Double or dual stimulation in poor ovarian responders: where do we stand?

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Abstract: Recent advances in our recognition of two to three follicular waves of development in a single menstrual cycle has challenged the dogmatic approach of ovarian stimulation for in vitro fertilization starting in the early follicular phase. First shown in veterinary medicine and thereafter in women, luteal phase stimulation–derived oocytes are at least as competent as those retrieved following follicular phase stimulation. Poor ovarian responders still remain a challenge for many decades simply because they do not respond to ovarian stimulation. Performing follicular phase stimulation and luteal phase stimulation in the same menstrual cycle, named as double stimulation/dual stimulation, clearly increases the number of oocytes, which is a robust surrogate marker of live birth rate in in vitro fertilization across all female ages. Of interest, apart from one study, the bulk of evidence reports significantly higher number of oocytes following luteal phase stimulation when compared with follicular phase stimulation; hence, performing double stimulation/dual stimulation doubles the number of oocytes leading to a marked decrease in patient drop-out rate which is one of the major factors limiting cumulative live birth rates in such poor prognosis patients. The limited data with double stimulation/dual stimulation–derived embryos is reassuring for obstetric and neonatal outcome. The mandatory requirement of freeze-all and lack of cost-effectiveness data are limitations of this novel approach. Double stimulation/dual stimulation is an effective strategy when the need to obtain oocytes is urgent, including patients with malignant diseases undergoing oocyte cryopreservation and patients of advanced maternal age or with reduced ovarian reserve.

Keywords: double stimulation, dual stimulation, number of oocytes, poor ovarian response

Introduction

Despite the remarkable progress in assisted reproductive technologies, management of poor ovarian responders (POR) still remains a challenge, simply because they do not respond to treatment. The prevalence of POR varies from 5.6% to 35.1%,1–5 depending on differences in the definition of poor response. Although many strategies have been proposed to treat such poor prognosis patients, there is still no clear superiority of one treatment versus another to enhance reproductive outcome.

Concise definition and stratification of subgroups of POR patients is essential for inter-study comparison of various interventions. The Bologna consensus criteria was first described in 2011 under the auspices of the European Society of Human Reproduction and Embryology (ESHRE) and has been a great achievement for classifying such patients.6 Before this criteria, it is of interest that more than 40 different definitions for poor ovarian response have been used among 47 randomized trials and no more than 3 trials used the same definition, whereas even trials from the same research groups used different definitions across different trials.7 As expected, a huge heterogeneity in study populations of the available studies and meta-analyses was seen, resulting in adoption of interventions of ambiguous value. Although the Bologna criteria was an important step, there is still marked heterogeneity of various subgroups regarding live birth rates (LBR).8–10 In our study of 821 POR patients fulfilling Bologna
criteria, prognosis, in general, was poor with less than 10% of LBR. However, the LBRs were not homogeneous and ‘young proven’ PORs had the most favorable pregnancy outcome.

Overall, the pregnancy rates attained with in vitro fertilization (IVF) in POR patients are low being less than 8%. Polyzos and colleagues in a cohort of 485 PORs reported an LBR per cycle of 7.1% in patients <40 years and 5.2% in women ≥40 years old; in this study, the only independent variable related to the LBR was the number of oocytes. Indeed, the number of eggs is a robust surrogate outcome for LBR in IVF across all female age groups; in women aged 35–37, the estimated effect of collecting three oocytes compared with two oocytes was a relative increase in the observed LBR by 28%. Thus, retrieving even one more oocyte in this patient population makes a huge difference in prognosis and any attempt that would increase the number of eggs would be a very important step to enhance reproductive outcome.

High drop-out rate is one of the major factors limiting the cumulative LBRs in POR patients. Although the etiologic factors for drop-out may differ from one population to another, poor prognosis per se is an important contributory factor, especially in POR patients. Pooling of oocytes and embryos have been reported to decrease the drop-out rate and hence increase the cumulative LBRs.

Establishment of efficient vitrification techniques at every stage of preimplantation embryo development along with our enhanced understanding of the physiologic, biochemical, and molecular mechanisms underlying antral follicular wave dynamics have permitted the first description of double stimulation (DS) in 2013 and a modified version of DS couples with preimplantation genetic testing for aneuploidy (PGT-A), named dual stimulation (DuoStim) in 2016, followed by several studies from different centers. The goal of this mini-review article is to cover the available evidence of DS/DuoStim in POR patients.

