Mild Ovarian Stimulation for in vitro Fertilization: Are We Ready to Change? A Meta-Analysis

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Key Words

In vitro fertilization · Intracytoplasmic sperm injection · Mild ovarian stimulation · Conventional stimulation for in vitro fertilization · Clomiphene citrate · Live birth rate · Ongoing pregnancy rate · Treatment outcomes

Abstract

Objective: To compare the efficacy of mild ovarian stimulation versus conventional stimulation in in vitro fertilization (IVF). **Design:** Meta-analysis. **Search Strategy:** A systemic literature search was carried out for prospective randomised clinical trials. We electronically searched using PubMed, Medline and Embase for all the studies published from 1990 to December 2011. **Interventions:** Mild ovarian stimulation IVF that uses lower doses and/or shorter duration of gonadotrophins in GnRH antagonist co-treated cycle compared with conventional stimulation IVF. **Main Outcome Measures:** Live birth rates per started cycle and ongoing pregnancy rates per started cycle of IVF. **Results:** On live birth rate, there was a significant difference in favour of the conventional stimulation [70/444 (15.7%) mild vs. 78/325 (24%) conventional] (OR 0.59, CI 0.41–0.85, $p = 0.004$). Similar findings were observed in the ongoing pregnancy data [140/696 (20%) mild vs. 144/547 (26%) in favour of conventional stimulation] (OR 0.72, CI 0.55–0.93, $p = 0.01$). The sub-analysis of

two studies showed a statistically significant reduction of hyperstimulation syndrome in favour of the mild stimulation (OR 0.27, CI 0.11–0.66). **Conclusion:** This analysis presents strong evidence in favour of conventional stimulation IVF, which therefore should currently be considered a treatment of choice for patients requiring IVF treatment.

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Introduction

A recent publication by Jones [1] reported on seven roads travelled to make assisted reproductive technology (ART) the success it is today, and suggested seven more roads to be travelled to continue to improve. Among them is to make ART safe, accessible and available to most infertile couples [1]. Furthermore, it is a public health challenge to make ART available, affordable and accessible with minimal adverse effects without compromising the effectiveness.

The conventional ovarian stimulation protocol aims to provide the maximum number of oocytes retrieved for fertilization and thus several embryos for selection and transfer [2]; however, it is not without complications. The prevalence of potentially fatal severe ovarian hyperstimulation syndrome (OHSS) is reported to be

0.5–5% [3]. Together with high-order multiple gestation, they remain a huge problem in ART treatments with significant morbidity and financial burden on health resources [4, 5]. Pinborg et al. [6] reported that 40% of children born following ART are twins and these babies had a 7.4-fold increase in delivery before 32 weeks of gestation with significant increase in the admission to the neonatal intensive care unit. The supraphysiological levels of steroid hormones seen in conventional ovarian stimulation are associated with adverse effects on endometrial receptivity [7] and may result in accentuated maturation of the endometrium leading to embryo-endometrial asynchrony and reduced implantation rates [8]. Similar detrimental effects have also been associated with oocytes and embryo abnormalities [9, 10]. The complexity of the long protocol, time consumption, patient discomfort, high costs, and emotional distress are further associated with high dropout rates from in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles [11–13].

The ideology that obtaining increased quantity of oocytes leads to better pregnancy rates might be unjustified and contradictory [14]. Studies that evaluated the relationship between the number of oocytes retrieved and the pregnancy outcomes, reported an increase in pregnancy rates with a maximum of 15 eggs [15, 16] and eventually the plateau or the decline in positive outcomes with an excess number of oocytes [16–18]. Furthermore, a recent meta-analysis suggests that the retrieval of a modest number of oocytes following mild stimulation is associated with higher implantation rates compared with patients where the same number of oocytes is retrieved following conventional stimulation [19]. With data to suggest comparable outcomes between mild ovarian stimulation and conventional stimulation protocols but fewer complications, lower costs, and significantly fewer dropouts in mild protocols [11, 12, 20], there is merit in considering these patient-friendly approaches. To facilitate the acceptance and the implementation of these strategies, we have decided to review all the published prospectively randomised papers that seek to evaluate the pregnancy outcomes in mild ovarian stimulation protocol versus conventional stimulation protocol.

