The Progestin-Primed Ovarian Stimulation (PPOS). Progestins instead of GnRH analogues to inhibit spontaneous ovulation during ovarian stimulation: is the beginning of a new era?

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The Progestin-Primed Ovarian Stimulation (PPOS). Progestins instead of GnRH analogues to inhibit spontaneous ovulation during ovarian stimulation: is the beginning of a new era?

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Abstract

Advancements in techniques for freezing oocytes and embryos in the field of assisted reproduction prompted new approaches to ovarian stimulation. A growing attention has been dedicated to progesterone and its derivatives to block the LH surge, since oocyte vitrification permits to remove the concerns about the possible harmful effect of progestins on endometrial receptivity. This review summarizes the state of art in the use of progestins to inhibit ovulation in ovarian stimulation protocols for IVF cycles compared to conventional ovarian stimulation. Progestin primed ovarian stimulation has shown to be effective in inhibiting spontaneous ovulation, without affecting the number of retrieved oocytes and the quality of the embryos obtained. Reproductive outcomes from ovarian stimulation with progestins seem to be similar to those derived from conventional ovarian stimulation, even if large trials are still needed to confirm this aspect. The approach with progestins permits a better control over LH levels, lower costs and an easier administration for the patient by oral assumption. For all these reasons PPOS could be the first choice for ovarian stimulation in fertility preservation, oocyte donation and in preimplantation genetic testing cycles. The so called "non conventional" ovarian stimulation protocols (luteal and random-start, double ovarian stimulation) which are always associated to oocyte or embryo freezing may be based on the use of progestins to control endogenous LH surge. Finally, since the "freeze all" strategy with delayed transfer is mandatory, high responders undergoing IVF could benefit more from this approach. Economic significance remains to be demonstrated, as long-term pregnancy outcomes.

Key Words

Ovarian stimulation, ovulation inhibition, GnRH analogues, progestins, progestin primed ovarian stimulation.

INTRODUCTION

In vitro fertilization (IVF) has been increasingly employed over the last decades. The retrieval of oocytes in an adequate number is based on the principles of ovarian stimulation. In addition to the gonadotropins for multiple follicles recruitment, it is mandatory to use a drug also for preventing the untimely outbreak of the recruited follicles. The first substances used to obtain ovulation inhibition were gonadotropin releasing hormone (GnRH) agonists, followed by GnRH antagonists. Gonadotropin releasing hormone analogues are though affected by multiple disadvantages. They are burdened by an important cost, poor manageability (the drug must be accurately prepared and needs subcutaneous injection) and various side effects. This has prompt interest in medical alternatives. After the publications of various studies on luteal phase ovarian stimulation, demonstrating consistent LH-suppression with no spontaneous surge, it has been investigated if exogenous progesterone (P) could be applied in ovarian stimulation cycles with the aim of ovulation inhibition. The obvious assumption, both in the luteal phase ovarian stimulation and in the stimulation in the follicular phase with exogenous progestins, is the total freezing of the entire cohort of embryos derived from retrieved oocytes (Massin, 2017). In prior decades, progesterone could not be considered for use during controlled ovarian stimulation because it was known to have a negative impact on endometrial receptivity. Since newly advanced vitrification techniques have made possible superior quality cryopreserved embryo and precise thawing, it has been possible to break through the standard sequence of ovarian stimulation-retrieval-transfer (Figure 1). Progesterone's ovulation inhibition and the freeze all-protocol's efficacy suggest that progesterone may be used as an alternative to a GnRH analogue for suppressing premature LH surge during controlled ovarian stimulation (COS) in IVF cycles using the freeze all-strategy. This review proposes to elucidate the state of the art of progesterone primed ovarian stimulation (PPOS), with its advantages and limitations.

MATERIALS AND METHODS

A literature search was conducted using PubMed until January 2019. The following keywords were used to generate the list of citations: ovarian stimulation, ovulation inhibition, GnRH analogues, progestins,

progestin primed ovarian stimulation. A systematic review of English-language publications was conducted. Articles and their references were examined for identifying other potential studies. All the articles considered of interest between those screened are reported in this review.

CONVENTIONAL PROTOCOLS FOR OVARIAN STIMULATION AND THE ROLE OF GNRH ANALOGUES

The advent of IVF saw oocyte retrieval from a single follicle in a natural cycle. The disadvantages of having only one oocyte to work with led to the introduction of ovarian stimulation for IVF. Ovarian stimulation is employed aiming to stimulate the growth of several follicles and, consequently, obtain as many high quality oocytes as possible (Cavagna et al., 2011). More oocytes means more embryos, which offer the possibility of embryo selection; this in turn helps to improve pregnancy rates (Mahajan, 2013).

In conventional ovarian stimulation protocols, the administration of exogenous gonadotropins maintains follicle-stimulating hormone (FSH) and LH levels above a critical threshold needed to stimulate the development of many follicles, thus allowing the retrieval of multiple oocytes in a single cycle (Alper and Fauser, 2017). The early rise in estradiol levels, due to the development of multiple follicles at the same time, may promote an extemporaneous LH surge, leading to spontaneous ovulation and to the consequent premature end of the respective cycle. In order to avoid such an effect, over the last 30 years, pituitary suppression has been employed using GnRH and its analogues. Initially, pituitary suppression was attempted using GnRH agonists and, more recently, GnRH antagonists were introduced. Final oocyte maturation and ovulation are then typically triggered with a bolus of GnRH agonist, hCG (a hormone that is biologically similar to LH but has a longer halflife), or both (Cavagna et al., 2011).

