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ARTICLE

Progestins versus GnRH analogues for pituitary suppression during ovarian stimulation for assisted reproductive technology: a systematic review and meta-analysis

BIOGRAPHY

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KEY MESSAGE

Progestins effectively inhibit premature ovulation. On the basis of low-quality evidence, progestins are as effective as gonadotrophin releasing hormone analogues. Randomized trials presenting intention to treat analysis are needed. Flexible progestin primed stimulation protocols deserve further study.

ABSTRACT

This systematic review and meta-analysis of comparative studies investigated whether progestins are as effective as gonadotrophin releasing hormone (GnRH) analogues for pituitary suppression in assisted reproduction. The primary outcome was live birth rate per woman. Secondary outcomes were live birth or ongoing pregnancy per woman and per embryo transfer, ongoing pregnancy, clinical pregnancy, numbers of oocytes and metaphase-two oocytes, duration of stimulation and gonadotrophin consumption. Adverse events included miscarriage, ectopic pregnancy and multiple pregnancy rates. The GRADE system was used to assess the quality of evidence. Seven studies involving a total of 2047 women were included. Three studies compared a progestin with a GnRH antagonist and four studies compared a progestin with a GnRH agonist. Most studies are non-randomized and report outcomes per embryo transfer, rather than per woman. Although progestins were similar to GnRH antagonists in effectiveness and safety parameters, they were associated with significantly higher live birth or ongoing pregnancy per embryo transfer compared with the short GnRH agonist protocol (RR 1.49, 95% CI 1.16 to 1.91). Progestin primed stimulation lasted significantly longer (mean difference 0.61 days, 95% CI 0.33 to 0.89) and required significantly more gonadotrophins (mean difference 433.2 IU, 95% CI 311.11 to 555.19) than the short GnRH agonist protocol, but the differences were clinically negligible. Safety parameters were similar between progestins and GnRH agonists. In conclusion, progestins can effectively prevent premature ovulation in assisted reproductive technology cycles. If larger and well-designed studies confirm these findings, progestins may be an effective and low-cost alternative to GnRH analogues when a fresh embryo transfer is not planned owing to a medical indication.

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KEYWORDS

Assisted reproduction
GnRH analogue
İn vitro fertilization
Ovarian stimulation
Progestin

INTRODUCTION

Ovarian stimulation for assisted reproductive technology (ART) involves three components: stimulation of multi-follicular growth; pituitary suppression to prevent a luteinizing hormone (LH) surge and ovulation before oocyte retrieval; and trigger for final oocyte maturation. Pituitary suppression is commonly achieved by gonadotrophin releasing hormone (GnRH) analogues. GnRH antagonists have become the most commonly used agents for over a decade, as they require fewer injections, provide similar pregnancy rates and lower the risk of ovarian hyperstimulation syndrome than the former standard of care, i.e. GnRH agonists (*Al-Inany et al., 2016*). Progestins are also capable of suppressing endogenous LH secretion from the pituitary (*La Marca and Capuzzo, 2019*). Unlike GnRH analogues, progestins can be used orally and cost significantly less than them. Early endometrial exposure to progestin, however, preclude a fresh embryo transfer (*Venetis et al., 2013*). Yet, with the advent of high-survival embryo vitrification and increasing number of oocyte cryopreservation cycles, progestins are being more frequently used in ART. Information about the effectiveness of progestins compared with GnRH analogues, however, is limited. We conducted a systematic review of the literature for studies comparing clinical outcomes of ART cycles using progestins or GnRH analogues for pituitary suppression and pooled the results in meta-analyses, where appropriate.

MATERIALS AND METHODS

Published randomized controlled trials (RCTs) and cohort studies that compared the effectiveness of a progestin with a GnRH analogue for pituitary suppression in ART were included. Only studies published in English as a full-text article were included.

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 as follows: live birth or ongoing pregnancy beyond 12 weeks per woman starting a stimulation cycle; live birth rate per embryo transfer procedure; live birth or ongoing pregnancy per embryo transfer procedure; clinical pregnancy (defined as evidence of a gestational sac at 6 weeks or later, confirmed with ultrasound) rate per embryo transfer procedure; number of oocytes retrieved per oocyte retrieval; number of metaphase two oocytes per oocyte retrieval; the duration of a stimulation cycle; and total gonadotrophin consumption per stimulation cycle.

Adverse events included ectopic pregnancy per embryo transfer; miscarriage per clinical pregnancy (defined as pregnancy loss before 20 completed weeks of gestation) and the number of stillbirths (pregnancy loss after 20 completed weeks of gestation); multiple pregnancy rate per embryo transfer; and ovarian hyperstimulation syndrome (OHSS) per stimulation cycle.

The following electronic databases, trial registers and websites were searched from the date of inception until 1 June 2019; *Cochrane Central Register of Controlled Trials (CENTRAL)*; *MEDLINE* via *PubMed*; *Web of Science*; and *Scopus*. Reference lists of the selected articles were screened manually.

As an example, the combination of keywords used for Medline is as follows; (((((ART OR assisted reproduction OR assisted reproduction techniques OR IVF OR in vitro fertilization OR in-vitro fertilization techniques OR subfertility OR infertility OR ovarian stimulation OR ovulation induction OR ICSI OR intracytoplasmic sperm injections OR progestin-primed ovarian stimulation OR PPOS OR controlled ovarian stimulation OR premature ovulation OR FET OR frozen embryo transfer OR poor responder*)) AND (medroxyprogesterone* acetate* OR MPA OR progestin* OR progesterone* OR dydrogesterone)) AND (SB-75 OR cetrotide OR cetrorelix acetate OR cetrorelix pamoate OR LHRH antagonist OR premature LH surge OR LH surge OR luteinising hormone surge OR GnRH antagonist OR Gonadotropins* OR menotropins)) AND ("2000/01/01"[PDat]: "2019/01/09"[PDat]) AND Humans[Mesh] AND English[lang])

Two authors (PA and SGC) screened the titles and abstracts yielded by the search and retrieved the full texts of all potentially eligible studies. These were checked for compliance with the inclusion criteria, and eligible publications were selected (ET, SY, SGC, PAC). Disagreement was resolved by discussion or by consultation with the senior author (BA). The selection process was documented with a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart. Two review authors (PA and SGC) independently extracted data from each of the eligible studies. Data extracted from each study was double checked by a third and the senior author (ET and BA).

