

Comparison of pregnancy rates for poor responders using IVF with mild ovarian stimulation versus conventional IVF: a guideline

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Mild-stimulation protocols with in vitro fertilization (IVF) generally aim to use less medication than conventional IVF. This guideline evaluates pregnancy and live-birth rates in patients expected to be poor responders using mild ovarian stimulation and natural-cycle protocols vs conventional IVF. (*Fertil Steril*® 2018;109:993–9. ©2018 by American Society for Reproductive Medicine.)

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The terms “natural,” “patient-friendly,” “mild,” “minimal,” and “minimally stimulating” in vitro fertilization (IVF) have appeared increasingly in the literature, clinic advertising, and the media. Research in the field of “minimal-stimulation IVF” has used several terminologies, causing confusion among clinicians, researchers, and patients. The International Glossary on Infertility and Fertility Care includes definitions developed for specific terms such as “natural cycle ART,” “modified natural cycle,” and “mild ovarian stimulation for IVF” (1). Various approaches to this technique share important features, including the use of oral agents such as clomiphene citrate (CC) and aromatase inhibitors, low-dose exogenous gonadotropins, gonadotropin-releasing hormone (GnRH) antagonists, and late follicular-phase administration of human chorionic gonadotropin (hCG) or luteinizing hormone (LH). For the purposes of this document, conventional IVF is defined as controlled ovarian stimulation (COS) with exogenous go-

nadotropins to induce multiple oocyte development for retrieval.

“Natural-cycle IVF” involves monitoring unstimulated ovaries and attempting to retrieve the oocyte from a dominant follicle prior to ovulation. This was the protocol utilized to achieve the first live birth through IVF (2). However, this approach was replaced by protocols utilizing ovarian stimulation with exogenous gonadotropins resulting in decreased cancellation rates, increased number of oocytes retrieved, and, ultimately, increased live-birth rates.

“Modified natural-cycle IVF” includes the use of GnRH antagonists in the late follicular phase (sometimes with add-back gonadotropin therapy) and ovulation trigger, typically with hCG. Proposed advantages of natural-cycle IVF include reduced cost per cycle, minimized risk of multiple gestation, lower risk of ovarian hyperstimulation, and less physical and emotional demands on the patient when compared with conventional IVF (3, 4). The lower multiple-gestation risk is a direct result of usually

obtaining a single oocyte and transferring a single embryo. Possible disadvantages of these strategies include increased chance of cycle cancellation from unexpected ovulation, no oocyte recovery or retrieval of an immature oocyte, and possible lower success rates.

“Mild ovarian stimulation for IVF” involves multiple strategies using the following agents as monotherapy or in combination: CC, aromatase inhibitors, low-dose exogenous gonadotropins, GnRH antagonists, and late follicular-phase hCG/LH. Some “low-dose” mild IVF protocols utilizing GnRH antagonists involve delaying low-dose gonadotropin stimulation until the mid-follicular phase, anywhere between cycle-days 3 to 7. This strategy may lead to the development of fewer oocytes than traditional IVF, with reduced gonadotropins utilized and less cost. Interpreting the literature on mild ovarian stimulation is challenging because the doses of added gonadotropins are not consistent and are similar to those used in conventional IVF in some studies.

Several studies have addressed the question of whether these approaches may be especially beneficial in specific subsets of patients. This document evaluates these strategies with respect to pregnancy and live-birth rates in patients who are expected to be poor

Received March 14, 2018; accepted March 14, 2018.

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Fertility and Sterility® Vol. 109, No. 6, June 2018 0015-0282/\$36.00

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<https://doi.org/10.1016/j.fertnstert.2018.03.019>

responders, based on the Bologna criteria (patients having at least two of the following features: maternal age ≥ 40 , an abnormal ovarian reserve test, and/or prior poor response to IVF [≤ 3 oocytes with a conventional-stimulation protocol]) (5).

LIMITATIONS OF THE LITERATURE

Several challenges exist when trying to interpret the efficacy of IVF with mild stimulation. There are no standard protocols or standard definitions of poor responders, which can make it challenging to compare studies and perform a meta-analysis. Many studies have a small sample size, which greatly limits their power to detect a difference between groups. Some studies use a similar dose of gonadotropins between the mild- and the standard-stimulation group. Finally, some studies lack an adequate comparison group (the mild-stimulation cycle is compared against the same patient's prior standard IVF cycle), and some use surrogate endpoints, rather than pregnancy or live-birth rates.