The GnRH agonists are more potent and have got a longer half-life than native GnRH, from which they are derived: developed in the 1980s, they bind to pituitary receptors in the hypophysis, and induce the release of large amounts of FSH and LH (flare-up effect), and an increase in the number of GnRH receptors (upregulation) (Kumar and Sharma, 2014). However, after prolonged use, internalization of the GnRH agonist-receptor complex occurs, which is accompanied by a decrease in the number of GnRH receptors

(downregulation). As a result, the pituitary becomes refractory to stimulation by GnRH, leading to a decrease in circulating gonadotropins and thus preventing premature LH surge.

GnRH antagonists, differently, promptly suppress pituitary gonadotropin by GnRH-receptor competition (Kumar and Sharma, 2014. The secretion of gonadotropins is decreased within hours of antagonist administration and no flare-up effect occurs. Moreover, discontinuation of GnRH antagonist treatment results in rapid, predicable recovery of the pituitary-gonadal axis as the pituitary receptor system remains intact. GnRH antagonists have provided clinicians with flexibility in terms of administration, offering patients a friendlier method of ovarian stimulation (Tarlatzis and Kolibianakis, 2007).

The utilization of GnRH analogues, however, may lead to a series of side effects.

Despite their long time clinical use, GnRH agonists are still associated with the complexity of achieving consistent downregulation and an increased risk of OHSS from a hCG trigger (Zhu et al., 2015). Moreover, the administration of GnRH analogues produces their accumulation and subsequent concentration in peripheral circulation with consequent possible extrapituitary effects. Since GnRH receptors have been described in the ovary and the presence of specific GnRH agonistic and antagonistic binding has been demonstrated in human luteinized granulosa cells, these compounds, particularly GnRH agonists, can induce the formation of functional follicular cysts (Mehta and Anand Kumar, 2000), probably as a result of their flare-up effects. The incidence of functional cysts has been reported to be in the range 2-40%, the frequency being higher in older women, when the administration of the agonist begins in the follicular phase rather than in mid-luteal phase, and in those women with increased concentrations of basal FSH (Fiszbajn et al., 2000). Other disadvantages of GnRH agonists include hypoestrogenaemia and a requirement for a prolonged period of downregulation with subsequent expensive costs. This extensive treatment period before desensitization implies not only an increased cost of treatment, but also a prolonged hormonal exposure, associated with menopausal symptoms, induced by a gonadotropin suppression.

Protocols with GnRH antagonists have fewer complications and are more convenient for patients because of the shorter treatment time and fewer injections. However, antagonists' effectiveness is still debated. According to multiple studies comparing GnRH agonist protocol and GnRH antagonist protocol, effectiveness, the number of oocytes retrieved and the embryos obtained are significantly lower when the

antagonist is used (Wang et al., 2017). The cycle cancellation rate furthermore seems higher in women who received GnRH antagonist protocols compared with GnRH agonist protocols (Kahyaoğlu et al., 2017). A varied proportion (0.34-38%) of patients using a GnRH antagonist is demonstrated to experience premature LH surge, especially older patients and patients with dimineshed ovarian reserve (Bosch et al., 2003; Reichman et al., 2014). GnRH antagonists indeed, at the doses currently in use in IVF programs, have been demonstrated unable to block the stimulating effect of exogenous estrogen on LH surge in women with unstimulated ovaries, suggesting that their clinical efficacy in IVF cycles is determined by the ovarian hyperstimulation process (Messinis et al., 2005; Messinis et al., 2010). It is moreover important to remind that, since the development of an antagonist with an acceptable pharmacokinetic and safety has been more difficult than the agonist's one, some experience is still needed in their use.

These disadvantages have prompted interest in exploring convenient alternatives to prevent premature LH surges in controlled ovarian stimulation, and the research is still ongoing.

THE PHYSIOLOGICAL ROLE OF ENDOGENOUS PROGESTERONE ON PITUITARY LH SURGE

Extensive research has been undertaken to elucidate the exact signals responsible for inducing pituitary surge secretion of LH at the basis of ovulation. The major regulatory factors of gonadotropin surge have been identified in hypothalamic GnRH, ovarian steroids such as estradiol and progesterone, and various others regulatory factors such as cytokines, leukotrienes, glucocorticoids, adrenergic and dopaminergic stimuli.

Gonadotropin releasing hormone is released in a pulsatile manner by neurons which have their origin in the arcuate nucleus; it is released in the median eminence in the perivascular space and then enters the capillaries of the hypophyseal portal system (Chabbert-Buffeta et al., 2000). Gonadotropin-releasing hormone has to be discharged with a frequency and amplitude within a critical range for having normal gonadotropin secretion. Gonadotropins are synthesized on rough endoplasmic reticulum in the gonadotropic cell, packaged into secretory granules and stored. Actual secretion is dependent on migration and activation of the mature secretory granule at the cell membrane (Shoham et al., 1995).