For dichotomous outcome measures, numbers of women with events in the control and intervention groups were used to calculate Mantel–Haenszel risk ratios, with 95% confidence intervals. A fixed or random effects model was used based on heterogeneity of the data as assessed by the I squareddh statistic. Multiple live births, pregnancies or gestational sacs in one woman counted as one event. For continuous outcome measures, the mean difference and its 95% confidence intervals were calculated.

When data were not suitable for a meta-analysis, the results of individual studies were summarized.

The GRADE system was used to assess the quality of available evidence. As cohort studies alongside RCTs were included, a formal risk of bias assessment tool was not used, and such studies were given a 'low quality' evidence directly.

The protocol for the present systematic review was registered in Prospero (PROSPERO 2019 CRD42019121621).

RESULTS

The electronic search returned 375 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, two of the studies were irrelevant and five studies compared different progestins with each other (FIGURE 1). In total, two prospective cohort (*Kuang et al., 2015*; *Iwami et al., 2018*), three retrospective cohort (*Zhu et al., 2015*; *2016*; *Yildiz et al., 2019*) and two RCTs (*Wang et al., 2016*; *Begueria et al., 2019*) were included.

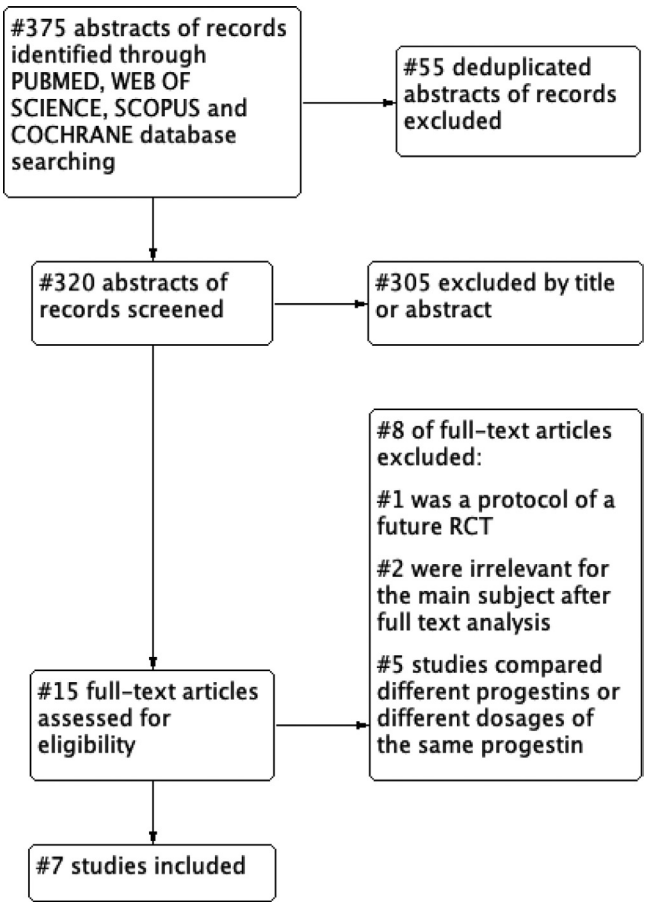

FIGURE 1 Study flow diagram.

The seven studies involved a total of 2047 women (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*; *Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*). Five studies included women undergoing ovarian stimulation for ART with own oocytes using GnRH analogues or progestins for pituitary suppression (*Zhu et al., 2015*; *2016*; *Kuang et al., 2015*; *Wang et al., 2016*; *Iwami et al., 2018*), two studies included oocyte donors (n = 303) and recipients (n = 499) (*Begueria et al., 2019*; *Yildiz et al., 2019*). Characteristics of included studies are presented in TABLE 1.

Four studies compared a progestin with a GnRH agonist: micronized progesterone versus triptorelin in a short GnRH agonist protocol (*Zhu et al., 2015*; *2016*), medroxyprogesterone acetate (MPA) versus triptorelin in a short GnRH agonist protocol (*Kuang et al., 2015*; *Wang et al., 2016*) and three studies compared a progestin with a GnRH antagonist (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*).

Zhu et al. (2015; *2016*) used 200 mg/day micronized progesterone; *Iwami et al. (2018)* used 20 mg/day dydrogesterone; and *Wang et al. (2016)* and *Kuang et al. (2015)* used 10 mg/day MPA to prevent premature ovulation. Oocyte donors were given 10 mg/day MPA (*Begueria et al., 2019*; *Yildiz et al., 2019*). In all but one of the included studies, progestins were started simultaneously with gonadotrophins (150–225 IU/day HMG or recombinant FSH) on cycle day 2 or 3. *Yildiz et al. (2019)* started progestin administration when the leading follicle diameter reached 14 mm or on the 7th day of stimulation, as in a flexible GnRH antagonist protocol.

In the progestin arms of five studies, good-quality embryos were cryopreserved at the cleavage stage, and poor-quality embryos were left for extended culture to blastocyst stage. Only embryos reaching good-quality blastocysts were later cryopreserved (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*; *Iwami et al. 2018*). Embryos were cryopreserved at different stages by *Begueria et al. (2019)*. All cryopreservation was with vitrification. Embryos derived from oocyte donors were transferred at different stages of embryo development, i.e. day 2 or 3 or blastocyst, fresh or cryopreserved to the recipients (*Begueria et al., 2019*). *Yildiz et al. (2019)* either cryopreserved oocytes for future use or transferred blastocysts derived from freshly inseminated oocytes from the donors.

COMPARISONS

Progestins versus GnRH antagonists

For primary outcome, live birth per woman starting stimulation cycle was not reported (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*). For secondary outcomes, live birth or ongoing pregnancy rate per woman was not reported (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*).