METHODS

This clinical practice guideline was based on systematic reviews of the literature performed in the electronic database MEDLINE through PubMed January 18–November 7, 2017. No limit or filter was used for the time period covered or English language, but articles were subsequently culled for English language. These electronic searches and examination of reference lists from primary and review articles yielded 766 studies, of which 21 studies were included (Evidence Table, available online).

A combination of the following medical subject headings or text words were used: advanced maternal age; affordable; assisted reproduction; bank; banking; cost analysis; cost benefit; cost effective; costs; cryopreservation; cryopreserve; diminished ovarian; economic; embryo; fertilization in vitro/economics; fertilization in vitro/methods; freeze; freezing; frozen; gonadotropins; ICSI; in vitro fertilisation; in vitro fertilization; intracytoplasmic sperm injection; IVF; low cost; low dose; low ovarian; low resource; low responder; low response; low-dose; maternal aging; micro dose; micro-dose; mild; mild ovarian stimulation; mild stimulation; mildly; mini dose; minidose; minimal; minimal stimulation; modified; modified cycle; natural; natural cycle; no stimulation; not stimulated; ovarian stimulation; ovary; ovulation induction; ovulation induction/economics; patient friendly; patient satisfaction; poor ovarian; poor responder; poor response; psychometrics; reduced ovarian; reproductive age; reproductive aging; sperm injections, intracytoplasmic; stimulated cycle; stimulation; stimulation protocol; thawed; unstimulated; vitrification; vitrified; vitrify.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed to develop inclusion/exclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, ovulation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist (Table 1).

LEVEL OF EVIDENCE

The level of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography.

Level I

- Systematic review of randomized controlled trials (RCTs)
- RCTs

Level II

- Systematic review of a combination of RCTs, controlled trials without randomization, and cohort studies
- Controlled trials without randomization
- Cohort studies
- Case-control studies

Level III

- Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees

QUALITY OF EVIDENCE

The quality of the evidence was evaluated using the following grading system, adapted from the Johns Hopkins Nursing Evidence-based Practice grading system

A: High Quality

- Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on a comprehensive literature review that includes thorough reference to scientific evidence

B: Good Quality

- Reasonably consistent results; sufficient sample size for the study design; some control; fairly definitive conclusions; reasonably consistent recommendations based on a fairly comprehensive literature review that includes some reference to scientific evidence

C: Low Quality or Major Flaws

- Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn

TABLE 1

Summary of inclusion/exclusion criteria.

Include

Level I and II studies, systematic reviews, meta-analyses

Human studies

English

Studies with a comparison group

Fresh cycles

Frozen-thawed cycles

ICSI

Day-3 transfers

Day-5 transfers

Women ≥ 40 y

Mild ovarian-stimulation protocols: ≤ 150 IU gonadotropins, cycles with oral agents, or no stimulation with or without antagonists

Comparison groups, conventional stimulation: >150 IU gonadotropins with luteal down-regulation, antagonists, flare

Women <40 y with diminished ovarian reserve based on AMH <1.1 or AFC <7 (ESHRE criteria, Ferraretti 2011 [5])

Women with proven low response: ≤ 3 oocytes retrieved with ≥ 150 IU/d FSH (ESHRE criteria, Ferraretti 2011 [5])

Note: AMH = antimüllerian hormone; AFC = antral follicle count; ESHRE = European Society of Human Reproduction and Embryology; FSH = follicle-stimulating hormone; GIFT = gamete intrafallopian transfer; ICSI = intracytoplasmic sperm injection; IUI = Intrauterine insemination; IVM = In vitro maturation; PCOS = polycystic ovary syndrome.

ASRM. Mild ovarian stimulation and poor responders. *Fertil Steril* 2018.

Exclude

Level III studies: descriptive studies, case series, case reports, letters, nonsystematic reviews, off-topic studies, opinions, and reports of expert committees

Animal studies

Non-English

Studies without a comparison group

PCOS patients

GIFT

IUI

IVM

STRENGTH OF RECOMMENDATIONS

The entirety of the literature was then used to develop recommendations based on the quality of the literature. The strength of the recommendation was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

(From consistent Level-I, high-quality [Grade A] studies)

Grade B: There is fair evidence to support the recommendations, either for or against.