Materials and Methods

Search Strategy and Identification of Literature

A computerized literature search of all reports which described randomised controlled trials and prospective comparative trials of mild ovarian stimulation versus conventional stimulation was

performed via PubMed, Medline (1990–December 31, 2011) and Embase (1990–December 31, 2011). Relevant additional articles were hand-searched. A combination of medical subject headings (MeSH) and text words were used to generate subsets of citation such as; ‘mild ovarian stimulation’, ‘minimal ovarian stimulation’, ‘ovarian stimulation protocol’, ‘patient-friendly strategies’, ‘soft stimulation’, ‘low ovarian response’, and ‘IVF or ICSI’. The menstrual disorders and subfertility group specialised register of controlled trials was also searched. The search was limited to trials in humans only. No language restrictions were placed on any search. The searches were conducted independently by T.M. and T.F.K. No written protocol of this review has been made or published.

Definitions

Mild Stimulation IVF

A mild cycle is defined as the method when follicle-stimulating hormone (FSH) or human menopausal gonadotrophin (hMG) is administered at lower doses, and/or for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds (anti-oestrogen or aromatase inhibitors) are used either alone or in combination with gonadotrophins with the aim to collect a fewer number of oocytes [21–23].

Conventional Stimulation IVF

Conventional stimulation IVF is defined as the term when GnRH agonist is used for pituitary down-regulation followed by conventional doses of stimulation with FSH or hMG, or when GnRH agonist is administered in a flare protocol with conventional doses of FSH or hMG, or when GnRH antagonist is used with conventional doses of early start of FSH or hMG [21–23].

Study Selection and Data Collection

Inclusion Criteria

Studies were included if they reported the pregnancy outcomes in patients treated with mild ovarian stimulation compared to those treated with conventional stimulation protocols. All prospective randomised trials including women below 38 years of age, regular menstrual cycle (25–35 days), BMI of 18–29, normal hormonal profile and absence of uterine or ovarian abnormalities were included.

Exclusion Criteria

Studies involving natural cycle conception, modified natural cycle conception, mild ovarian stimulation in a poor responder, oocytes donation, embryo donation and intrauterine inseminations were excluded.

The following data was collected from all the trials included: patient demographics, pattern of menstrual cycle, ovarian stimulation protocol, the number of oocytes retrieved, insemination technique (IVF/ICSI), fertilization rates, the number of embryos transferred, the clinical pregnancy rates, the ongoing pregnancy rates (OPRs), and the live birth rates (LBRs) where available.

Outcome Measures

The ideal primary outcome measure is the LBRs. However, due to differences in the studies regarding the number of embryos transferred and the measure of their outcomes, the chosen primary outcome measure is the OPR. Other outcome measures such as clinical pregnancy rates, number of oocytes retrieved, number of

Table 1. Validity criteria and scoring for methodology assessment of studies

Category	Score	Method
A Randomization	3	Randomized by central means (telephone and pharmacy) or sealed envelopes
	2	Alternating numbers
	1	Methods not described
B Group demographics	2	Demographics comparable
	1	Demographics not described
C Placebo use	2	Placebo or other treatment used in control group
	1	No placebo or other treatment
D Follow-up	2	Outcome data for primary analysis complete
	1	Outcome data incomplete
E Co-intervention	2	Other than for use of treatment versus control, protocol involved same drugs
	1	Difference in protocols that may lead to contaminated results
F Patient and cycle differentiation	3	Only first treatment cycle included
	2	Patients included for more than one cycle
	1	Cycles and patients not differentiated

Table 2. Validity criteria score for each selected trial

Study (first author)	Score, %	Randomization	Demographics	Placebo/other	Follow-up	Co-intervention	Cycles
Baart, 2007 [7]	100	3	2	2	2	2	3
Blockeel, 2011 [30]	100	3	2	2	2	2	3
Heijnen, 2007 [20]	100	3	2	2	2	2	3
Hohmann, 2003 [9]	93	3	2	2	2	2	2
Karimzadeh, 2010 [28]	100	3	2	2	2	2	3

embryos transferred, cycle cancellation rates, and complications such as OHSS were also studied and reported where possible. For the purpose of this review, clinical pregnancy rate was defined as the presence of the fetal heart beat on ultrasound at 7 weeks of gestation and the OPR was defined as the presence of the fetal heart beat on ultrasound at 12 weeks of gestation.