**Search procedure**

Criteria for inclusion were established before literature search. Inclusion was limited to studies that were published of randomized controlled trials (RCTs), prospective/retrospective cohort studies and case series reports comparing the ovarian stimulation (OS) characteristics, embryological data, and pregnancy outcome between follicular phase stimulation (FPS) and luteal phase stimulation (LPS) in the same ovarian cycle. A thorough search of Pubmed database was performed using combinations of the following keywords: ‘IVF’, ‘In vitro fertilization’, ‘Intracytoplasmic Sperm Injection’, ‘ICSI’, ‘Assisted Reproductive Techniques’, ‘Assisted Reproductive Technologies’, ‘ART’, ‘Follicular Wave’, ‘DuoStim’, ‘Luteal phase stimulation’, ‘Luteal phase ovarian stimulation’, ‘Dual stimulation’, ‘Double stimulation’, ‘Ovarian stimulation’, ‘Fertility preservation’. After screening from the title and abstract, we excluded the data published as abstract, meeting proceeding, book chapter, review articles, and articles published in languages other than English. Finally, we included 12 studies comparing FPS and LPS in the same ovarian cycle (Table 1).

**Physiologic basis of DS/DuoStim: theories of follicular development**

The physiologic mechanisms underlying recruitment and selection of antral follicles in women are not fully elucidated. Three distinct theories of follicular recruitment have been proposed, including continuous recruitment (theory 1), single recruitment episode (theory 2), and follicular waves (theory 3). Single recruitment episode and follicular waves theories are, indeed, part of the cyclic recruitment concept. According to the continuous recruitment theory (theory 1), small antral follicles ≤4–6 mm are recruited to grow continuously, at all stages of reproductive life, independent of gonadotropins. The follicle destined to ovulate is selected, by chance, from the continuous supply of antral follicles, by being at the right stage of maturity to respond to the rise in follicle-stimulating hormone (FSH) that occurs following luteal regression. According to the single recruitment episode theory (theory 2), a cohort of 2–5 mm follicles is recruited from a continuous supply of antral follicles once during each menstrual cycle. Follicular waves have been described in veterinary medicine, although, some species-specific differences appear to exist. In a large population of healthy women, emergence of follicular waves is...
a wave of 4–14 follicles $\geq 4–5$ mm was detected either two or three times during the interovulatory interval; $^{22}$ 68% of women exhibited two waves of follicle recruitment during the interovulatory interval, while the remaining 32% exhibited three waves (Figure 1(a) and (b)). In women with two follicular waves, an anovulatory wave emerged at the time of ovulation (i.e. early luteal phase) followed by emergence of the ovulatory wave during the early follicular phase. In women with three waves, an anovulatory wave emerged at the time of ovulation, a second anovulatory wave emerged during the mid to late luteal phase, and a third wave (the ovulatory wave) emerged in the early to mid-follicular phase. $^{22}$ The wave theory challenges the classical concept of folliculogenesis and is the basis for DS/DuoStim.

**How to perform double/dual stimulation?**

DS/DuoStim, with the intention to increase the number of retrieved eggs, is performed in a single menstrual cycle and composed of FPS and LPS. Although POR patients are the primary target, fertility preservation cases, in whom time is an important issue, may also benefit from this approach.

The recent available evidence suggests that, in POR patients, mild OS regimens (low-dose gonadotropins with/without oral agents), when compared with traditional OS protocols, offer comparable reproductive outcome albeit lower cost. $^{45,46}$ Across all the available studies on DS/DuoStim, different OS protocols have been described for FPS and LPS. Regarding FPS, luteal estrogen priming may be used to promote synchronization and coordination of follicular growth. $^{47,48}$ Either mild or conventional OS regimens can be employed for FPS and LPS. For mild OS, clomiphene citrate (CC), letrozole (LE) with/without low-dose exogenous gonadotropins can be used. Conventional OS using a 225–450 IU daily dose of exogenous FSH with/without luteinizing hormone (LH)/LH-like activity can also be used for FPS and LPS.

Different strategies can be employed to avoid premature LH surge during FPS and LPS, including GnRH-antagonist (GnRH-ant) use, exogenous progestins and/or Ibuprofen. A flexible GnRH-ant scheme is the most commonly employed strategy; GnRH-ant is started when the leading follicle attains a mean diameter of 12–14 mm and is continued until and including the day of triggering. Exogenous progestins may also be used for this purpose, especially during LPS, not only to avoid premature LH surge but also to avoid menses during oocyte retrieval to decrease the risk of infection. $^{25,29}$ Although Ibuprofen is used in some studies, the precise role to avoid premature ovulation in this patient population needs to be proven in further studies. $^{50,51}$