The major control element regulating gonadotropin levels is the ovarian steroid feedback on the anterior pituitary. Since it has been observed that GnRH neurons do not possess classic steroid receptors, the surge inducing signals seem to be transmitted to the GnRH neurosecretory system through a series of one or more interneurons (Harris et al., 1999).

Estradiol plays a central role in the secretion of LH by the pituitary gland. Produced by the granulosa cells of the developing follicle, it exerts negative feedback on LH production in the early follicular phase of the ovarian cycle. During follicular phase, however, once estrogen levels reach a critical level as oocytes mature within the ovary in preparation for ovulation, they begin to exert positive feedback on LH production, leading to the LH surge. The LH surge increases intrafollicular proteolytic enzymes, weakening the wall of the ovary and allowing for the mature follicle to pass through (Holesh and Lord, 2017). This changing from a negative to a positive feedback on LH secretion happens via both the pituitary and the hypothalamus. In the pituitary region, it is caused by an increase in sensitivity to GnRH (due to increase in GnRH receptors on gonadotropic cells); a possible enhancement of the availability of GnRH in the pituitary via an inhibition of GnRH metabolism; a lowering of the GnRH concentration needed for the secretion of LH. At the hypothalamic level, the effect is direct through the neuropeptide kisspeptin: steroid-sensitive kisspeptin neurons are located in the anterior ventral periventricular nucleus and neighboring periventricular nucleus, and coexpress estrogen and progesterone receptors (Messinis et al., 2014; Stephens et al., 2015).

Progesterone is also a key signal in the complicated midcycle dynamics. It is a steroid hormone that is responsible for preparing the endometrium for uterine implantation of the fertilized egg. If a fertilized egg implants, the corpus luteum secretes progesterone in early pregnancy until the placenta develops and takes over progesterone production for the rest of the pregnancy (Holesh and Lord, 2017).

The neuroendocrine effects of progesterone are mediated by the classic progesterone nuclear receptors (PRs). They exist in different isoforms and are upregulated by estrogen, while progesterone downregulates its own receptors (Chabbert-Buffeta et al., 2000). Despite the importance of progesterone in the control of GnRH surge generation, the neural mechanisms through which progesterone interact with estradiol to regulate the gonadotropin surge are not completely understood. Progesterone's action may be synergistic with, or antagonist to, the actions of estradiol, depending on hormone ratios and timing of exposure (Custodia-Lora

and Callard, 2002). Progesterone seems to have a permissive role in the preovulatory LH peak: experiments have shown a rise in progesterone preceding the LH surge by several hours in the preovulatory period (Hoff and al., 1983); in various studies, exogenous progesterone has been shown to induce a LH peak if administered in estrogen-primed women (Liu and Yen, 1983). On the other side, progesterone is known to have an inhibitory effect on ovulation. Studies originally focused on contraception have shown that progesterone is able to block the LH surge (Evans and al., 2002; Heikinheimo et al., 1996). Its inhibitory effect on follicular growth has been at the basis of the design of progestin-only contraceptives, which suppress follicular growth and thus inhibit ovulation after a sustained administration. The administration timing of progesterone has been shown to be critical in determining its effect upon the preovulatory LH surge, whether it is stimulating or inhibiting, in different animal studies. Various analysis suggested that LH surge generation is characterized by an estradiol-dependent period, during which the estradiol signal is read, and an estradiol-independent period, during which the signal is transmitted through a cascade of neuronal events to the GnRH neurosecretory system, with the release of a surge of GnRH. Progesterone has been demonstrated to block the estradiol-induced signal soon after its transmission (immediately after estradiol removal), in the early part of estradiol-independent period of surge generation, probably via the inhibition of transmission of the stimulatory signal through the intraneuronal system than link the estradiol-receptive neurons with the GnRH neurons (Harris et al., 1999). Progesterone changes cause nonetheless dramatic modifications in GnRH pulse frequency: its removal induces an acceleration of the pulse generator, while its administration slows the pulse frequency, with LH secretion being consequently modified (Chabbert-Buffeta et al., 2000). Progesterone priming seems in fact to slow the LH pulse frequency, augments the pulse amplitude and reduces the mean plasma LH levels compared with those in untreated women in some studies (Soules et al., 1984).

EXOGENOUS PROGESTINS AND PITUITARY INHIBITION

Progestins are hormones that produce numerous physiological actions. In women, these include developmental effects, neuroendocrine actions involved in the control of ovulation, the cyclical preparation

of the reproductive tract for fertilization and implantation, and major actions on mineral, carbohydrate, protein, and lipid metabolism. Progesterone represents the only natural progestin (Brunton et al., 2011).

The therapeutic use of progestins largely reflects extensions of their physiological activities. The two most frequent uses of progestins are for contraception, either alone or with an estrogen, and in combination with estrogen for hormone therapy of postmenopausal women. Progesterone has also been historical largely used in preventing threatened abortion for its quality of inhibition of uterine contractility, even if this treatment is of questionable benefit. It is also used worldwide for the prevention of preterm birth, for endometrioisis and uterine fibroids. Progesterone-receptor antagonists also are available. The main use of anti-progestins has been for medical abortion as well as for uterine fibroids, but other uses are theoretically possible.