Data and Statistical Analysis

A score was allocated to each trial using the validated scoring system [24]. Six methodological variables such as randomization, group demographics, placebo use, follow-up, co-intervention and patient and cycle differentiation were chosen (table 1). Each trial was assessed and ranked for its methodological conduct and its potential to introduce bias. Trials were allocated scores that were divided by maximum possible and a percentage performance was given to each trial. Performance scores ranged from 79 to 100% (table 2). The data on the outcomes of each included trial were summarized in two-by-two tables. The Peto odds ratio (OR) with its 95% confidence interval (CI) was calculated as the odds of an event in the mild stimulation group divided by the odds of an event in the conventional stimulation group in IVF/ICSI treatment. Statistical significance was inferred when the OR did not include 1.

The weight of each study in each analysis was calculated as inversely proportional to the variance. The degree of heterogeneity of studies was calculated using the χ^2 test, with the p value of <0.05 considered the limit of statistical significance, and I^2 statistics was used to describe the percentage of total variation across studies. An I^2 value of 0% was considered to signify no observed heterogeneity, while the values of 25, 50 and 75% were considered to indicate low, moderate and severe degrees of heterogeneity respectively. The applicable studies were re-analysed to find an explanation for any differences and also applied RevMan software to do a fixed effect meta-analysis. Analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, Ill., USA, 1999).

Results

Our search strategy identified 68 citations. Following the reading and scrutiny of the manuscripts, 43 studies were excluded by title and abstract and 20 did not meet the inclusion criteria by protocol. Therefore five studies

Table 3. Characteristics of included studies

Study (first author)	Design	Inclusion criteria	Study protocol (mild stimulation)	Control stimulation protocol (conventional)
Baart 2007 [7]	RCT	Women below 38 years of age, regular indication for IVF, regular menstrual cycle, BMI of 19–29, sperm count >5 million/ml, no previous IVF cycle not resulting embryo transfer and no uterine or ovarian abnormalities	Fixed 150 IU/day of FSH from cycle day 5; GnRH antagonist 0.25 mg/day was initiated when the leading follicle is 14 mm	Long GnRH agonist for 2 weeks and then fixed doses of 225 IU/day of FSH
Blockeel 2011 [30]	RCT	Regular indications for IVF, age between 18 and 36 years, BMI of 18–29, regular menstrual cycle, normal CD2 FSH, no PCOS and no severe endometriosis	Fixed 150 IU/day of FSH from cycle day 5; GnRH antagonist 0.25 mg/day was initiated on CD6	Fixed 150 IU/day of FSH from cycle day 2; GnRH antagonist 0.25 mg/day was initiated on CD6
Heijnen 2007 [20]	Parallel group, non-inferiority randomised trial	Regular indication for IVF or ICSI, menstrual cycle length of 25–35 days, BMI of 18–28, age <38 years, no previous IVF or healthy born child from IVF	Fixed 150 IU/day of FSH from cycle day 5; GnRH antagonist 0.25 mg/day was initiated when the leading follicle is 14 mm; combined with single embryo transfer	Long GnRH agonist for 2 weeks and then fixed doses of 150 IU/day of FSH
Hohmann 2003 [9]	Prospective randomised trial	Regular indication for IVF or ICSI, BMI of 19–29, age 20–38 years, regular menstrual cycle, no severe endometriosis or uterine or ovarian abnormalities, no more than three previous IVF cycles, no previous cycle with poor response or OHSS	Fixed 150 IU/day of FSH from cycle day 5; GnRH antagonist 0.25 mg/day was initiated when the leading follicle is 14 mm	Long GnRH agonist for 2 weeks and then fixed doses of 150 IU/day of FSH <i>or</i> fixed 150 IU/day of FSH from cycle day 2; GnRH antagonist 0.25 mg/day was initiated when the leading follicle is 14 mm
Karimzadeh 2010 [28]	Prospective randomised controlled trial	First IVF attempt, age 18–35 years, BMI of 18–30, regular menstrual cycle length of 26–35 days, basal FSH <10 IU/l	CC 100 mg/day from CD3 to CD7; fixed 75 IU/day of FSH from CD5; GnRH antagonist 0.25 mg/day was initiated when the leading follicle is 12 mm and additional 75 IU/day of hMG to initial gonadotrophins	Long GnRH agonist for 2 weeks and then flexible doses of 150–225 IU/day of FSH