GnRH-agonist (GnRH-a) is most commonly used to trigger final oocyte maturation for both FPS and LPS. Dual/double triggering has been recently suggested to increase the number of eggs retrieved and enhance reproductive outcome in POR patient undergoing IVF. $^{52–54}$ In a retrospective study of 384 cycles fulfilling Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) Group 4 patients, the dual triggering was associated with significantly higher oocyte yields compared to single triggering.
Table 1. The available studies with their design, follicular/luteal phase stimulation protocols, modes of trigger and conclusions.

| Author            | Design               | Inclusion criteria                                                                 | N  | FPS Protocol                               | FPS Trigger    | LPS Protocol                               | LPS Trigger    | Conclusions                  |
|-------------------|----------------------|-------------------------------------------------------------------------------------|----|--------------------------------------------|----------------|--------------------------------------------|----------------|-----------------------------|
| Kuang and colleagues25 | Pilot study          | At least two of the following criteria: (1) >40 years old, (2) history of ovarian surgery, (3) history of poor response, ≤3 oocytes with conventional stimulation, (4) AFC ≤<5, day 2-3 FSH 10–19 IU/L | 38 | CC: 25 mg/day [from D3 to trigger-1 day] + LE: 2.5 mg/day [from D3 for 4 days] + hMG: 150 IU [from D3, every other day] + ibuprofen 0.6 g on the trigger day and trigger +1 day | GnRH-a         | LE: 2.5mg/day + [from OPU/OPU +1 day until at least one follicle reaches 12 mm] + hMG 225 IU/day [from OPU/OPU +1 day] + MPA 10 mg/day + ibuprofen 0.6 g on the trigger day and trigger +1 day | GnRH-a         | Significantly more oocytes after LPS |
| Ubaldi and colleagues24 | Prospective noninferiory | AFC ≤<6 + AMH <1.5 mg/ml and/or ≤5 oocytes retrieved in previous cycle | 51 | rec-FSH 300 IU/day + rec-LH 75 IU/day [from D3] + GnRH-ant [when the leading follicle reaches 13–14 mm] | GnRH-a         | rec-FSH 300 IU/day + rec-LH 75 IU/day [from OPU + 5 day] + GnRH-ant [when the leading follicle reaches 13–14 mm] | GnRH-a         | Number of oocytes, M-2 oocytes, fertilization, blastulation and euploidy rates comparable with FPS and LPS. Increased yield of >1 euploid blastocyst with DuoStim |
| We and colleagues26 | Retrospective         | At least two of the following criteria: (1) >40 years old, (2) history of poor response, ≤3 oocytes with conventional stimulation, (3) AFC ≤<6 | 23 | CC: 50 mg or LE: 2.5 mg/day [from D2, for 5 days] + hMG:75–150 IU/day [following CC or LE from D2] Medication to avoid LH surge is NA | GnRH-a         | CC: 50 mg/day or LE: 2.5mg/day [from OPU + 1 day to 1 follicle reaches 12 mm] + hMG:225 IU/day + MPA 10 mg/day | 10,000 IU hCG | Significantly more oocytes collected after LPS |
| Zhang and colleagues26 | Retrospective         | At least two of the following criteria: (1) >40 years old or any other risk for POR, (2) history of poor response, ≤3 oocytes with conventional stimulation, (3) AFC ≤<5–6 or AMH <0.5–1.1 ng/ml | 153 | CC 50 mg/day [from D3 until triggering day] + hp-FSH 150 IU/day [if the follicles grow <1 mm/day] + ibuprofen 0.3 g every 6 h from the trigger to OPU day | GnRH-a         | hp-FSH 150–225 IU/day | 10,000 IU hCG | Significantly more oocytes and embryos following LPS. Significantly higher implantation rate with LPS-derived embryos |
| Rashtian and Zhang27 | Retrospective         | Day 3 FSH >15 IU/ml + AFC ≤<8 and at least one failed conventional IVF cycle | 69 | Oral contraceptive pill for at least 1 week before starting FPS, CC: 50 mg/day [until the trigger day] + LE: 2.5 to 4 mg/day [for 3 days] + FSH: 75 IU/day + GnRH-ant [when the estradiol level] >500 pg/ml or the follicle reaches >14 mm | GnRH-a         | CC:50 mg day + LE: 2.5mg/day + FSH: 75 IU/day [from OPU + 1 day] Medication to avoid LH surge is NA | hCG            | Similar number of oocytes at FPS and LPS; performing DS doubles the number of oocytes when compared with FPS-only. |
| Zhang and colleagues27 | Retrospective         | At least 2 of the following criteria: (1) >40 year old or any other risk factor for POR, (2) history of poor response, ≤3 oocytes with a conventional stimulation, (3) AFC ≤<5–7 or AMH <0.5–1.1 ng/ml | 61 | CC 50–100 mg/day [from D3, for 4 days] + hMG 75–150 IU/day [from D3] Medication to avoid LH surge is NA | 250 µg rec-hCG | CC 50–100 mg/day + hMG 75 IU–150/day [from OPU + 2–7 days] + Hydrogesterone 20mg/day | NA             | Significantly more oocytes albeit lower M-2 rate with LPS. Similar CPR and LBR with FPS- and LPS-derived embryos. |

