydrosalpinx • Immunologic diseases • Any contraindications to ovulation stimulation	MPA 10mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=1002	MIP 200 mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=186
Zhu 2107 c	PC	• Age<40 years • AFC >4 • FSH <10 IU/L	• PCOS • Endometriosis ≥ Grade 3 • Administration of hormonal treatments in the previous 3 months • Any functional ovarian cyst with E_2>100 pg/ml • Any contraindications to ovulation stimulation	MIP 100 mg Trigger: Triptorelin 0.1 mg n=75	MIP 200 mg Trigger: Triptorelin 0.1 mg n=75
Dong 2017	RCT	• Age 20-40 • BMI 18-25 kg/m^2 • Tubal factor, Male factor, Unexplained infertility	• AFC<3 or >20 • FSH>10 IU/L • Functional ovarian cysts on day 3 • Significant systemic disease • Any contraindications to ovulation stimulation	MPA 10mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=150	MPA 4 mg Trigger: triptorelin 0.1 mg + hCG 1000 IU n=150

In four studies, good quality embryos were frozen at the cleavage stage, and poor-quality embryos were left for extended culture to blastocyst stage. Only embryos reaching good quality blastocysts were later frozen.(2,9,7,10) In the other study, two good quality embryos were cryopreserved at cleavage stage and left all the rest to extended culture, those reaching good quality blastocysts were later cryopreserved.(8)

DISCUSSIONS

The results of our review show that there is limited information about the effectiveness of different progestins for pituitary suppression. However, DYG, MIP and MPA all seem to effectively prevent premature ovulation in ART cycles.

The dosage of progestins in the original studies have been selected somewhat arbitrarily, and later studies comparing lower dosages with the initially employed higher dosages, reported similar clinical outcome, suggesting MPA is similarly effective at 4 mg/day as it is at 10 mg/day (moderate quality evidence based on one RCT, requiring replication of the finding) and MIP is similarly effective at 100 mg/day and 200 mg/day (low to very low quality evidence based on a single retrospective cohort study) dosages. It should be noted that 100 mg/d MIP required shorter stimulation and less gonadotropin than 200 mg/d dosage. This could suggest that milder suppression of endogenous gonadotropins with lower progestin dosage can be advantageous by not only avoiding the cost and inconvenience of GnRH analogue injections but also by decreasing exogenous gonadotropin consumption. Alternatively, progestins can be started later in the cycle. Indeed, Yildiz et al. started progestin on the 7th day of stimulation or when the leading follicle reached 14 mm, rather than starting simultaneously with gonadotropins at the beginning of stimulation, and collected more oocytes than collected with a flexible GnRH antagonist cycle.(6) Yildiz et al.'s results suggest that the suppression of endogenous gonadotropins later in the cycle can yield more oocytes.

One of the suggested advantages of progestins is their

low cost. The only study on the cost-effectiveness of progestins as an alternative to GnRH analogue use for pituitary suppression has shown that when freezing all embryos were planned, progestin cycles cost $2079 less than GnRH antagonist cycles but $823 more than short agonist cycles per live birth.(11) However, these figures should be taken with caution since the study was done in the United States and medication and procedure costs vary greatly among countries.(11,12)

However, we present an unbiased overview of the current literature and identify gaps in knowledge for future research.

CONCLUSIONS

In conclusion, also if future high-quality trials confirm the assumptions of this study, progestins in general can become a reasonable alternative to GnRH analogues in ART cycles when a fresh embryo transfer is not intended.

The presence of a limited number of trials/studies, most of which are not randomized nor accounts for every woman starting stimulation are drawbacks, preventing definitive conclusions on the subject.

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