For live birth per embryo transfer, only one study, including oocyte donors, recipients of embryos derived from oocytes retrieved from MPA and GnRH antagonist cycles, had similar live birth rates (31/153 [20%] versus 42/155 [27%], respectively; RR 0.75, 95% CI 0.50 to 1.12) (*Begueria et al., 2019*). Of note, proportions of recipients who had cleavage or blastocyst stage embryos, as well as proportions of recipients who underwent one or two embryo transfers were similar between the two groups (*Begueria et al., 2019*).

Live birth or ongoing pregnancy rate per transfer was similar with progestins and GnRH antagonist protocols (RR 0.97, 95% CI 0.81 to 1.15; I^2 = 7%; three studies; 896 embryo transfer cycles) (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*) (FIGURE 2).

Women using autologous oocytes and donor oocytes were analysed separately. *Iwami et al. (2018)* reported a similar ongoing pregnancy rate per cryopreserved embryo transfer in progestin and GnRH antagonist groups with autologous oocytes (78/195 [40%] versus 77/202 [38.1%], respectively; RR 1.05, 95% CI 0.82 to 1.34; P = 0.70), and the pooled analysis of the two studies involving donor oocytes also showed similar live birth or ongoing pregnancy rates (RR 0.90, 95% CI 0.70 to 1.14; I^2 = 39%) (FIGURE 2).

Clinical pregnancy rate per embryo transfer was similar with progestin and GnRH antagonist protocols (RR 0.92, 95% CI 0.71 to 1.19, I^2 = 73%; three

TABLE 1 CHARACTERISTICS OF INCLUDED STUDIES

Author/ year	Design	Inclusion criteria	Exclusion criteria	Progestin group	Control group
Kuang et al. (2015)	Prospective cohort	• Age ≤42 years • Regular menstrual cycles • AFC >3 • FSH <10 IU/L	• FSH >10 IU/l or no AFC • PCOS • Endometriosis ≥Grade 3 • Hormonal treatment in the previous 3 months • Any functional ovarian cyst with oestradiol >100 pg/ml • Any contraindication to ovarian stimulation	HMG and MPA 10 mg Trigger: triptorelin 0.1 mg and HCG 1000 IU *n* = 150	Short protocol (HMG + triptorelin 0.1 mg) Trigger: HCG 2000–5000 IU *n* = 150
Zhu et al. (2015)	Retrospective cohort	• ≤38 years • Regular menstrual cycles • AFC >4 • FSH <10 IU/L	• FSH >10 IU/l or no AFC • PCOS • Endometriosis ≥Grade 3 • Hormonal treatments in the • previous 3 months • Any contraindication to ovarian stimulation • Documented cycles with no oocytes retrieved	HMG and MIP 200 mg Trigger: triptorelin 0.1 mg *n* = 187	Short protocol (HMG + triptorelin 0.1 mg) Trigger: HCG 3000 IU *n* = 187
Zhu et al. (2016)	Retrospective cohort	• ≤38 years • PCOS	• Documented ovarian failure • Endometriosis ≥Grade 3 • Any contraindication to ovarian stimulation • Documented cycles with no oocytes retrieved	HMG and MIP 200 mg Trigger: triptorelin 0.1 *n* = 123	Short protocol (HMG and triptorelin 0.1 mg) Trigger: HCG 3000 IU *n* = 77
Wang et al. (2016)	Randomized controlled trial	• Age 18-39 years • PCOS	• FSH >10 IU/l or no AFC • Endometriosis ≥Grade 3 • Hormonal treatment in the previous 3 months • Known poor ovarian response • Any contraindication to ovarian stimulation	HMG and MPA 10 mg Trigger: triptorelin 0.1 mg and HCG 1000 IU *n* = 60	Short protocol (HMG and triptorelin 0.1 mg) Trigger: HCG 2000 IU *n* = 60
Iwami et al. (2018)	Prospective cohort	• Age <41 years • AMH >1.0 ng/ml • First or second IVF/ ICSI	• Cycles with no oocyte retrieved • Endometriosis ≥Grade 3 • Any contraindication to ovarian stimulation	HMG and dydrogesterone 20 mg Trigger: buserelin and HCG 1000 IU *n* = 125	HMG Ganirelix or cetrorelix 0.25 mg Trigger: buserelin and HCG 1000 IU *n* = 126
Begueria et al. (2019)	Randomized controlled trial	• First time donors aged 18–35 years • AFC >8	• Irregular menstrual cycles • Hormonal treatment in the previous 3 months • Any functional ovarian cyst with oestradiol >70 pg/ml • Any medication interacting with MPA metabolism	Recombinant FSH and MPA 10 mg Trigger: triptorelin 0.3 mg *n* = 108 donors *n* = 153 recipients	Recombinant FSH and ganirelix 0.25 mg Trigger: triptorelin 0.3 mg *n* = 108 donors *n* =155 recipients
Yıldız et al. (2019)	Retrospective cohort	• Donors aged 20–35 years	• Any contraindication to ovarian stimulation	Recombinant FSH + MPA 10 mg Trigger: leuprolide acetate 1 mg *n* = 87[a] donors *n* = 86 recipients	Recombinant FSH + cetrorelix 0.25 mg Trigger: leuprolide acetate 1 mg *n* = 87[a] donors *n* = 105 recipients

[a] Same donors were stimulated with two different protocols.AFC, antral follicle count; HMG, human menopausal gonadotrophin; ICSI, intracytoplasmic sperm injection; MIP, micronized progesterone; MPA, medroxyprogesterone acetate; PCOS, polycystic ovary syndrome.

studies; 896 embryo transfer cycles) (FIGURE 3).

When women using autologous oocytes and donor oocytes were analysed separately, *Iwami et al. (2018)* reported similar clinical pregnancy rates with autologous oocytes in progestin and GnRH antagonist groups (103/195 [52.8%] versus 100/202 [49.5%], respectively (RR 1.07, 95% CI 0.88 to 1.29), and the recipients of fresh oocytes in the donor studies also had similar clinical pregnancy rates in progestin and GnRH antagonist groups (RR 0.84; 95% CI 0.55 to 1.28) (*Begueria et al., 2019*; *Yildiz et al., 2019*) (FIGURE 3).