(Continued)
| Author and colleagues | Design | Inclusion criteria | N | FPS Protocol | FPS Trigger | LPS Protocol | LPS Trigger | Conclusions |
|-----------------------|--------|-------------------|---|--------------|-------------|--------------|-------------|-------------|
| Jin and colleagues | Retrospective | At least two following criteria: (1) 40 years old, (2) history of poor response, <3 oocytes with conventional stimulation, (3) FSH ≥ 12 mIU/mL, AMH < 1.2 ng/mL or AFC ≤ 6 | 76 | CC 50–100 mg/day or LE: 5 mg/day (from D3 for 5 days) + hMG: 150–300 IU/day (from D3), GnRH-ant: 0.125 mg/day when the follicle reaches 12 mm or LH ≥ 8 IU/L | GnRH-a or hCG (5000–10,000 IU) | CC 50–100 mg/day + hMG 190–300 IU/day (from OPU + 3 days) | 5000–10,000 IU hCG | Significantly higher number of oocytes and embryos with LPS when compared with FPS. Simlar pregnancy outcome with FPS- and LPS-derived embryos. |
| Madani and colleagues | Prospective | <3 oocytes with conventional stimulation + at least one of the following criteria: (1) ≥ 40 years old or other risk factors for POR (2) AFC ≤ 5–7 or AMH < 0.5–1.1 ng/mL | 121 | CC 25 mg/day (from D3 to trigger-1 day) + LE: 2.5 mg/day (from D3, for 5 days) + hMG: 150 IU (from D3) every other day + Ibuprofen 0.6 g on the trigger day and trigger + 1 day | GnRH-a | LE: 2.5 mg/day (from OPU + 1 day until at least one follicle reaches 14 mm) hMG: 225 IU/day (from OPU + 1 day) + Ibuprofen 0.6 g on the trigger day and trigger + 1 day | GnRH-a | DS is time efficient and patient friendly |
| Alsberg and colleagues | Retrospective | Bologna criteria | 54 | Single-dose Coriofollitropin alfa 150 mg (D3-1 day) + rec-FSH 300–375 IU/day (from stimulation D3) | rec-FSH, urinary hCG or GnRH-a | Single-dose Coriofollitropin alfa 150 mg (OPU + 4 day) + rec-FSH 300–375 IU/day (from stimulation D3) | rec-FSH, urinary hCG or GnRH-a | Significantly higher number of oocytes but similar number of embryos with FPS. DuoStim is a valid alternative to FPS-only decreasing the risk of cycle cancelation. |
| Luo and colleagues | Retrospective | At least two of the following criteria: (1) ≥ 40 years old, (2) history of poor response, <3 oocytes with conventional stimulation, (3) AMH < 1.1 ng/mL or AFC ≤ 7 | 304 | rec-FSH or hp-FSH and hMG [150–300 IU/day] + GnRH-ant (from stimulation D3) | rec-hCG, urinary hCG or GnRH-a | hMG 225 IU/day + MPA 10 mg/day (OPU + 1 day) | GnRH-a | Significantly higher number of oocytes and cryopreserved embryos with FPS. rec-FSH or GnRH-a performs better than urinary hCG for triggering FPS. |
| Bourdon and colleagues | Observational | Poor prognosis patients fulfilling POSEIDON criteria [Groups 1–4] and ≤ 42 years old | 53 | 300 IU/day FSH or hMG + GnRH-ant (from stimulation D3) | GnRH-a | 300 IU/day FSH or hMG + GnRH-ant (from stimulation D3) | GnRH-a | The only study reporting significantly less number of oocytes with FPS. |
| Vaiarelli and colleagues | Multicentre observational study | At least two of the following criteria: AMH ≤ 1.5 ng/mL, AFC ≤ 6, ≤ 5 oocytes retrieved in a previous cycle, ≥ 35 years old | 827 | Pre-treatment with luteal estradiol priming 4 mg/day + rec-FSH 300 IU/day + rec-LH: 150 IU/day (from D3), GnRH-ant (at least one follicle reaches 13–14 mm) | GnRH-a | rec-FSH 300 IU/day + rec-LH: 150 IU/day (from OPU + 5 days) + GnRH-ant (at least one follicle reaches 13–14 mm) | GnRH-a | Significantly higher number of M-2 oocytes with FPS. Blastulation and euploidy rates comparable following FPS and LPS. The rate of patients with at least one euploid blastocyst increases from 42.3% to 65.5% with DuoStim when compared with FPS-only. |