Besides natural progesterone, produced and secreted normally in the human female by the corpus luteum, the placenta and in small quantities by the adrenal cortex, there is a broad spectrum of steroids with progesterone-like actions, derived from different parent compounds. Close to the natural progesterone there is retroprogesterone, followed by the 17-hydroxyprogesterone (i.e. medroxyprogesterone acetate) and the 19-norprogesterone derivatives. A clinically important group and the basis for the success of hormonal contraception are the 19-nortestosterone derivatives, subdivided in estranes (i.e. norethindrone, norethisterone acetate) and gonanes (i.e. norgestrel, levonorgestrel). Also spirolactone derivatives have been developed for clinical use (i.e. drospirenone).

Two isoforms of the progesterone receptor exists, PR-A and PR-B, encoded by a single gene. The biological activities of PR-A and PR-B are distinct: in most cells, PR-B mediates the stimulatory activities of progesterone; PR-A strongly inhibits this action and is also a transcriptional inhibitor of other steroid receptors. Current data suggest that co-activators and co-repressors interact differentially with PR-A and PR-B, and this may account, at least in part, for the differential activities of the two isoforms. One of the essential requirements of any compound with progesterone-like activity is being able to bind to the progesterone receptors.

All progestins have in common the so-called progestogenic effect, which is the induction of a characteristic change in the estrogen-primed endometrium (Schindler et al., 2003). The final progestogenic activity of any substance depends also on administration's route and timing. This is often expressed by the difference in the

dose required for the endometrial transformation in a woman, called the transformation dose, and it varies widely between different progestins. There are large differences between progestins in the multitude of other biological effects elicited; ovulation inhibition capacity is one of those. Progestins have been selected for clinical use on differences of the dose necessary for inhibition of ovulation: as an example, while medroxyprogesterone acetate may interfere with ovulation at a dose of 10 mg/day, 300 mg of progesterone occur to obtain the same effect. This implies that over the years progestins have been used in clinical practice much more broadly than progesterone itself: since to obtain the same effect a lower dose is required, lower costs are needed (Table 1).

THE USE OF PROGESTINS TO PREVENT THE LH SURGE IN OVARIAN STIMULATION CYCLES

Since progestins have been demonstrated to inhibit ovulation, it has been asked if exogenous progesterone could replace the use of agonists or antagonists of GnRH in ovarian stimulation protocols (Massin, 2017). Different studies have demonstrated consistent LH-suppression during ovarian stimulation in the luteal phase, with no spontaneous LH surge (Kuang et al., 2014; Wang et al., 2016a). It has been presumed that those pituitary glands secretions could have been transiently suppressed by high doses of progesterone during luteal-phase ovarian stimulation. This supposition are in agreement with Letterie's study (Letterie, 2000), showing that a combination of ethinil estradiol and norethindrone administered for 5 days beginning on day 6 or 8 of the menstrual cycle permitted folliculogenesis, but inhibited midcycle LH surge and consequently ovulation during controlled ovarian stimulation. The obvious assumption, both in the luteal phase ovarian stimulation and in the stimulation in the follicular phase with exogenous progestins, is the total freezing of the entire cohort of embryos derived from retrieved oocytes. In prior decades, progesterone could not be considered for use during controlled ovarian stimulation because it was known to have a negative impact on endometrial receptivity. Since newly advanced vitrification techniques have made possible superior quality cryopreserved embryo and precise thawing, it is no longer required the transfer of fresh embryos to a uterus that has been newly subjected to hormonal stimulation. The transfer of cryopreserved-thawed embryos in the freeze-all embryo protocol has nontheless been reported in some studies to result in

improved pregnancy and delivery outcomes (Devroey et al., 2011; Doody, 2014; Wong et al., 2014). Progesterone's LH suppression and the freeze all-protocol's efficacy suggest that progesterone may be used as an alternative to a GnRH analogue for suppressing premature LH surge during controlled ovarian stimulation in IVF cycles using the freeze all-strategy.