For the number of oocytes and metaphase two oocytes collected, two studies reported similar numbers of oocytes and metaphase two oocytes collected from progestin and GnRH antagonist arms. *Iwami et al. (2018)* reported collection of 10.7 ± 6.6 versus 11.1 ± 5.1 oocytes, and 8.5 ± 5.4 versus 8.7 ± 4.3 metaphase two oocytes from progestin and GnRH antagonist cycles, respectively ($P > 0.05$ for all comparisons). *Begueria et al. (2019)* reported collection of mean of 15.1 versus 14.7 metaphase two oocytes, from progestin and GnRH antagonist groups, respectively. They did not report SD but reported the mean difference with 95%

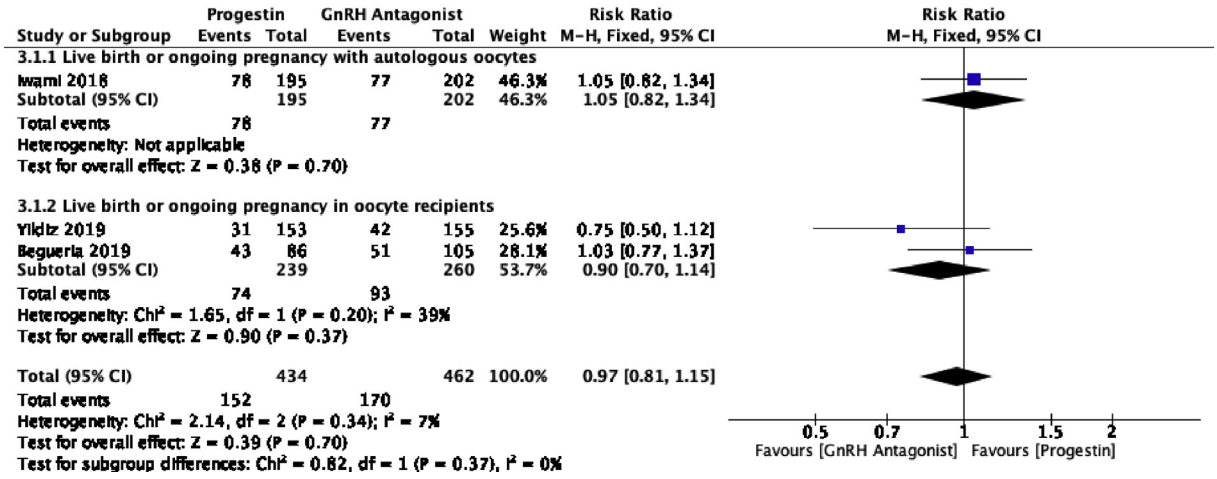

FIGURE 2 Progestin versus gonadotrophin releasing hormone antagonists: live birth or ongoing pregnancy rate per embryo transfer.

CI as 0.48; –1.83 to 2.78, which excluded a significant difference at 0.05 level.

In contrast, *Yildiz et al. (2019)* reported collecting significantly more oocytes with progestin than GnRH antagonist (median 33 [25th to 75th percentile = 21–39] versus 26 [18–36] in progestin and GnRH antagonist arms, respectively; $P = 0.02$) and metaphase two oocytes (24 [17–34] versus 21 [15–28] in progestin and GnRH antagonist arms, respectively; $P < 0.01$).

Duration of stimulation was similar in both groups in all three studies (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*). *Iwami et al. (2018)* reported 14.74 ± 1.99 versus 14.11 ± 1.73 days in progestin and GnRH antagonist arms, respectively ($P = 0.08$); *Begueria et al. (2019)* reported 11.2 ± 2.1 versus 11.2 ± 2.4 days ($P = 0.98$) and *Yildiz et al. (2019)* reported 11 (10–11) versus 11 (10–11) days ($P = 0.13$) for MPA and GnRH antagonist groups, respectively.

For total gonadotrophin consumption, *Iwami et al. (2018)* used on average 1957.30 ± 682.86 IU in the progestin group and 1519.84 ± 541.86 IU in the GnRH antagonist group ($P < 0.001$). *Begueria et al. (2019)* used 2162 ± 495.2 IU versus 2163 ± 555 IU ($P = 0.99$), and *Yildiz et al. (2019)* used 2475 (2250–2475) versus 2400 (2250–2475) ($P = 0.35$) in the progestin and GnRH antagonist groups, respectively.

Adverse events

Ectopic pregnancy per embryo transfer

Although no ectopic pregnancies were reported in the studies by *Iwami et al. (2018)* and *Yildiz et al. (2019)*, *Begueria et al. (2019)* did not report the incidence of ectopic pregnancy in oocyte recipients.

Miscarriage rates

Miscarriage rate per pregnancy was similar in progestin and GnRH antagonist groups (RR 1.03, 95% CI 0.65 to 1.64, $I^2 = 0\%$; three studies; 442 pregnancies) (*Iwami et al., 2018*; *Begueria et al., 2019*; *Yildiz et al., 2019*) (FIGURE 4).

When women using autologous oocytes and donor oocytes were analysed separately, *Iwami et al. (2018)* reported similar miscarriage rates in the progestin and GnRH antagonist groups, (25/103 [24.3%] versus 23/100 [23%], respectively; RR 1.06, 95% CI 0.64 to 1.73), and the recipients of fresh oocytes in the donor studies also had similar miscarriage rates in progestin and GnRH antagonist groups (RR 1.0, 95% CI 0.58 to 1.70) (*Begueria et al., 2019*; *Yildiz et al., 2019*) (FIGURE 4).

