ACTA MEDICA TRANSILVANICA March 26(1):59-62
DOI: 10.2478/amtsb-2020-0016
Online ISSN 2285-7079

THE EFFECTIVENESS OF PROGESTINS FOR PITUITARY SUPPRESSION DURING OVARIAN STIMULATION IN IVF PROCEDURES

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Keywords: *progestins, Ovarian stimulation, IVF*

Abstract: *Progestins are capable of suppressing endogenous luteinizing hormone (LH) secretion from the pituitary; are less expensive than GnRH analogues. This systematic review summarizes the effectiveness of progestins as compared with GnRH analogues and identifies some of the future research perspectives. Several public resources were screened with a combination of keywords related to assisted reproductive technology, progesterone, GnRH analogue and ovarian stimulation. Overall, duration of stimulation, gonadotropin consumption and oocyte yield were similar with progestins and GnRH analogues. The live birth, ongoing and clinical pregnancy rates per embryo transfer were similar with progestins and GnRH analogues. There is still a low quality of evidence. Available information is reassuring regarding obstetric and neonatal outcomes with the use of progestins. As a wider implication, progestins can present an effective option for women who do not contemplate a fresh embryo transfer, anticipated hyper responders, preimplantation genetic testing, oocyte donors, double stimulation cycles.*

INTRODUCTION

Pituitary suppression is commonly achieved by gonadotropin releasing hormone (GnRH) analogues. GnRH antagonists have become the most commonly used agents for over a decade, since they require less injections, provide similar pregnancy rates and lower risk of ovarian hyperstimulation syndrome than the former standard of care, i.e. GnRH agonists.(1) Progestins are also capable of suppressing endogenous luteinizing hormone (LH) secretion from the pituitary.(2) Unlike GnRH analogues, progestins can be used orally and cost significantly less than GnRH antagonists. However, early endometrial exposure to progestin precludes a fresh embryo transfer.(3) Yet, with the advent of high-survival embryo vitrification and increasing number of oocyte cryopreservation cycles progestins are being more frequently used in ART. However, there is limited information about the effectiveness of progestins as compared with GnRH analogues.

AIM

This systematic review summarizes the effectiveness of progestins as compared with GnRH analogues and identifies some of the future research perspectives.

MATERIALS AND METHODS

Briefly, we searched Cochrane Central Register of Controlled Trials (CENTRAL); Medline via PubMed; Web of Science; Scopus and manually screened the reference lists of selected articles. Search period was from the date of inception of each database until 1 April 2020. There were included all studies that compared the effectiveness of a progestin with GnRH analogue for pituitary suppression in ART, which were published as full text in English. 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 and iv) ovarian hyperstimulation syndrome (OHSS) per stimulation cycle*.

RESULTS

We included 10 studies comparing progestins with GnRH antagonists, six with GnRH agonists (one of which was treated as two separate studies since there were two distinct study populations involved, Shen et al. 2020) (4), and six with other progestins or different dosages of the same progestin (figure no. 1).

There are several important limitations of the available studies; i) majority of them were conducted in the same center by the two groups of investigators from China, ii) in most studies patients were allocated to different protocols in a non-randomized manner, iii) pregnancy outcomes were reported per transfer rather than per woman starting stimulation. Moreover, cumulative live birth rates per stimulation, which is the most relevant outcome measure was not reported at all.

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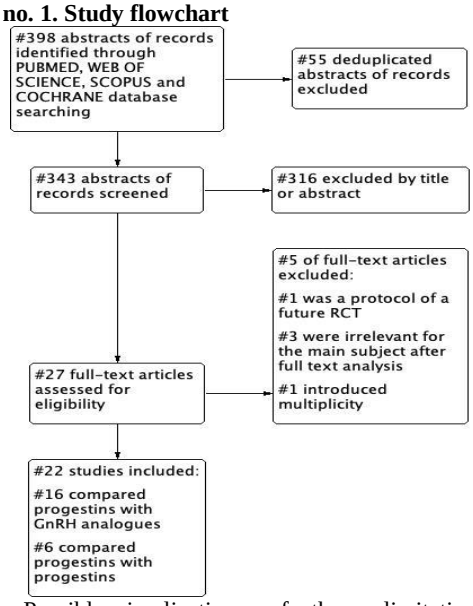
Article received on 02.11.2020 and accepted for publication on 26.02.2021