met the inclusion criteria and were analysed. The characteristics of all the included studies are listed in table 3. All five studies included were prospective and randomised. They were all approved by the local ethics committees.

The patient characteristics were comparable for all the studies, including regular indications for IVF/ICSI, age below 38 years, regular menstrual cycles (25–35 days) and absence of severe endometriosis and uterine abnormalities. In these studies mild ovarian stimulation [21–23] was compared with conventional ovarian stimulation for IVF/ICSI.

The primary outcomes were LBRs and OPRs per cycle started. The secondary outcomes such as number of oocytes retrieved, total number of gonadotrophins used, cycle cancellation rates and OHSS rates were also reported (table 4).

Primary Outcomes

Live Birth Rate

Although the singleton term gestation, LBR should be considered the best endpoint for ART [25, 26], most studies still report LBRs without being specific about the gestation and large proportion of them report the OPRs only. One study that reported LBRs as an outcome showed sta-

Table 4. Treatment outcomes of included studies

Reference (first author)		Primary outcomes		Secondary outcomes			
		LBRs ^a	OPRs ^a	number of oocytes retrieved ^b	total number of gonadotrophins used per cycle ^d	OHSS ^a	Number of cycles cancelled ^a
Baart 2007 [7]	Mild	NR	12 (19)	8.3±4.7	NR	NR	NR
	Conv.	NR	7 (17)	12.1±5.7	NR	NR	NR
Blockeel 2011 [30]	Mild	NR	10 (25)	10.3±6.2	1,177±295 ^e	NR	NR
	Conv.	NR	10 (27.7)	8.9±4.7	1,364±226	NR	NR
Heijnen 2007 [20]	Mild	70 (15.8)	78 (17.6)	6.9±4.8	1,307±529 ^e	6 (1.4)	80 (18)
	Conv.	78 (24)	93 (28.6)	8.5±4.3	1,832±758	12 (4)	27 (8)
Hohmann 2003 [9]	Mild	NR	8 (16.3)	7 (1–27) ^c	NR	NR	NR
	Conv.	NR	8 (17.8)	9 (1–25)	NR	NR	NR
Karimzadeh 2010 [28]	Mild	NR	32 (32)	5.4±1.5	12.1±4.3	0 (0)	4 (4)
	Conv.	NR	26 (26)	9±2.2	22±3.6	6 (6)	0 (0)
Total	Mild	70 (15.8)	140 (20)	37.9±17.2	2,496.1±828.3	6 (2)	84 (16)
	Conv.	78 (24)	144 (26)	47.5±16.9	3,218±987.6	18 (5.5)	27 (9)

NR = Not recorded; Conv. = conventional.

^a Data expressed as n (%). ^b Data expressed as mean ± SD unless stated otherwise. ^c Values expressed as median (range). ^d Data expressed as mean number of ampoules ± SD unless indicated. ^e Data expressed as mean total dose of rFSH (IU) ± SD.

tistically significant difference [70/444 (15.7%) mild vs. 78/325 (24%) conventional] in favour of conventional stimulation (OR 0.59, CI 0.41–0.85, $p = 0.004$; fig. 1a).

Ongoing Pregnancy Rate

Five studies with a total number of 284 patients also reported statistically significant difference [140/696 (20%) mild vs. 144/547 (26%) conventional] in favour of conventional stimulation for OPRs per started cycle (OR 0.72, CI 0.55–0.93, $p = 0.01$; fig. 1b).