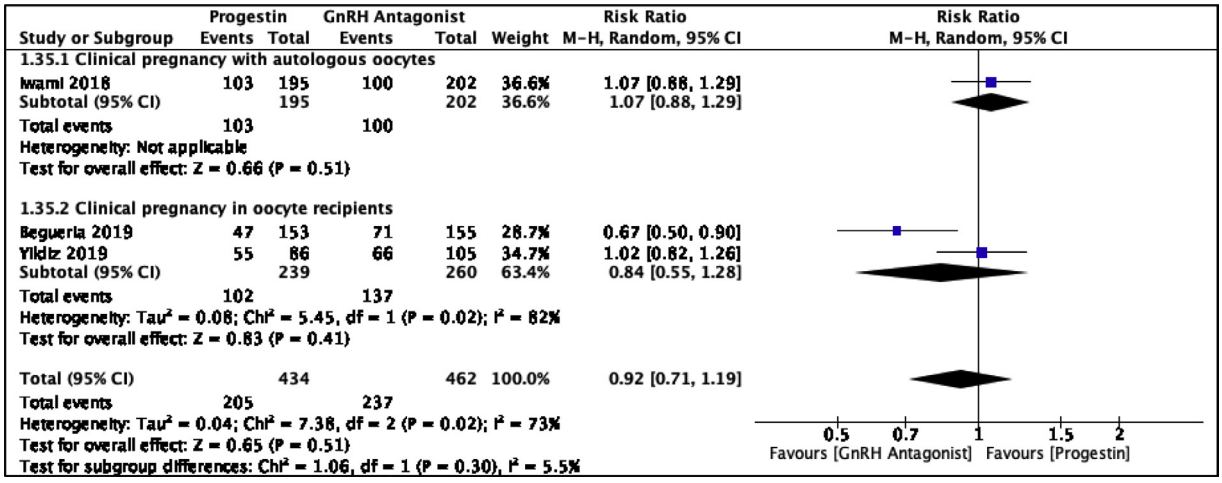

FIGURE 3 Progestin versus gonadotrophin releasing hormone antagonists: clinical pregnancy rate per embryo transfer.

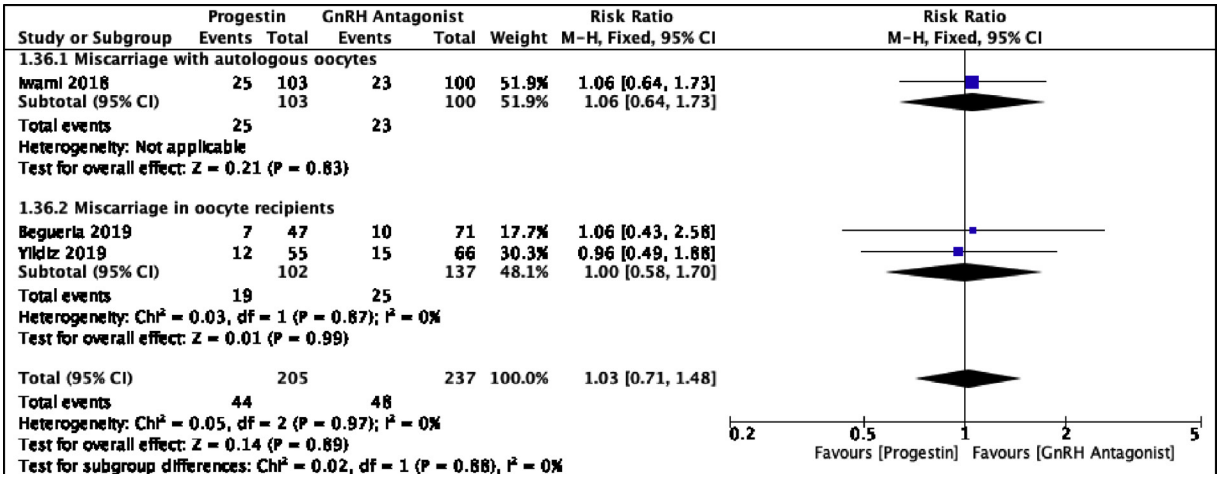

FIGURE 4 Progestin versus gonadotrophin releasing hormone antagonist: miscarriage rate per pregnancy.

Multiple pregnancy per embryo transfer

Iwami et al. (2018) reported similar multiple pregnancy rates in the progestin and GnRH antagonist groups (3/195 [1.5%] versus 2/202 [1%], respectively; RR 1.55, 95% CI 0.26 to 9.20). *Yildiz et al. (2019)* also reported similar multiple pregnancy rates in oocyte recipients from progestin-primed ovarian stimulation (PPOS) and GnRH antagonist cycles (18/86 [20.9%] versus 20/105 [24.8%], respectively, RR 0.85, 95% CI 0.50 to 1.44).

Ovarian hyperstimulation syndrome per stimulation cycle

Iwami et al. (2018) reported similar OHSS rates in the progestin and GnRH antagonist groups (1/125 [0.8%] versus 1/126 [0.8%], respectively; RR 1.01, 95% CI 0.06 to 15.94). *Begueria et al. (2019)* reported no serious adverse events, including OHSS, and no cases of OHSS were reported by Yildiz *et al*. (personal communication, unpublished data) (*Yildiz et al., 2019*).

Progestins versus GnRH agonist

For primary outcome, live birth rate per woman starting stimulation was not reported. For secondary outcome, live birth rate or ongoing pregnancy rate per woman starting stimulation was not reported. Live birth rate per embryo transfer was similar in progestin and GnRH agonist groups (RR 0.83, 95% CI 0.39 to 1.78, I^2 = 87%; two studies; 445 embryo transfer cycles) (*Kuang et al., 2015*; *Zhu et al., 2016*) (FIGURE 5).

Live birth rate or ongoing pregnancy per embryo transfer was significantly higher with progestin than GnRH agonist (RR 1.49, 95% CI 1.16 to 1.91, I^2 = 0%; four studies; 1045 embryo transfer cycles) (*Kuang et al., 2015*; *Wang et al., 2016*; *Zhu et al., 2015*; *2016*; *Zhu et al., 2016*) (FIGURE 6).