Figure no. 1. Study flowchart

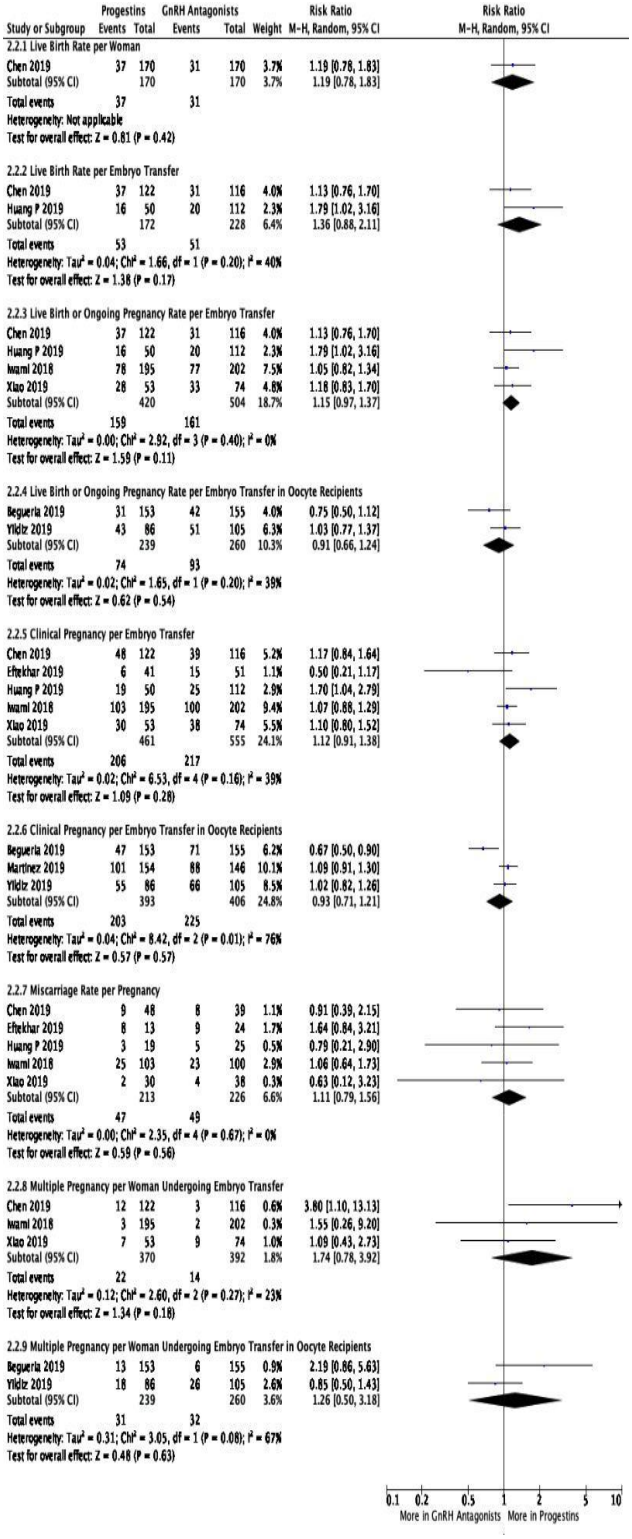


Possible implications of these limitations vary depending on the outcome of interest. In order to address these shortcomings, it can be useful to separate outcomes in two categories; the first category includes outcomes related to the response to ovarian stimulation (ROS), i.e. duration of stimulation, total gonadotropin consumption, number of oocytes and mature oocytes collected, risk of OHSS, while the second category includes outcomes after embryo transfer (ET), i.e. pregnancy, multiple pregnancy, miscarriage and live birth rates. We are presenting as numeric data the ET outcomes for the both GnRH antagonists and agonists. The outcomes in ROS category were reported per woman starting stimulation cycle and the major risk is selection bias in the non-randomized studies. Despite similar baseline characteristics regarding age and ovarian reserve parameters being reported for study groups in all papers, it is impossible to completely rule out systematic differences in other parameters that can probably effect ovarian response between the groups, e.g. the selection of starting gonadotropin dosage, which would have an impact on total gonadotropin consumption and could have been effected by the knowledge of pituitary suppression protocol planned for a patient, or monitoring could have been done differently. Yet, we think outcomes in this category are more reliable than outcomes in the ET category. The latter is crippled by the failure to report pregnancy/live birth rates per woman starting stimulation and cannot account for women not reaching an embryo transfer or women undergoing multiple embryo transfers. The proportion of women undergoing ET over women starting stimulation ranged between 25 – 91% in PPOS arms and 50 – 88% in comparators and were significantly different between PPOS and GnRH analogue groups in some studies (data not shown). Moreover, observations in ROS category can have higher generalizability than the observations in ET category. The data is dominated by studies on Chinese women, while ethnic differences may arguably have an effect on pregnancy and live birth rates, ovarian response does not seem to be effected by ethnic background based on limited data.(5,6,7)