Secondary Outcomes

Ovarian Hyperstimulation Syndrome

The sub-analysis of two studies showed statistically significant reduction of hyperstimulation syndrome in favour of the mild stimulation (OR 0.27, CI 0.11–0.66, $p = 0.0004$). No significant heterogeneity was detected between the studies.

Number of Oocytes Retrieved per Cycle and Total Number of Ampoules of Gonadotrophins Used per Cycle

Analysed studies showed that significantly fewer number of eggs are retrieved in the mild stimulation protocols

versus the conventional approach ($p = 0.000$) and significantly less number of ampoules of gonadotrophins are used per cycle in the mild stimulation protocols ($p = 0.000$).

Number of Cycles Cancelled

The total number of cycles cancelled, including the poor follicular growth and the failure to achieve embryo transfer, were significantly fewer in the conventional protocol than in the mild (OR 2.55, CI 1.62–4.02, $p < 0.0001$).

Discussion

Over the last 30 years, IVF treatment has improved with recognizable developments in laboratory performance in terms of fertilization techniques, culture techniques for embryo development, embryo selection and cryopreservation of surplus embryos over and above improved ovarian stimulation protocols [27]. However, the introduction of mild stimulation protocols is still met with resistance in many units and the common reason is the lack of robust evidence to influence the current clinical practice in IVF. In this meta-analysis the convention-

Fig. 1. Mild ovarian stimulation versus conventional stimulation. LBRs (a) and OPRs (b) per fresh embryo transfer.

al ovarian stimulation IVF showed significantly improved LBRs and OPRs when compared to mild stimulation regimens. The LBRs per fresh embryo transfer from a study with a total number of 148 patients significantly favoured conventional stimulation (OR 0.59, $p = 0.004$) [20], therefore making it the treatment of choice in ART at this point.

It is interesting to note that data from the study by Heijnen et al. [20] showed no significant difference in the cumulative LBRs in both regimens (43.4% in the mild regimen vs. 44.7% in the conventional regimen). This observation underlines the need for more randomised controlled trials on cumulative LBR comparing the two regimens. The potential value of the mild regimen is a reduction of complication rate in ART. We observed a significantly lower risk of OHSS in the mild stimulation group as also reported by a number of authors suggesting this regimen as a viable strategy for the prevention of OHSS [20, 28, 29]. In the current study it was also observed that a significantly lower number of ampoules of gonadotrophins were used per cycle in the mild group compared to the conventional group and similar findings were showed by Blockeel et al. [30]. Polinder et al. [31]

reported significantly lower mean direct medical costs per IVF cycle for the mild regimen (EUR 1,559 vs. 1,977, $p = 0.001$) mainly due to the lower cost of medication. Due to its less complex nature, fewer ampoules of drugs and shorter duration used, it has been shown that mild stimulation IVF is also associated with a diminished level of patient distress [32]. The above facts propose mild stimulation as an attractive option for a low resource setting and selected group of patients at risk for OHSS.

Due to lack of large randomised controlled trials, this meta-analysis identified and analysed data from well and properly conducted prospective randomised trials that seek to add valuable information on the treatment outcomes in IVF stimulation protocols. However, the notable weakness in the paper is the lack of data on LBRs, and the heterogeneity amongst the different studies (fig. 1b). An attempt was made to minimize the heterogeneity by maintaining strict inclusion criteria in terms of patient profile and indications for ART (table 1), adherence to the definition of mild ovarian stimulation [21–23] in comparison to conventional ovarian stimulation and by analysing LBRs and OPRs since they would be affected equally in both arms.

In conclusion, this paper showed significantly better outcomes in terms of LBRs and OPRs per started cycle all in favour of conventional stimulation IVF, therefore currently remaining the preferred treatment of choice. However, in the limited resource setting and in a well-selected group of good prognosis patients, mild stimulation IVF may be considered a treatment option due to its potential benefits such as lower risk of OHSS, lower medication cost, less complexity in nature and lower levels of patient distress. In the future, more data on LBRs in both mild and conventional stimulation IVF is still required for proper and accurate comparison.

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The authors have no conflicts of interest to disclose.

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