(From principally Level-II, good-quality [Grade B] studies)

Grade C: There is insufficient evidence to support the recommendations, either for or against.

(From Level-II, low-quality [Grade C] studies, or when there is conflicting data from good-quality studies)

IS MILD OVARIAN STIMULATION WITH LOW-DOSE GONADOTROPINS ALONE AS EFFECTIVE AS NORMAL- OR HIGH-STIMULATION PROTOCOLS FOR POOR-RESPONDER PATIENTS?

There are two randomized controlled trials (RCTs) that showed similar clinical pregnancy rates in poor-responder patients receiving mild ovarian stimulation vs standard high-dose stimulation IVF (6, 7). One open-labeled, multicenter, randomized, controlled non-inferiority trial included patients older than 35 years, with baseline follicle-stimulating hormone (FSH) >10 IU/ml, antral follicle count (AFC) ≤ 5 , or history of poor ovarian response or cycle cancellation (6). Patients (mean age 36 years in both groups) either received

mild ovarian stimulation (fixed 150 IU FSH and antagonist, $n=195$) or conventional stimulation (fixed 450 IU human menopausal gonadotropins [hMG] and long, mid-luteal agonist, $n=199$). No significant differences were observed between mild and conventional ovarian stimulations, respectively, in clinical pregnancy rate (15.3% vs 15.5%, risk ratio [RR] 0.86; 95% confidence interval [CI] 0.55–1.34) and biochemical pregnancy (20% vs 18%; RR 1.10; 95% CI 0.66–1.84) per number of women, and early pregnancy loss (16.6% vs 12.9%; RR 1.20; 95% CI 0.36–4.17) and twin pregnancy (10% vs 22.5%; RR 0.41; 95% CI 0.10–1.65) per number of clinical pregnancies. The duration of ovarian stimulation was significantly lower in the mild vs conventional strategy (8.42 ± 2.89 vs 9.67 ± 3.10) with a mean difference of -1.2 days (95% CI -1.88 to -0.62). Also, a significantly lower amount of gonadotropins was used in the mild-stimulation strategy, with a mean difference of -3135 IU (95% CI -3331 to -2940) (6). This study did not report on cumulative pregnancy rates with supernumerary embryos, nor did it report on live-birth rates.

The other RCT evaluated the effect of doubling the starting dose of gonadotropins on ovarian response in IVF patients with a low AFC (7). The study enrolled 52 patients with an AFC of <5 follicles of 2–5 mm diameter before starting their first IVF cycle. Patients were randomized to receive either 150 IU ($n=26$) or 300 IU ($n=26$) of recombinant FSH (rFSH) as a starting dose in a long-suppression protocol. Mean age was 40.4 years in the 150 IU group vs 42.2 years in the 300 IU group ($P=.77$). In patients who were stimulated with the standard dose of 150 IU, the dose was doubled after 7 days of stimulation if the estradiol level was <200 pmol/liter (54.5 pg/mL) or after 10 days if the estradiol was <500 pmol/L (136 pg/mL). The dose was fixed for patients receiving the 300 IU protocol. Patients in the lower-dose group I received 2100 IU (1455–

4440 IU) total of gonadotropins and those in the higher-dose group II received 3600 IU (3000–4800 IU). Patients did not differ in the number of oocytes collected (three for both groups, $P=.79$) and ongoing pregnancy rates (8% for lower FSH dose and 4% for higher FSH dose, $P=.55$). Eleven patients were cancelled before oocyte retrieval due to poor response (19% in the mild-dose group, 23% in the conventional-dose group, $P=.73$). The study was likely not powered to demonstrate no difference between the groups regarding pregnancy outcomes.

Summary Statement:

- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing mild ovarian-stimulation protocols using low-dose gonadotropins (≤ 150 IU/d) to conventional-gonadotropin protocols, but there are no data about live-birth rates. From two Level-I, good- to high-quality (Grade A, B) studies. Grade B.