AFC, antral follicle count; AMH, anti-mullerian hormone; CC, clomiphene citrate; CPR, clinical pregnancy rate; DS, double stimulation; DuoStim, dual stimulation; FPS, follicular phase stimulation; FSH, follicle-stimulating hormone; GnRH-a, GnRH agonist trigger; GnRH-ant, GnRH antagonist; hCG, human chorionic gonadotrophin; hMG, human menopausal gonadotrophin; hp-FSH, highly purified FSH; hp-hMG, highly purified hMG; LBR, live birth rate; LE, letrozole; LPS, luteal phase stimulation; MPA, medroxyprogesterone acetate; M-2 oocyte, metaphase-2 oocyte; M-2 rate, metaphase-2 oocyte rate; NA, not available; OPU, oocyte pick up; POR, poor ovarian responders; POSEIDON, Patient-Oriented Strategies Encompassing Individualized Oocyte Number; rec-FSH, recombinant FSH; rec-hCG, recombinant hCG; rec-LH, recombinant LH.
higher number of retrieved oocytes, metaphase II oocytes, fertilized oocytes, day-3 embryos, and top-quality day-3 embryos. To our knowledge, no study has employed dual/double triggering for either FPS or LPS during DS/DuoStim. Although urinary and recombinant human chorionic gonadotropin (hCG) use is associated with similar number of oocytes and clinical pregnancy rates (CPR) in IVF, a recent study suggested that the use of GnRH-a or recombinant hCG (rec-hCG) performed better than urinary hCG (u-hCG) in both the FPS and LPS.

Current available evidence comparing FPS and LPS in POR patients

Concomitant FPS and LPS was first reported in a 41-year-old POR woman by Xu and Li in 2013. For FPS, they used 50–100 mg CC coupled with a daily dose of 150 IU FSH; despite two leading follicles of 16 and 18.5 mm in mean diameter in the right ovary on the day of triggering with GnRH-a, no oocyte could be retrieved. Although the patient wanted to drop-out at this stage, she was persuaded to undergo LPS, since she had had two antral follicles in the left ovary. Following LPS with 100 mg CC and a daily dose of 150 IU hMG, triggering was accomplished 10,000 IU u-hCG and one oocyte was retrieved; a cleavage stage embryo was cryopreserved. Of interest, the egg retrieval was performed 21 and 25 h after triggering in FPS and LPS, respectively. Unfortunately, the patient did not conceive with frozen embryo transfer (FET) of the available embryo.

Since this initial case report, several studies with different design, different OS regimens during FPS and LPS, and number of patients have been reported in PORs. Although DS has also been employed for fertility preservation, the available studies for this purpose have been excluded in this mini-review.

Kuang and colleagues, in a pilot study, reported the so-called ‘Shanghai protocol’, in 38 POR patients fulfilling Bologna criteria. For FPS, CC (25 mg/day) was started on cycle day 3 and continued until the day before triggering; in addition, LE at a dose of 2.5 mg/day was used during cycle days 3–6 along with 150 IU human menopausal gonadotropins (hMG) every other day starting from cycle day 6. Ibuprofen 0.6 g on the trigger day and the following day was prescribed. One day after egg retrieval, if the patient had at least two antral follicles 2–8 mm in diameter, LPS was performed, using LE (2.5 mg/day) and 225 IU daily hMG. Medroxy-progesterone acetate (MPA) and ibuprofen were used to avoid premature ovulation. GnRH-a triggering was employed for triggering for both FPS and LPS. Following FPS, the mean number of oocytes retrieved was 1.7 ± 1.0; this figure was 3.5 ± 3.2 following LPS (p=0.001). Of the 38 patients, 26 (68.4%) succeeded in producing 1–6 cleavage stage cryopreserved embryos; 21 patients underwent 23 FET, resulting in 11 ongoing pregnancies (47.8%).