A dozen of studies are available in literature so far, involving more than 2500 patients. The first study on the use of a progestin during controlled ovarian stimulation has been published by Kuang in 2015 (Kuang et al., 2015). It aimed to investigate the use of medroxyprogesterone acetate (MPA) to prevent LH surge and to compare cycle characteristics and pregnancy outcomes in subsequently frozen-thawed embryo-transfer cycles, using a short protocol as a control. Medroxyprogesterone acetate was used as an alternative to progesterone for its advantages: it is progestative, slightly androgenic and does not interfere with the measurement of endogenous progesterone production. In the study group, human menopausal gonadotropin (hMG, with a dose of 150 UI/day in patients with an antral follicle count higher than 20 or slightly elevated FSH basal value, while for all other patients a dose of 225 UI/day was used) and MPA (10 mg/day) were simultaneously administered beginning on menstruation cycle day 3. From menstruation cycle day 7-8, every 2-4 days, ultrasound follicular monitoring was performed and serum LH, FSH, estradiol (E2) and P concentrations were measured. As well as in all the other studies mentioned, the progestin was administered until the day of ovulation triggering. Ovulation was induced with triptorelin (0.1 mg), a GnRH agonist, or co-triggered by triptorelin and hCG (1000 UI) when at least three dominant follicles reached 18 mm in diameter. A short protocol was used in the control group, with the administration of triptorelin (0.1 mg/day) beginning on menstruation cycle day 2 and hMG (150-225 UI/day, with the same administration dose criteria used in the study group) beginning on menstruation cycle day 3. Aspirated oocytes were then fertilized in vitro, and viable embryos were cryopreserved for later transfer in a subsequent cycle in both protocols, after adequate preparation of the endometrium. The number of oocytes retrieved in the study group was slightly higher but did not reach significant difference compared with the short protocol ($p > 0.05$), and the mean stimulation duration and hMG dose were significantly higher than those in the control group ($p < 0.05$). No significant differences were found in oocyte maturation rate, fertilization rate and cleavage rate between the two groups ($p > 0.05$). Also, the number of good-quality embryos and cryopreserved embryos showed no significant difference between the two groups. No patient experienced moderate or severe OHSS during the

study. No significant difference was found in the incidence of premature LH surge in the study group compared with the control group (0.7% vs 0%, $p > 0.05$). No statistically significant differences were found in the clinical pregnancy rates, implantation rates, and live-birth rates in the study group and controls ($p > 0.05$). It is important to consider that no congenital malformations were found in any of the live-birth babies. The results of the study provided first-time evidence that MPA is an effective oral alternative for the prevention of premature LH surge in woman undergoing controlled ovarian stimulation, and the pregnancy outcomes from frozen-thawed embryo transfer cycles indicated that the embryos originating from this regimen had similar development potential as those from the control group.

This same protocol has been applied among patients with polycystic ovary syndrome (PCOS) in a prospective controlled study, comparing the MPA protocol with a short protocol (Wang et al., 2016b). Women with PCOS planning to have an IVF represent a therapeutic challenge: they are predisposed to poor oocyte quality, low fertilization rates and high miscarriage rates. Moreover, they are at high risk of developing OHSS when stimulated. There is therefore an unsatisfied interest in alternative ways of ovarian stimulation with improved efficacy and decreased OHSS incidence in those patients. The fertilization rate and the ongoing pregnancy rate per transfer in the study group resulted higher than those in the control group (77.69 ± 16.59 % vs 70.54 ± 19.23 %, $p < 0.05$; 58.67 % vs 42.86 %, $p < 0.05$). Two cases of OHSS were reported in the short protocol group, while none was seen in the MPA group ($p > 0.05$); a possible reduction in the incidence of moderate to severe OHSS using MPA should though be viewed with caution as the data is small .

Since the identification of a minimum dose of MPA is desiderable, another randomised prospective controlled trial was conducted comparing progestin primed ovarian stimulation protocols using 4 mg versus 10 mg of MPA (Dong et al., 2017). Prior contraception studies indicated that 10 mg MPA could be used to inhibit ovulation, while 5 mg MPA failed to inhibit ovulation (Wikström et al., 1984); this study however didn’t show any premature LH surge in the group receiving 4 mg/day of MPA. The number of oocytes retrieved and viable embryos were similar between the two groups ($p > 0.05$). The administration of 4 mg/day of MPA was then demonstrated to be sufficient to prevent un untimely LH rise in ovarian stimulation cycles.

The follicular phase dynamics of progestin primed minimal stimulation and natural cycle IVF have been prospectively compared also in poor responders (Chen et al., 2017). Since these patients cannot benefit from increasing gonadotropin doses, natural cycle IVF with minimal ovarian stimulation is a friendly option. In order to avoid untimely ovulation in natural cycle, MPA was explored in blocking premature LH surge. The incidence of spontaneous LH surge and premature ovulation were significantly lower in the MPA group (1.0% vs 50%, $p < 0.05$; 2% vs 10.8%, $p < 0.05$), being nonetheless higher the number of oocytes and viable embryos harvested ($p < 0.05$). Progesterone priming is therefore a promising approach to overcome premature ovulation in minimal stimulation for poor responders.

Some inconsistencies have been reported regarding the reproductive outcomes with the use of MPA. In a recent trial (Begueria, ESHRE Barcelona 2018, Hum Reprod 33 suppl 1 2018; i108, O-239,), aiming to evaluate the non-inferiority of MPA compared to a GnRH antagonist on the number of mature oocytes retrieved at pick-up in oocyte donation cycles, Begueria et al. reported that reproductive outcomes in recpients were unexpectedly lower with MPA. Biochemical pregnancy rate was 44.3% vs 56.2% ($p = 0.042$); clinical pregnancy rate 29.9% vs 42.5% ($p = 0.026$); ongoing pregnancy rate 27.4% vs 36.9% ($p = 0.085$), and live birth rate 15.4% vs 26.0%, ($p = 0.036$) for MPA and GnRH antagonists, respectively. Given that this was a non-inferiority study with number of retrieved oocytes as primary outcome, further investigations specifically aiming to assess live birth as main outcome are needed.