IS MILD OVARIAN STIMULATION WITH ORAL SUPEROVULATION AGENTS (WITH OR WITHOUT LOW-DOSE GONADOTROPINS) AS EFFECTIVE AS NORMAL- OR HIGH-STIMULATION PROTOCOLS FOR POOR-RESPONDER PATIENTS?

Low-dose Gonadotropins and Oral Superovulation Agents

Several RCTs have compared outcomes between mild ovarian stimulation with oral superovulation agents with low-dose gonadotropins and normal- or high-stimulation protocols (8–12). In the largest of these trials, 695 patients with diminished ovarian reserve were randomized to mild stimulation (mean age 38.5 years, 100 mg CC on cycle-days 2–6, 150 IU rFSH per day started on cycle-day 5, GnRH antagonist started on cycle-day 8) or a long GnRH-agonist protocol (mean age 37.5 years, 300–450 IU rFSH per day) (8). Poor responders were defined by the following criteria: day-3 FSH between 10–20 IU/L, antimüllerian hormone (AMH) between 0.14–1 ng/mL, and AFC between 4–10. Compared to the traditional stimulation group, the mild stimulation group had a significantly lower oocyte yield (2.7 ± 2.3 vs 4.8 ± 3.3 , $P<.01$) and a significantly higher cycle-cancellation rate (13.0% vs 2.7%, $P<.01$). Although the study was not powered to detect differences in the pregnancy rates, the authors reported similar clinical pregnancy rates per transfer (23.2% vs 19.9%, $P=\text{not significant [NS]}$) and per cycle start (13.2% vs 15.3%, $P=\text{NS}$) (8).

Other published RCTs are limited by factors such as an inadequate sample size to interpret pregnancy outcomes, lack of a consistent definition of poor responder, and the use of surrogate endpoints. In one study, 95 patients meeting two out of three Bologna criteria were randomized to one of three arms: 450 IU gonadotropins per day ($n=31$), 300 IU gonadotropins per day ($n=31$), or 150 IU gonadotropins per day plus letrozole 5 mg/day for the first 5 days of stimulation

($n=33$) (9). There was no significant difference in the mean number of oocytes retrieved among the three groups (3.4 ± 1.6 vs 3.7 ± 1.5 vs 3.5 ± 1.9 , $P=\text{NS}$). The study was not powered to examine clinical pregnancy rate per started cycle (4/31 [13%] vs 5/31 [16%] vs 5/33 [15%], $P=\text{NS}$) (9).

Another small study randomized 58 poor responders (based on Bologna Criteria) to either traditional-dose IVF (starting at 300 IU of gonadotropins, with maximum at 450 IU) vs a mild ovarian-stimulation protocol with 100 mg CC on days 2–6 of the cycle, adding an antagonist and 150 IU of gonadotropins when a lead follicle was ≥ 14 mm (13). There were significantly more oocytes retrieved in the traditional-stimulation group (3.0 vs 1.0, $P<.001$), but the study was not powered to detect a difference in live-birth rates (12.0% vs 9.1%, $P=.719$) (13).

In a small pilot study, 38 women with poor ovarian response were randomized to letrozole 2.5 mg/day for cycle-days 3–7 with 75 IU rFSH on days 3 and 8, or to a long GnRH agonist protocol with 300–450 IU rFSH per day (10). The total dose of rFSH was significantly lower in the letrozole group (150 ± 0 IU vs $2,865 \pm 228$ IU, $P<.001$), but the study was not powered to show a difference in the mean number of oocytes retrieved (1.6 ± 0.8 vs 2.1 ± 0.7 , $P=\text{NS}$) or clinical pregnancy rate per treatment cycle (3/13 [23%] vs 6/25 [24%], $P=\text{NS}$) (10). Another small RCT demonstrated similar clinical pregnancy rates per cycle start among 60 women assigned to an antagonist protocol with letrozole 5 mg for cycle-days 2–6 and 150 IU highly purified hMG daily starting on cycle-day 7, or to a microdose GnRH agonist-flare protocol with 300 IU hMG per day (4/30 [13.3%] vs 5/30 [16.6%], $P=.72$; odds ratio [OR]=.77; 95% CI .19–3.20) (11). In another small study, 77 women with poor response were randomized to 100 mg CC for 5 days followed by 150 IU hMG per day ($n=42$), or to standard stimulation with at least 300 IU hMG per day ($n=35$) (12). Only one clinical pregnancy was achieved in each group (12). Finally, one group published two retrospective studies demonstrating improved pregnancy rates with CC/hMG compared with hMG alone or GnRH agonist-hMG (14, 15). These studies were limited by overlap between study populations, inadequate sample size to assess differences in pregnancy outcomes, and lack of adjustment for confounders.