Clinical pregnancy rate per embryo transfer was significantly higher with progestin than GnRH agonist (RR 1.14, 95% CI 1.02 to 1.28, I^2 = 0%; four studies, 1045 embryo transfer cycles) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*) (FIGURE 7).

Number of oocytes per woman was similar in progestin and GnRH agonist cycles (mean difference 0.42, 95% CI −0.40 to 1.24, I^2 = 0; four studies; 994 oocyte collection cycles) (Supplementary Figure 1) (*Kuang et al., 2015*; *Wang et al., 2016*; *Zhu et al., 2015*; *2016*).

Number of metaphase two oocytes per woman was similar in progestin and GnRH agonist cycles (mean difference −0.06, 95% CI −0.18 to 0.07, I^2 = 0; four studies; 994 oocyte collection cycles) (Supplementary Figure 2) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

Duration of stimulation was significantly longer with the progestin than GnRH agonist (mean difference 0.61 days, 95% CI 0.33 to 0.89; I^2 = 41%; four studies; 994 stimulation cycles) (Supplementary Figure 3) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

Total gonadotrophin consumption was significantly higher in progestin than GnRH agonist cycles (mean difference

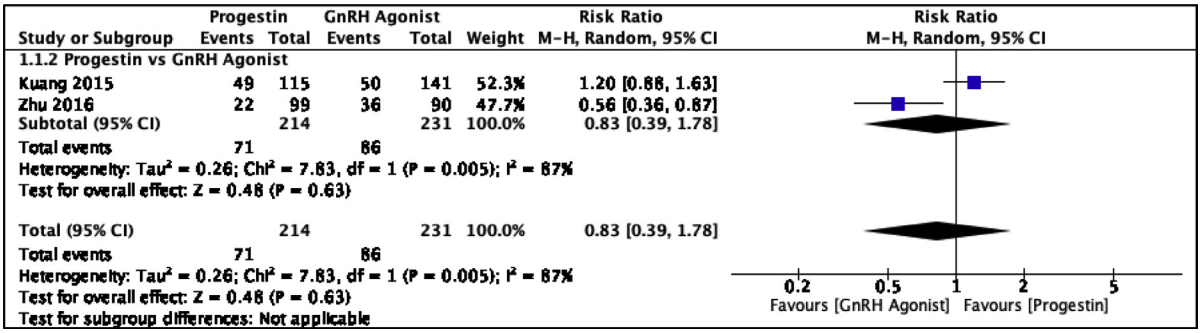

FIGURE 5 Progestins versus gonadotrophin releasing agonists: live birth rate per embryo transfer.

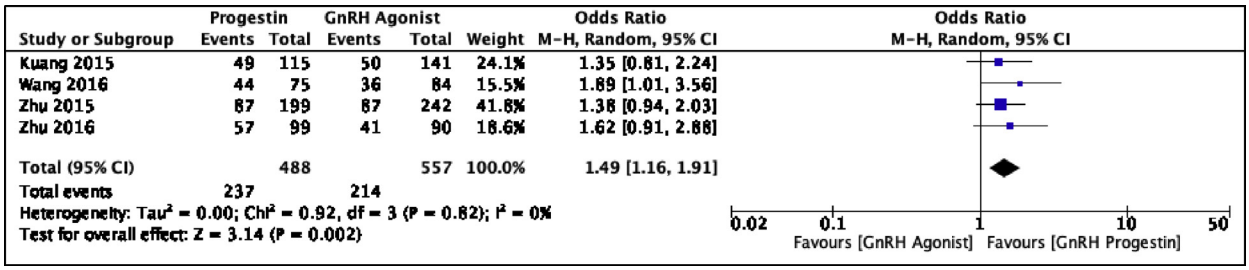

FIGURE 6 Progestin versus gonadotrophin releasing hormone agonist: live birth or ongoing pregnancy rate per embryo transfer.

433.2 IU, 95% CI 311.11 to 555.19, I^2 = 65%; four studies; 994 stimulation cycles) (Supplementary Figure 4) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*).

Adverse events

Ectopic pregnancy per embryo transfer was similar between progestin and GnRH agonist cycles (RR 2.26, 95% CI 0.69 to 7.43, I^2 = 0%; four studies; 1045 embryo transfer cycles) (FIGURE 8) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

Miscarriage rate per pregnancy was similar in progestin and GnRH agonist cycles (RR 0.77, 95% CI 0.46 to 1.31; four studies, I^2 = 0%) (FIGURE 9) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

Multiple pregnancy rate per embryo transfer was similar in progestin and GnRH agonist cycles (RR 1.05, 95% CI 0.61 to 1.81; four studies, I^2 = 48%,) (FIGURE 10) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

OHSS per stimulation cycle was similar in progestin and GnRH agonist cycles (RR 0.41, 95% CI 0.08 to 2.02; four studies; I^2 = 0%) (FIGURE 11) (*Kuang et al., 2015*; *Zhu et al., 2015*; *2016*; *Wang et al., 2016*).

DISCUSSION

The results of the present systematic review suggest 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 cryopreserved embryo transfers. Safety profile of progestins seem similar with GnRH analogues. The quality of evidence concerning their effectiveness in oocyte yield and live birth rate compared with GnRH analogues, however, is yet low and more research is strongly needed.