Progestins other than MPA have been explored in PPOS protocols (Zhu et al., 2015). Conducted under the same conditions as with MPA, a retrospective study compared Utrogestan taken orally in the form of soft capsules (200 mg/day) with hMG with a short protocol. Despite the higher amount of hMG (1884.22 ± 439.47 vs 1446.26 ± 550.48, $p < 0.05$), the numbers of mature oocytes were not significantly different in these groups of normal responders. In contrast, the number of viable embryos was significantly higher in the Utrogestan group compared with the short protocol, despite not being any significant difference in the ongoing pregnancy rate.

Utrogestan protocols have also been demonstrated to be feasible to improve the oocyte quality in a study conducted on PCOS patients (Zhu et al., 2016). PCOS patients were administered Utrogestan (200 mg/day) and hMG (150-225 UI/day) from menstruation cycle day 3 and compared to PCOS patients being given a

short protocol. No difference was shown in the number of OHSS in each group ($p > 0.05$). The fertilization rate, viable embryo rate per oocyte retrieval, clinical pregnancy rate and implantation rate were significant higher in the study group than those in the control group ($p < 0.05$) showing a possible new choice for PCOS patients undergoing ovarian stimulation in combination with embryo cryopreservation.

The Utrogestan and hMG protocol used for the previous study's patients was applied also in a randomized controlled study aiming to demonstrate the efficacy of a lower dosage of Utrogestan (Zhu et al., 2017a). A dose of Utrogestan of 100 mg/day was used in the study group, while in the control group 200 mg/day were employed. The pituitary LH levels were suppressed after 6 days of Utrogestan treatment at 100 mg/day, no premature LH surge was observed and there were no significant differences between the study and the control group throughout the ovarian stimulation. Utrogestan's safety has been investigated in a recent retrospective cohort study by Wang et al. (Wang et al., 2018), in which neonatal outcomes and live birth defects after Utrogestan primed ovarian stimulation were compared to those of the infants conceived after conventional ovarian stimulation. No treatment-related difference was shown between the two groups, the congenital malformations being only related to the multiple births.

Medroxyprogesterone acetate is generally preferred over Utrogestan because the administration of a natural exogenous progesterone such as the latter can interfere with serum progesterone measurement, leading to the possible neglect of potential premature luteinisation (Yu et al., 2018). However, MPA may lead to stronger pituitary suppression and thus may require a higher dosage of gonadotropin and a longer ovarian stimulation duration than that of the conventional ovarian stimulation protocol (Kuang et al., 2015). In the attempt to test new synthetic progestins that represent the most suitable option for PPOS, dydrogesterone (DYG) has recently been studied as a part of a PPOS protocol in comparison with MPA. The results showed comparable oocyte retrieval and viable embryo numbers between the two groups, with similar pregnancy outcomes. Moreover, DYG could effectively suppress the premature LH surge, although not interfering with the measurement of endogenous progesterone (Yu et al., 2018). Similar results have been obtained also comparing DYG and Utrogestan: in a prospective controlled study published in 2017 (Zhu et al., 2017b), DYG showed to be similar to Utrogestan in the prevention of premature LH surges and in terms of clinical outcomes. Dydrogesterone's extensive worldwide use for the treatment of threatened and recurrent

miscarriage as well as for the luteal phase support in infertile patients suggests also its long-term safety (Yu et al., 2018) (Table 2).

ADVANTAGES AND DISADVANTAGES OF PROGESTINS IN OVARIAN STIMULATION

The studies previously mentioned show that the use of progesterone during ovarian stimulation is effective in blocking the LH surge, whether endogenous or exogenous, and it does not affect the number of oocytes collected or the quality of the embryos obtained. Total freezing of the oocytes (or embryos) obtained and delayed transfer are although mandatory. In particular, the data shown are very reassuring regarding fertility preservation and oocyte donation, since these situations doesn't require consequent embryo transfer (Massin, 2017). The potential harmful effect of the hormonal environment on endometrial receptivity are therefore avoided. Recent data show also non-inferiority of the PPOS protocol compared to the GnRH antagonist for outcomes such as clinical pregnancy and ongoing pregnancy rate (Iwami et al., 2018).

Some studies have reported concerns about prolonged exposure of the developing follicles to progesterone. Although previous studies and a meta-analysis (Melo et al., 2006; Shapiro et al., 2010; Venetis et al., 2013) have showed that late follicular phase progesterone elevation has no adverse effect on oocyte and embryo quality, suggesting that elevated exposure of the developing follicles to progestins is safe, several recent publications have challanged this concept. Elevated progesterone levels on the day of oocyte maturation induction have in fact been said to significantly reduce top quality blastocysts formation rate (Huang et al., 2016; Vanni et al., 2017). Progesterone elevation on the day of hCG administration has been said also to adversely affect cumulative live birth rate per oocyte retrieval cycle (Bu et al., 2014), even if this result seems more dependent on progestins' detrimental effect on the endometrium.