Summary Statement:

- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing mild ovarian-stimulation protocols using a combination of oral agents and low-dose gonadotropins (≤ 150 IU/d) to conventional-gonadotropin protocols. Data about oocyte yield are mixed. From two Level-I, good- to high-quality (Grade A, B) and several low-quality studies (Grade C). (Grade B).

Oral Agents Alone

Only one RCT has compared outcomes between oral agents alone and conventional high-dose gonadotropin stimulation among poor responders undergoing IVF (16). In that study,

291 women (mean age 38 years in both groups) with elevated FSH or a previous poor response were randomized to 150 mg CC per day (n=145) or GnRH-agonist protocol with 450 IU rFSH per day (n=146). The study was continued for 2 years but terminated early due to poor recruitment. Delivery rates were similarly poor between groups (3% vs 5%, $P=.77$), but the study was not adequately powered to compare the strategies for this outcome (16). Two small retrospective studies demonstrated similarly low clinical pregnancy rates regardless of stimulation protocol (17, 18).

Summary Statement:

- In women considered to be poor responders, there is insufficient evidence to recommend for or against IVF with mild ovarian stimulation using oral agents alone over conventional-gonadotropin stimulation. From one Level-I and two Level-II, low-quality (Grade B and C) studies. Grade C.

ARE NATURAL OR MODIFIED-NATURAL CYCLES AS EFFECTIVE AS NORMAL- OR HIGH-STIMULATION PROTOCOLS FOR POOR-RESPONDER PATIENTS?

The use of natural cycles or modified-natural cycles in poor responders has been evaluated in limited studies. One RCT included 140 consecutive patients who were randomized to either natural-cycle IVF vs microdose-flare cycles, although the authors note that 11 women assigned to the natural group refused the randomization and chose another treatment (19). There were 59 patients (mean age 39.3 years) who underwent 114 natural cycles, and 70 patients (mean age 42.1 years) who underwent 101 microdose-flare cycles. The pregnancy rate per cycle was low in both groups: 6.1% in the natural-cycle group and 6.9% in the traditional-stimulation group ($P=NS$) (19).

Several retrospective studies have evaluated stimulation protocols in poor responders, some including comparison groups (20–22), while others used patients' previous failed cycles (23–26) as a comparison. One of the largest studies with comparison groups included 304 patients, 30 of whom underwent a natural cycle versus the remainder who underwent one of several traditional-stimulation protocols (20). No significant difference among the groups was found in clinical pregnancy rates per transfer for natural-cycle (20.0%), gonadotropin-only (5.6%), long-agonist (3.8%), co-flare (1.9%), microdose-flare (15.4%), or antagonist (14.4%) protocol ($P=.083$) (20). When comparing natural cycle and all combined traditional stimulations, clinical pregnancy rates per transfer were 20% versus 0.08%, $P=.051$ (ASRM Practice Committee calculation by Fisher's exact test). A significant limitation to this retrospective study is that cycles cancelled before retrieval or transfers were not reported (20). Another study included 433 patients, 52 of whom underwent a modified-natural cycle vs traditional stimulation with either a long-agonist (n=288) or antagonist (n=200) protocol (21). The per-cycle clinical pregnancy rates were 9.6% for modified-natural cycle,

8.5% for antagonist protocol, and 8.6% for long-agonist protocol ($P=NS$) (21).