In 2016, Wei and colleagues confirmed the initial results of Kuang and colleagues, with the same protocol adopted in 23 POR patients fulfilling Bologna criteria; the number of oocytes was significantly higher with LPS when compared with FPS (3.5 ± 3.4 versus 1.6 ± 1.1, p = 0.01). In the same year, Ubaldi and colleagues, using a prospective paired noninferiority observational study design, performed the so-called DuoStim in 51 POR patients [anti-mullerian hormone (AMH) ≤1.5 ng/ml, antral follicle count (AFC) ≤6 follicles, and ≤5 oocytes retrieved in previous IVF cycles]. There were two distinctions from the previous two studies; first, a GnRH-ant protocol with a fixed recombinant FSH (rec-FSH) 300 IU/day dose combined with recombinant LH (rec-LH) 75 IU/day were used in both FPS and LPS. Second, PGT-A was performed. A GnRH-a was used for triggering final oocyte maturation for both FPS and LPS. In this study, the number of metaphase-2 (M-2) oocytes, fertilization rate, number of biopsied blastocysts, and euploidy rates were comparable following FPS and LPS. The authors concluded that DuoStim increased the final euploid blastocyst yield per ovarian cycle when compared with FPS-only.

In 2017, Zhang and colleagues, in a retrospective study of 153 POR patients fulfilling Bologna criteria, in line with the previous studies, reported that LPS resulted in significantly more oocytes, M-2 oocytes, and zygotes when compared with FPS. Of interest, in this study, embryos obtained following LPS yielded higher implantation rates (7.84 versus 27.69, p = 0.014).

In 2018, three retrospective studies were reported on DS. Jin and colleagues, in 260 POR patients fulfilling Bologna criteria, compared DS (Group A, n=76) to LPS-only with conventional
and at least one failed conventional IVF. Alsbjerg and colleagues reported a regimen. The authors concluded that this protocol can be a time-efficient and patient friendly alternative. UHCG and rec-hCG trigger in patients undergoing conventional IVF with fresh embryo transfer (POSEIDON Group I and II). In 2020, three studies evaluated the performance of DS/DuoStim. Luo and colleagues, using a retrospective study design, performed DuoStim in 304 patients fulfilling Bologna criteria. For FPS, exogenous gonadotropin at a daily dose of 150–300 IU and a GnRH-ant was used. Triggering final oocyte maturation was accomplished with u-hCG (10,000 IU), rec-hCG (250 µg), or a GnRH-a. If ≥ 2 follicles 5–10 mm were noted one day after egg retrieval, LPS was carried out using hMG at a daily dose of 225 IU along with 10 mg/day daily dose of MPA. Consistent with the previous studies, the authors reported that LPS resulted in a significantly higher number of oocytes retrieved, normally fertilized oocytes, cleaved embryos, cryopreserved embryos, and good quality embryos when compared with those counterparts during FPS. The three different agents used for triggering at the end of FPS resulted in comparable embryological outcome. However, of interest, the rates of cryopreserved embryos and good quality embryos were significantly higher following LPS in those patients who were triggered by rec-HCG or GnRH-a when compared with u-hCG at the end of FPS or LPS. This unexpected finding is in contrast with previous studies reporting comparable oocyte yield and CPR following FPS and LPS. In a recent French observational cohort study, 77 patients underwent DS; of those 77 patients, 30 were poor prognosis patients fulfilling POSEIDON criteria (Group I, n = 12; Group II, n = 23; Group III, n = 5; Group IV, n = 13) and the remaining 24 underwent DS for fertility preservation. In contrast to the previous studies, the number of oocytes was significantly higher following FPS compared with LPS (4.83 ± 3.26 versus 3.64 ± 3.18, p = 0.019, respectively). Of note, the total FSH dose and duration of stimulation during FPS were significantly less when compared with LPS. Differences in patient population might contribute to the discrepant results with the previous studies since in this study not only patients with diminished ovarian reserve (POSEIDON Groups III and IV) were included but also those with hypo-response despite adequate ovarian reserve (POSEIDON Group I and II).
Ubaldi and colleagues\textsuperscript{24} have contributed several manuscripts on DuoStim\textsuperscript{14,35,58-60} following their initial noninferiority study in 2016. As mentioned previously, distinct from the previous studies, PGT-A and single euploid vitrified–warmed blastocyst transfer is their policy. DuoStim protocol involved a pretreatment with luteal oestradiol priming (4 mg/day of oestradiol valerate) on day 21 of the previous menstrual cycle to promote the synchronization of the follicular growth. FPS was started with a fixed dose of rec-FSH 300 IU/day plus rec-LH 150 IU/day for 4 days. A flexible GnRH-ant is administered daily following identification of a leading follicle of 12–14 mm in diameter both during FPS and LPS until the day of ovulation trigger. The final maturation of oocytes is triggered with a subcutaneous bolus of GnRH-a. Five days after the first retrieval, LPS is started with the same protocol and daily dose regardless of the number of visible antral follicles. A total of 310 patients fulfilling at least two of the following parameters, AMH $\leq 1.5$ ng/ml, AFC $\leq 6$, previous oocytes retrieved $\leq 5$, and maternal age $\geq 35$ years, underwent DuoStim.\textsuperscript{58} The mean number of M-2 oocytes was significantly higher following LPS compared with FPS (4.7 $\pm$ 3.0 versus 4.0 $\pm$ 2.5, $p < 0.01$). The fertilization, blastulation, and euploidy rates were comparable. Importantly, the rate of patients obtaining one euploid blastocyst increased from 42.3\% (131/310) after FPS to 65.5\% (203/310) with the contribution of LPS.\textsuperscript{58} A recent study reported no significant differences in the miRNA signature of the follicular fluid during FPS and LPS stages,\textsuperscript{65} complementing embryological and chromosomal equivalence between these two stages.