Other than women seeking fertility preservation, PPOS may be proposed as a first-choice protocol in all conditions where ovarian stimulation and oocyte retrieval are not followed by a fresh embryo transfer (Table3). Ovarian stimulation in donors and in Preimplanation Genetic Tetsing (PGT) cycles may be obviously based on progestin instead of GnRH analogue administration. As well as all "non conventional" ovarian stimulation protocols (luteal and random start, double ovarian stimulation) implying the "freze all"

and segmentation of the cycle may be associated to the use of PPOS. Other patients that can benefit from progesterone block protocols are those at risk of OHSS. One important advantage of the association between a progestin and FSH/hMG in high responders is that the triggering may be exerted by the GnRH agonist and this helps to avoid early onset OHSS. As well, cryopreservation of all embryos with delayed transfer can diminish the risk of late onset OHSS.

Other advantages over the use of a progestin in the prevention of LH surge are oral administration, easier access, and more control over LH levels (Wang et al., 2016). This program is also friendlier with the patients, since fewer injections are required and it is much less expensive.

The potential economic advantage of the application of protocols with progesterone is easily understood by making a mere calculation of what would be the expense for one of these protocols compared to protocols with GnRH analogues. Although in some of the studies mentioned before the duration of stimulation with FSH/hMG was higher in PPOS protocols than in those using analogues, in most studies the difference was not significant. The cost related to gonadotropin is therefore not significantly different between the two protocols. The substantial economic difference becomes evident by comparing the cost of GnRH analogues to the progestins' one. The total expense for the GnRH analogue in a GnRH antagonist cycle may vary from 190 to 320 euros. Economic burden is drastically reduced in case of use of progestins. When using MPA a total expense of 10-15 euros is sufficient to inhibit ovulation in the IVF cycle. Cost effectiveness of progestins compared to GnRH antagonists has been highlighted also in a recent article by Evans et al. (Evans et al., 2019), limited to planned freeze only cycles and for high responders patients where a freeze only is likely and OHSS risk is high. Despite these advantages, progesterone block strategies associated with delayed embryo transfer may have some weaknesses. The total dose of gonadotropins used in those protocols could be higher in comparison with common protocols; nonetheless, patients need to return and be re-scheduled for frozen embryos transfer. Data on consecutive frozen-thawed embryo transfer is still small. Those protocols furthermore require a change in current IVF programs practice, the need for a good cryopreservation program, and further evaluation on medical and economical aspects, since many conclusions are based on retrospective studies with limited number of patients.

CONCLUSIONS

The application of progestins to inhibit ovulation in ovarian stimulation cycles for IVF has been shown to be effective and safe, with good results reported in terms of number and quality of the oocytes and embryos obtained and low OHSS risk. The large-scale application of progestin primed ovarian stimulation could be revolutionary for several reasons. The growing application of IVF makes preferable the employee of techniques as handy as possible for the patients, possibly converting the route of administration from subcutaneous injections to oral intake. The progestins' cost compared to GnRH analogues' one seems also extremely beneficial. However, further studies are needed, especially on long-term obstetrical outcomes, before this protocol can be introduced large-scale.

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TABLES

Table 1. Progestogenic effect at the endometrium level and anti-gonadotropic effect of the various progestins (adapted from Schindler et al., 2003).

Table 2. Schematic representation of the studies published on progestin primed ovarian stimulation.