Progestins versus GnRH Antagonists

Progestins were compared with GnRH antagonists in ten studies. Three were RCTs (8,9,10) two were prospective (11,12) and five were retrospective cohort studies.(13,14,15,16,17) Regarding ET outcomes, only one study reported live birth rate per woman starting stimulation.(9) There were 170 women in each group and women in the PPOS and GnRH antagonist groups had similar live birth rates (21.8% vs 18.2%, respectively, p=0.42) However, in addition to the lack of allocation concealment, it is unclear whether women underwent multiple embryo transfers, i.e. fresh followed by frozen transfers if the fresh transfer did not result in live birth. Moreover, the trial was underpowered for comparison of live birth rates (figure no. 2).

Figure no. 2. Progestins versus GnRH Antagonists – Embryo transfer outcomes

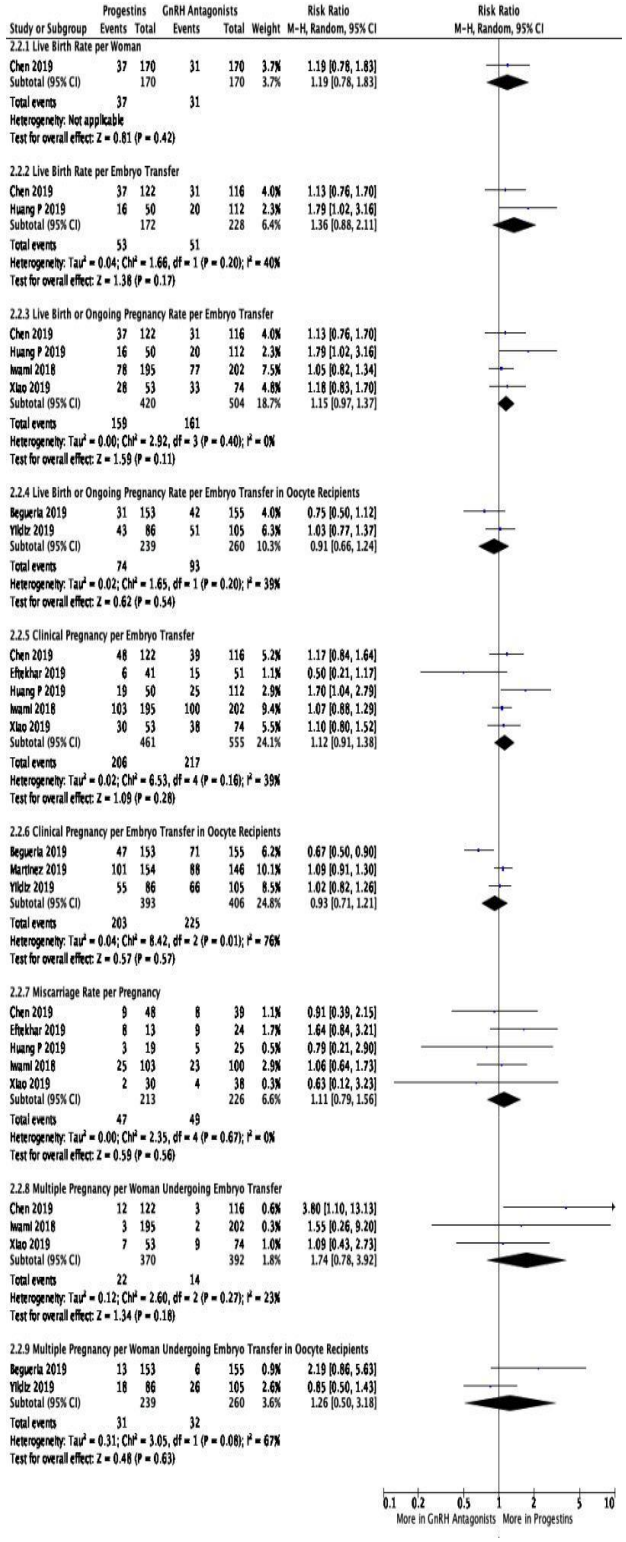


Progestins vs GnRH agonists

Progestins were compared with GnRH agonists in six

studies. Two were RCTs, one prospective and three were retrospective cohort studies.(4,18,19,20,21,22) One of the RCTs was indeed a quasi-randomized trial and assignment was by patient numbers, which clearly breaches the principle of allocation concealment.(19) All studies were from the Dept. of Assisted Reproduction of Shangai Ninth People's Hospital and included women with an anticipated normal ROS or PCOS.

Figure no. 3. Progestins versus GnRH Agonists – Embryo transfer outcomes



Regarding ET outcomes (figure no. 3), none of the studies reported live birth rate or ongoing pregnancy rate per woman starting stimulation.

Live birth rate (RR = 0.83, 95% CI = 0.39 to 1.78, two studies, 445 transfers) (18,21) and live birth or ongoing pregnancy rate per embryo transfer (RR =1.06 95%CI = 0.87 to 1.28, 6 studies, 1490 transfers) (4,18,19,20,21,22) were similar with progestins and GnRH agonists. Sensitivity analyses for trial design, short or long GnRH agonist protocol, MPA or MIP, ovarian reserve status suggested similar results.

DISCUSSIONS

This study suggests that progestins are capable of effectively preventing premature ovulation in ART cycles. Progestins seem to provide higher pregnancy rates than the short GnRH agonist protocol following frozen embryo transfers. Safety profile of progestins seems similar with GnRH analogues. However, the quality of evidence concerning their effectiveness with regard to oocyte yield and live birth rate in comparison to GnRH analogues is yet low and there is a strong need for more research.