First and foremost, only two RCTs have been published, only one of which compared a progestin with the current standard of care, a GnRH antagonist, for pituitary suppression (*Wang et al., 2016*; *Begueria et al., 2019*). Moreover, the only RCT that compared a progestin with a GnRH antagonist did so in oocyte donors, who did not undergo embryo transfer themselves (*Begueria et al., 2019*). Intriguingly, although oocyte donors receiving a progestin or a GnRH antagonist produced similar number of oocytes, the recipients of embryos derived from progestin primed cycles had significantly lower clinical pregnancy, yet statistically similar live birth rates with recipients of embryos derived from GnRH antagonist cycles (*Begueria et al., 2019*). In contrast, *Yildiz et al. (2019)* reported similar clinical pregnancy rates in oocyte recipients from PPOS and GnRH antagonist cycles. The study by *Yildiz et al. (2019)* is retrospective, as they compared two cycles of the same oocyte donors, one with PPOS and one with GnRH antagonist; however, baseline characteristics of the donors were essentially the same, as would be expected from a RCT. This intriguing observation in the RCT involving donors is in contrast with the results from other studies that have been included in this meta-analysis, i.e. the non-randomized studies comparing progestins with GnRH agonists reported clinical pregnancy rates per embryo transfer favouring progestins. It is also methodologically problematic. First and foremost, comparing outcomes between the recipients, while the donors were randomized to receive progestin or GnRH antagonist, comprises a unit of analysis error. Despite the recipients of embryos derived from progestin or GnRH antagonist primed cycles being similar for the characteristics reported in the original publication, it is impossible to rule out other systematic differences between the recipients, as the latter was not randomly allocated. Therefore, this finding should be interpreted with caution, until data from other properly designed studies become available. It is noteworthy that, livebirth rates, the single most important outcome measure that trumps all others in ART, were similar between the two groups of recipients (*Begueria et al., 2019*). In addition, pooled analysis comparing live birth or ongoing pregnancy from both donor studies also reported similar results. Moreover, several studies have reported similar blastocyst euploidy rates, pregnancy and live birth rates with the transfer of embryos derived from oocytes collected in the luteal phase and from oocytes collected after the follicular

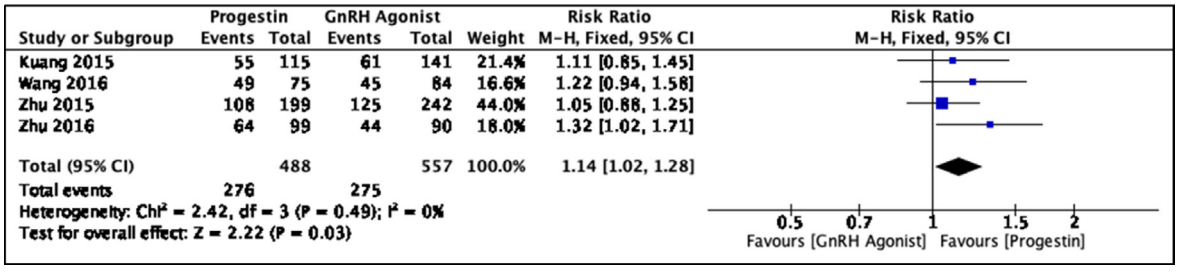

FIGURE 7 Progestin versus gonadotrophin releasing hormone agonist: clinical pregnancy rate per embryo transfer.

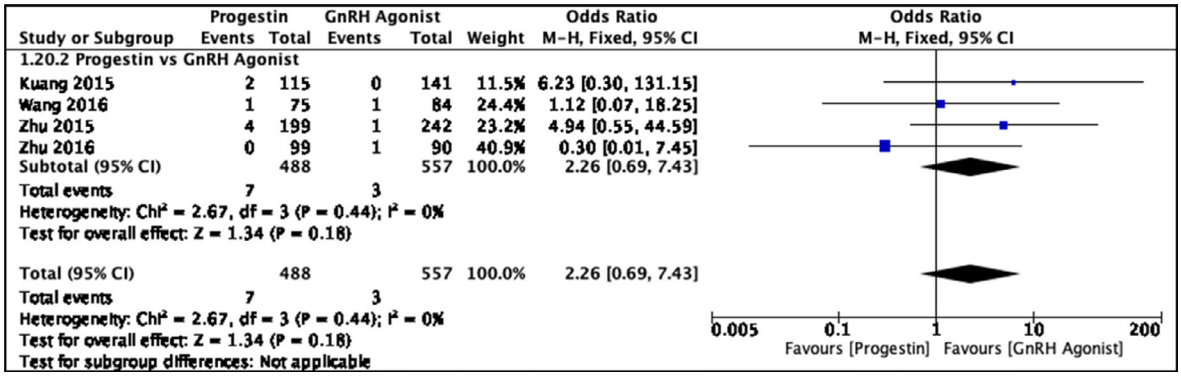

FIGURE 8 Progestin versus gonadotrophin releasing hormone agonist: ectopic pregnancy per embryo transfer.

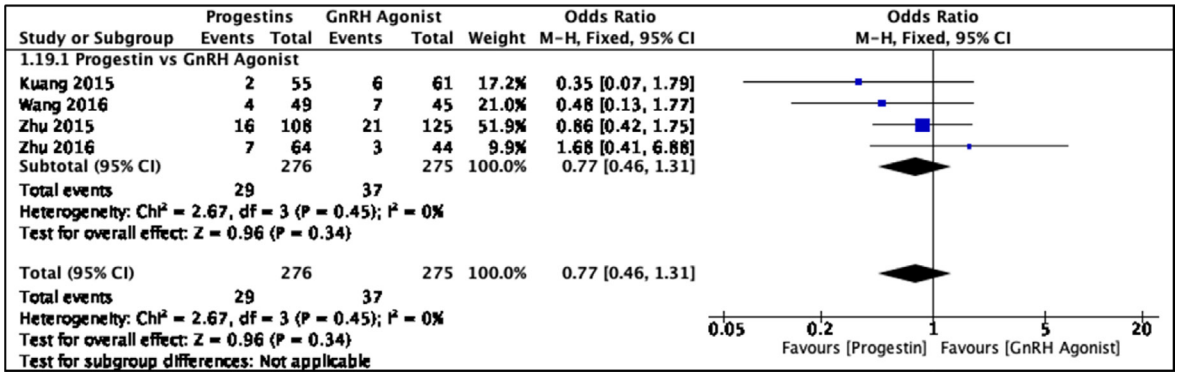

FIGURE 9 Progestin versus gonadotrophin releasing hormone agonist: miscarriage rate per pregnancy.