FIGURE

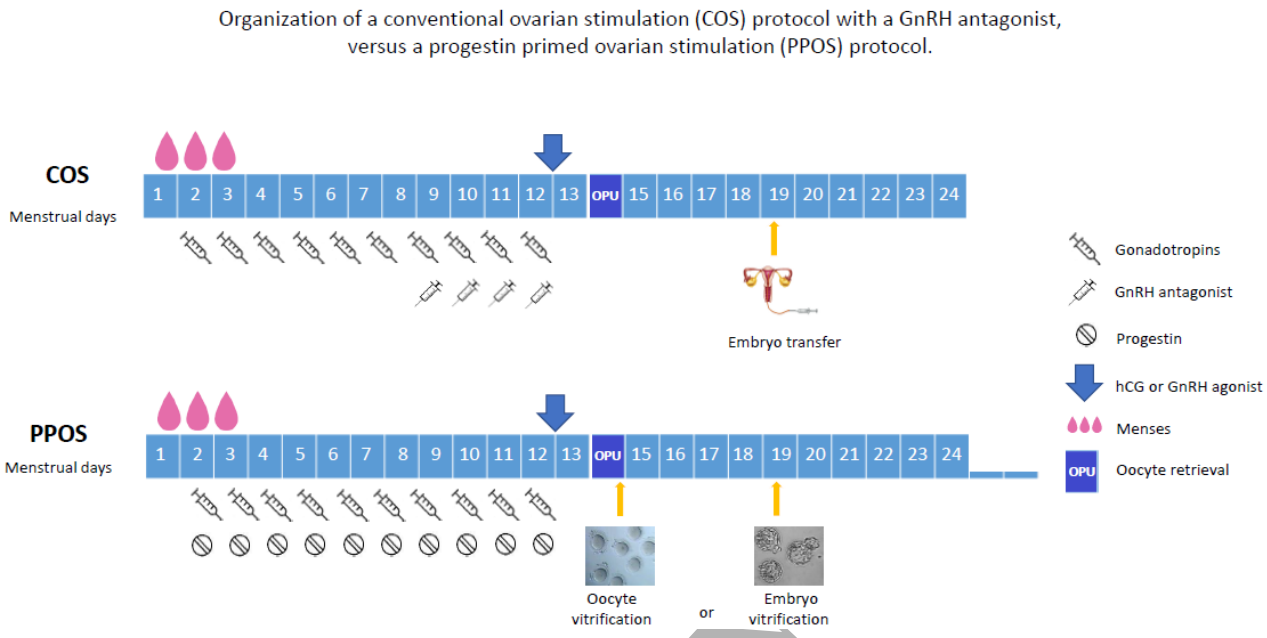

Figure 1. Organization of a conventional ovarian stimulation (COS) protocol with GnRH analogues, both with the use of an agonist (A) and an antagonist (B), versus a progestin primed ovarian stimulation (PPOS) protocol (C).

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Key message

Ovulation inhibition by exogenous progestins in ovarian stimulation cycles is safe, effective and economical. Pregnancy outcomes are promising and risk for OHSS seems lower when compared with conventional stimulation protocols.

Table 1. Progestogenic effect at the endometrium level and anti-gonadotropic effect of the various progestins (adapted from Schindler et al., 2003).

Progestin	Transformation dose (mg/cycle)	Transformation dose (mg/day)	Ovulation inhibition dose (mg/day)
Progesterone	4200	200-300	300
Dydrogesterone	140	10-20	>30
Medrogestone	60	10	10
Medroxyprogesterone acetate	80	5-10	10
Cyproterone acetate	20	1.0	1
Norethisterone acetate	30-60	/	0.5
Levonorgestrel	6,0	0.15	0.05
Dienogest	6.0	/	1.0
Nomegestrol acetate	100	5.0	5.0
Drospirenone	50	/	2.0

Table 2. Schematic representation of the studies published on progestin primed ovarian stimulation.

	Progestin **Population** **Study design**	**Group**	**Number of patients**	**Number of oocytes**	**Number of embryos**	**Implantation rate**	**Pregnancy rate**
Kuang et al., 2015	MPA Normal responders Prospective controlled study	Study group (10 mg MPA)	150	9.9 ± 6.7	7.0 ± 5.3	31.9%	47.8%
		Control group (Short agonist)	150	9.0 ± 6.0	6.4 ± 4.4	27.7%	43.3%
Wang et al., 2016b	MPA PCOS patients Prospective RCT	Study group (10 mg MPA)	60	15.2 ± 7.8	10.6 ± 5.9	48.6%	65.3%
		Control group (Short agonist)	60	15.8 ± 8.4	9.7 ± 5.2	42.6%	53.5%
Dong et al., 2017	MPA Normal responders Prospective RCT	Study group (4 mg MPA)	150	9.6 ± 5.9	3.7 ± 3.0	30.1%	43.7%

		Control group (10 mg MPA)	150	9.8 ± 6.3	4.2 ± 2.6	30.9%	46.0%
Chen et al., 2017	MPA Poor responders Prospective controlled study	Study group (10 mg MPA)	102	1.0	1.1	21.4%	11.8%
		Control group (Natural cycle)	102	0.7 p < 0.05	0.8 p < 0.05	15.3%	5.9%
Zhu et al., 2015	Utrogestan Normal responders Retrospective study	Study group (200 mg Utrogestan)	187	10.9 ± 5.7	7.5 ± 4.4	33.5%	54.2%
		Control group (Short agonist)	187	10.6 ± 6.2	7.1 ± 4.5	34.0%	51.6%
Zhu et al., 2016	Utrogestan PCOS patients Retrospective study	Study group (200 mg Utrogestan)	123	13.2 ± 7.4	9.0 ± 5.2	46.6%	64.6%
		Control group (Short agonist)	77	13.1 ± 7.9	7.8 ± 4.7	31.3% p < 0.05	48.8% p < 0.05

Zhu et al., 2017a	Utrogestan Normal responders Prospective RCT	Study group (100 mg Utrogestan)	150	9.8 ± 5.7	6.5 ± 4.0	38.6%	50%
		Control group (200 mg Utrogestan)	150	10.2 ± 5.4	6.7 ± 4.0	36.0%	51.3%
Yu et al., 2018	Dydrogesterone Normal responders Prospective RCT	Study group (20 mg DYG)	260	10.8 ± 6.3	6.9 ± 4.4	40.0%	57.6%
		Control group (10 mg MPA)	256	11.1 ± 5.8	7.0 ± 4.5	45.9%	62.3%
Zhu et al., 2017b	Dydrogesterone Normal responders Prospective controlled study	Study group (20 mg DYG)	125	8.22 ± 5.46	2.23 ± 2	38.68%	66.67%
		Control group (100 mg Utrogestan)	125	8.8 ± 5.62	2.69 ± 2.38	35.71%	69.47%

Note: Number of oocytes and number of embryos values are means ± SD

Table 3 Indications for PPOS

When PPOS can be proposed as a first-choice protocol
Donor stimulation
Fertility preservation
PGT-A and PGT-M cycles
Double ovarian stimulation (and non conventional protocols)
IVF in women at risk of OHSS