**Comparison of DS/DuoStim ve FPS-only**

In line with the above given data, and as expected, the available four studies\textsuperscript{14,30,61,62} comparing DS/DuoStim with conventional OS (single FPS) in POR patients report significantly less cycle cancellation rates\textsuperscript{30,61} and significantly higher number of oocytes\textsuperscript{30,61,62} M-2 oocytes,\textsuperscript{61,62} blastocysts,\textsuperscript{14} and cryopreserved/available embryos\textsuperscript{30,61} with DS/DuoStim.

**Critics of the available data**

It is clearly evident that DS/DuoStim increases the number of oocytes when compared with FPS-only. It is of interest that, apart from one study,\textsuperscript{34} the number of oocytes retrieved at LPS is either the same\textsuperscript{24,27,31} or higher\textsuperscript{25,26,28-30,32,33,35} when compared with FPS (Table 2). The reason for this is not clear but may be related to more synchronous follicular development due to high estrogen and progesterone levels during LPS.\textsuperscript{59} Moreover, such in \textit{vivo} milieu at the LPS stage may lead to an increase in angiogenic factors, thereby promoting the sensitivity of granulocytes to FSH.\textsuperscript{63} Another hypothesis is a possible flare-up effect derived from the GnRH agonist trigger in the FPS, which might induce a down-regulation in the expression of AMH in the follicles from the anovulatory wave, thereby increasing the number of follicles with a 3–4 mm diameter recruited in the LPS.\textsuperscript{64} However, all these speculations need to be confirmed, as well as the role of endocrine and paracrine factors better unveiled, to understand the mechanisms modulating the recruitment of follicles growing in the anovulatory wave of the ovarian cycle. However, one should also keep in mind that different OS regimens with higher gonadotropin consumption\textsuperscript{25,26,31-34} and duration of stimulation\textsuperscript{26,33-35} may also contribute to higher number of oocytes at LPS.

LPS-derived oocytes show similar competence as FPS-derived ones, including fertilization, blastulation, and euploidy rates.\textsuperscript{24,35,58} A recent study reported no significant differences in the miRNA signature of the follicular fluid during FPS and LPS stages,\textsuperscript{65} complementing embryological and chromosomal equivalence between these two stages.

A recent DELPHI consensus reported that ‘we recommend that it should only be used when the need to obtain oocytes is urgent, including patients with malignant diseases undergoing oocyte cryopreservation and patients of advanced maternal age or with reduced ovarian reserve’.\textsuperscript{66} The recent ESHRE Ovarian Stimulation Guideline for IVF/ICSI states that ‘Due to absence of RCT, comparing a double stimulation within a same cycle with mandatory postponed transfer and two conventional stimulations, we cannot recommend the double stimulation in poor responder patients’.\textsuperscript{67} Future randomized controlled trials comparing two consecutive conventional OS (two FPS-only) with DS/DuoStim are warranted to delineate the role of this strategy in PORs. Moreover, in the personalized medicine era, other large-scale studies are warranted to delineate the features, beyond classification as of
Table 2. The laboratory data and reproductive performance of follicular and luteal phase stimulation of the available studies.