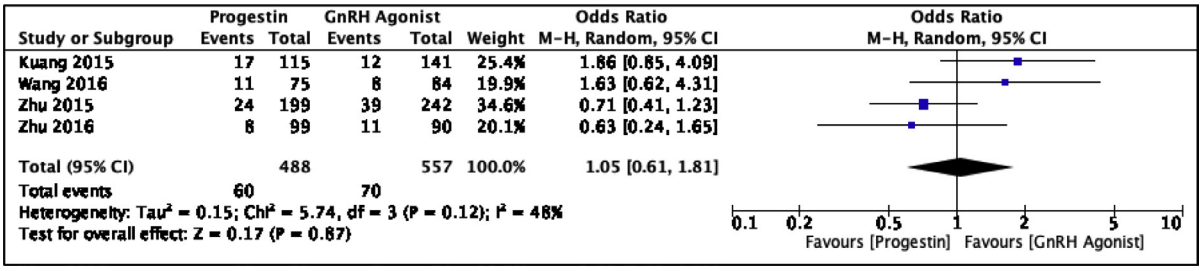

FIGURE 10 Progestin versus gonadotrophin releasing hormone agonist: multiple pregnancy rate per embryo transfer.

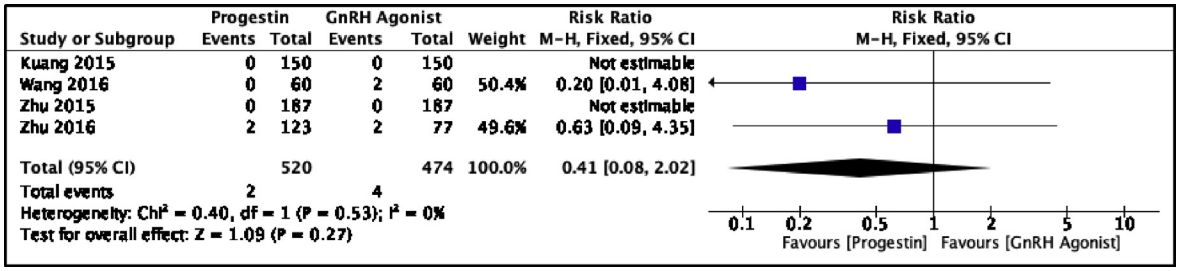

FIGURE 11 Progestin versus gonadotrophin releasing hormone agonist: ovarian hyperstimulation syndrome rate per stimulation cycle.

phase. In the former, developing follicles are exposed to high levels of endogenous progesterone, and yet seem to preserve their potential (*Ubaldi et al., 2016*; *Vaiarelli et al., 2018*). Arguably, synthetic progestins or exogenous progesterone may have different effects on growing follicles than endogenous progesterone.

A recent publication reporting obstetric outcome and the prevalence of congenital anomalies in children born from PPOS cycles included 546 children and is reassuring (*Zhu et al., 2017*). Yet, more RCTs comparing progestins with GnRH analogues are clearly needed.

Compared with the short GnRH agonist protocol, stimulation with PPOS lasted on average 0.6 of a day longer but this difference can be regarded as clinically negligible. Similarly, PPOS seemed to require on average 433 IU more gonadotrophins, despite yielding similar numbers of oocytes. Whether this would be the case compared with the more common long GnRH agonist protocol, or comprises an economic disadvantage, needs more study. Indeed, a cost-effectiveness study comparing PPOS with the short GnRH agonist and GnRH antagonist protocols suggested that PPOS was associated with significantly higher cost per live birth when conventional protocols using GnRH analogues were completed with a fresh transfer (*Evans et al., 2019*). The short GnRH agonist protocol was still associated with a lower cost per live birth than PPOS even in planned freeze all cycles. PPOS was only more cost effective than the GnRH antagonist protocol in planned freeze all cycles. The underlying assumptions of these cost-effectiveness analyses were similar live birth rates with PPOS, the short GnRH agonist and GnRH antagonist protocols, and 462 IU higher gonadotrophin consumption with PPOS than the protocols using GnRH analogues. The increased cost of PPOS cycles were caused by increased gonadotrophin consumption and 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). These results, however, should be taken with caution, because our meta-analysis suggest significantly higher live birth or ongoing pregnancy rate per transfer with PPOS than the short GnRH agonist protocol, possibly violating the assumption of equal live birth rates with both protocols in the cost-effectiveness study; the three studies directly comparing PPOS with GnRH antagonists (*Begueria et al., 2019*, *Iwami et al., 2018*, *Yildiz et al., 2019*) were not used to inform the assumptions of the cost-effectiveness study (*Evans et al., 2019*), and even though we were not able to pool the results they do not seem to consistently corroborate the assumption of higher gonadotrophin consumption with PPOS than GnRH antagonist cycles, i.e. two of the three studies reported similar gonadotrophin consumption with both protocols (*Begueria et al., 2019*; *Yildiz et al., 2019*). Moreover, progestins were started early in the follicular phase simultaneously with gonadotrophins in all but one of the included studies. The findings of *Yildiz et al. (2019)* suggest that later commencement of progestin with the 'flexible PPOS', can provide less suppression of endogenous gonadotrophins and may avoid longer duration of stimulation and higher gonadotrophin consumption, while yielding more oocytes in contrast to the other studies. If confirmed in other studies, the increased number of oocytes can possibly result in higher cumulative live birth rates. All these areas require further research, and we do not think that PPOS combined with an elective freeze all approach is currently justified for all ART cycles, because avoiding a fresh transfer does not seem beneficial in the absence of a medical indication, e.g. high ovarian response risking both decreased live birth rates and increased risk of OHSS (*Ata and Seli, 2017*).

The protocol of the present review was registered in Prospero, and a transparent reproducible methodology was followed. The quality of the available evidence and the authority of the present systematic review can only be as high as that of the original studies. The presence of a limited number of trials, most of which are not randomized nor accounts for every woman starting stimulation are drawbacks, preventing definitive conclusions on the subject. In the present systematic review, an unbiased overview of the current literature is, however, presented, and gaps in knowledge for future research are identified. 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.

In conclusion, if future high-quality trials confirm the findings of the present review, progestins can become the agent of choice for pituitary suppression in ovarian stimulation cycles when a fresh embryo transfer is not intended, e.g. 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.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.01.027.

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