The underlying assumptions of these analyses regarding the cost effectiveness were i) similar live birth rates with PPOS, the short GnRH agonist and GnRH antagonist protocols, and ii) 462 IU higher gonadotropin consumption with PPOS than the protocols using GnRH analogues. The increased cost of PPOS cycles were due to i) increased gonadotropin consumption and ii) the cost of additional monitoring and embryo thawing for the first transfer (even when the cost of freezing supernumerary embryos after the first fresh transfer in GnRH analogue protocols was assumed to balance out the cost of total embryo freezing in PPOS cycles).

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. However, we present an unbiased overview of the current literature and identify gaps in knowledge for future research. A reliable comparison between progestins and GnRH antagonists, the current standard of care for pituitary suppression is urgently needed, such as a comparison between flexible and the common PPOS.

Future Perspectives

An increasing number of studies suggest similar ROS and pregnancy outcomes per transfer with PPOS and GnRH analogues. MPA, DYG and MIP seem to be effective inhibitors of premature ovulation and provide similar quality oocytes as evidenced with pregnancy outcomes. Embryo euploidy rates as well as obstetric outcomes seem to be similar with PPOS and GnRH analogues. However, more high quality RCTs, comparing PPOS with both GnRH agonists and antagonists, which report live birth rates per woman starting stimulation, ideally in a cumulative manner, are needed from different centers and countries. Gonadotropin starting dosages and the requirements for dose adjustments must be pre-specified in these trials. Different progestins and PPOS protocols, e.g. fPPOS, require further assessment.

Avoiding GnRH analogue injections and taking progestin pills are assumed to be more convenient for the patients, however, none of the studies reported on side effects, or compared them with those in conventional OS cycles. Patient satisfaction should be properly assessed and compared in future studies. Different routes of administration or progestins, e.g. vaginal, transdermal, can be investigated.

Cost-effectiveness analyses based on local costs would be informative to assess the cost effectiveness of PPOS outside the U.S. with updated reliable information especially regarding gonadotropin consumption from good quality studies. Finally, more information on the course of pregnancy, obstetric

complications, neonatal and long-term infant outcomes, including health and development of children is needed.

CONCLUSIONS

In conclusion, if future high-quality trials confirm the assumptions of this review, progestins can become the agent of choice for pituitary suppression in ovarian stimulation cycles when a fresh embryo transfer is not intended, such as preimplantation genetic testing or fertility preservation cycles with oocyte or embryo cryopreservation. This would be a real benefit by eliminating the need for relatively costly GnRH analogues.

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