| Author                  | No. of oocytes | Fertilization rate | No./rate of cryopreserved embryos | Clinical pregnancy rate | Miscarriage/early pregnancy loss | Ongoing pregnancy/live birth rate |
|-------------------------|----------------|-------------------|-----------------------------------|-------------------------|----------------------------------|----------------------------------|
|                         | FPS LPS        | FPS LPS           | FPS LPS                           | FPS LPS                | FPS LPS                          | FPS LPS                          |
| Kuang and colleagues    | 1.7 ± 1.0      | 3.5 ± 3.2         | 69.8% 75.6%                       | 0.9 ± 1                | 1.3 ± 1.4 [Cleavage + Blastocyst] | 61.5 [8/13] 71.4% [5/7]          |
|                         |                |                   |                                   |                         |                                  | 12.5 [1/8] 20% [1/5]             | 53.8% [7/13] 57.1% [4/7]         |
| Ubaldi and colleagues   | 5.1 ± 3.4      | 5.7 ± 3.3         | 69.7% 78.6%                       | 0.6 ± 0.8              | 0.7 ± 0.8*                       | 85.7% [6/7] 75% [4/8]            |
|                         |                |                   |                                   |                         |                                  | 16.7% [1/6] 16.7% [1/6]           | 71.4% [5/7] 62.5% [5/8]          |
| Wei and colleagues      | 1.6 ± 1.1      | 3.5 ± 3.4         | 100% 100%**                       | NA                     | 50% [1/2] 33% [4/12]             |                                  |
|                         |                |                   |                                   |                         |                                  | 0% [0/2] 0% [0/12]              | NA                               |
| Zhang and colleagues    | 2.2 ± 1.6      | 3.3 ± 2.6         | 75.9% 73.1%                       | NA                     | NA                               | 10.71% [3/28] 38.89% [14/36]     |
|                         |                |                   |                                   |                         |                                  | 0% [0/3] 14.2% [2/14]            | 10.7% [3/28] 27.8% [10/36]      |
| Rashian and Zhang       | 1.6 ± 0.2      | 1.9 ± 0.2         | NA  NA                            | NA  NA                 | NA  NA                          | 21.4% [3/14] 13.8% [4/29]        |
|                         |                |                   |                                   |                         |                                  | 0% [0/3] 25% [1/4]              | 14.3% [2/14] 10.2% [3/29]       |
| Zhang and colleagues    | 1.3 ± 0.9      | 1.8 ± 1.1         | 78.5% 86.9%                       | NA  NA                 | NA  NA                          | 35% [7/20] 37.5% [12/32]         |
|                         |                |                   |                                   |                         |                                  | 0% [0/7] 8.1% [1/12]            | NA  NA                          |
| Jin and colleagues      | 1 (1–2)        | 2 (1–4)           | 96.0% 95.7%                       | NA  NA                 | NA  NA                          |                                  |
| Madani and colleagues   | 1.52 ± 1.1     | 1.50 ± 1.98       | NA  NA                            | 1.75 ± 0.99            | 0.85 ± 1.22* [Cleavage]          | NA  NA                          |
| Alisberg and colleagues | 2.4 ± 2.1      | 3.7 ± 2.6         | NA  NA                            | 1.5 ± 0.9              | 1.8 ± 1.8 [Cleavage + Blastocyst]| NA  NA                          |
| Luo and colleagues      | 1.71 ± 1.3     | 3.58 ± 4.5       | 62.43% 62.50%                     | 0.9 ± 0.78             | 1.82 ± 2.54 [Cleavage + Blastocyst]| NA  NA                          |
| Bourdon and colleagues  | 5.25 ± 3.38    | 3.83 ± 3.14       | NA  NA                            | NA  NA                 | NA  NA                          | 42.85% [6/14] 21.15% [11/52]     |
| Vaiarelli and colleagues| 4.8 ± 2.1      | 6.6 ± 6.6       | NA  NA                            | 1.5 ± 0.8              | 1.8 ± 1.1*                       | NA  NA                          |

FPS, follicular phase stimulation; ICSI, intracytoplasmic sperm injection; LPS, luteal phase stimulation; NA, not applicable.

*p = 0.001.
*<p = 0.01.
**p < 0.001.
*<p = 0.040.
*<p = 0.035.
*p level not available.
*<p = 0.03.
*<p = 0.002.
*p = 0.000.
*<p = 0.000.
*p = 0.001.
*<p < 0.1.

No. of euploid blastocysts.
*Fertilization rate with ICSI.
**No. of M2 oocytes.
a poor prognosis, to predict which couples might benefit the most from a DS/DuoStim protocol.

The mandatory freeze-all and lack of cost-effectiveness data are the weaknesses of DS/DuoStim. Although initial findings of comparable obstetric and neonatal outcome of FPS- and LPS-derived embryos are reassuring, further large-scale studies are warranted for the long-term safety of this approach.

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