Using the definition of poor responder based on the Bologna criteria, a retrospective cohort study included poor responders who underwent 161 cycles (n=106 women, mean age 41.3 years) of modified natural-cycle IVF or 164 cycles (n=136 women, mean age 40.7 years) of high-dose FSH IVF (dose varied between 300 IU and 450 IU/day) (22). In the modified-natural cycle group, ultrasound monitoring started on day 6, and when a 14-mm follicle was present, 150 IU of rFSH and GnRH antagonist were initiated concomitantly and continued daily thereafter until the day of hCG administration when the follicle reached a mean diameter of ≥ 16 mm. Live-birth rates were significantly higher in the modified-natural cycle vs high-dose group (7.5%, 95% CI 3.1–11.8 vs 3.1%, 95% CI 0.4–5.7; OR 4.01, 95% CI 1.14–14.09), after adjusting for basal FSH, female age, and cause of infertility. There was also a significantly lower total gonadotropin dose (490.0 ± 35.2 IU vs 2826.1 ± 93.7 IU, $P<.001$) and proportion of cancelled cycles (7.5% vs 16.5%, $P=.02$) in the modified natural-cycle group. While this study suggests that modified natural-cycle IVF is associated with a higher probability of live birth and significantly lower gonadotropin consumption compared with the high-dose FSH protocol, any conclusions should be viewed with caution, due to the study's retrospective nature and low live-birth rate ($<10\%$) in both groups (22).

A small retrospective cohort study compared women with poor response; group 1 consisted of 27 women treated with up to 8 ampules per day of FSH who proceeded to retrieval with ≤ 3 dominant follicles, and group 2 included 30 women (35 cycles) with prior cancelled traditional IVF cycles with subsequent natural-cycle IVF (26). Pregnancy rates per retrieval were not significantly different between groups 1 and 2, respectively (2/27 [7.4%] vs 5/30 [16.6%]), though the study design and the small sample size limit conclusions for this study (26). Other small cohort studies using the patients' previous failed cycles with traditional stimulation showed feasibility, but are not able to demonstrate effectiveness (23–25).

Summary Statement:

- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing natural-cycle protocols to conventional-gonadotropin protocols. From two small RCTs and several Level-II, low- to good-quality (Grade B and C) studies. Grade B.

WHAT IS THE COST-EFFECTIVENESS OF IVF WITH MILD OVARIAN STIMULATION COMPARED WITH CONVENTIONAL IVF IN POOR RESPONDERS?

In poor-responder patients, a non-blinded RCT published in 2012 evaluated costs as well as delivery rates per started cycle (16). Women with a day-3 serum FSH >12 IU/mL on at least two occasions or prior poor response to hyperstimulation

were included, with a mean age of 38 years in both groups. The two-armed study compared 148 women who were treated with CC 150 mg/day from day 3 to day 7 of the cycle with 156 women who were treated with 450 IU of rFSH with GnRH agonist in a short-protocol format, both with day-2 or -3 embryo transfers. The study included a single treatment cycle for each group. The study was continued for 2 years but terminated early due to poor recruitment, which limits the power to determine a difference between the groups. The live-birth rate per started cycle in the CC group was 3% (95% CI 1%–7%) and in the high-dose gonadotropin group was 5% (95% CI 2%–9%; $P=.77$). Included costs were calculated based only on medications and medical procedures for infertility, not pregnancy-related costs. The mean costs per patient cycle were €2,803 and €5,423 for the CC and high-dose gonadotropin groups, respectively. The mean costs per delivery were €81,294 and €113,107 in the CC and high-dose gonadotropin groups, respectively (16). The authors did not perform a complete sensitivity analysis to determine the outcomes based on a variety of costs. This study concluded that in poor responders, mild stimulation IVF is cost-effective, though live-birth rates were extremely low in both groups.

Summary Statement:

- In women considered to be poor responders, there is fair evidence to support the recommendation that mild ovarian stimulation is cost-effective, though live-birth rates are extremely low in both groups. From one Level-I, good-quality (Grade B) study. Grade B.

CONCLUSIONS

Mild ovarian-stimulation protocols with IVF generally aim to use less medication compared with conventional IVF. In patients expected to be poor responders with IVF (based on poor response to a prior IVF cycle, age ≥ 40 years, and/or Bologna criteria), pregnancy rates tend to be low regardless of protocol. There is fair to good evidence that clinical pregnancy rates are not substantially different using mild-stimulation protocols compared with conventional IVF in poor-responder populations. Based on one study, mild stimulation with CC was cost-effective compared to conventional IVF with high-dose gonadotropins.

UNANSWERED QUESTIONS

- Current studies do not compare different mild ovarian-stimulation protocols directly to determine if one is superior for the poor-responder population with respect to cost and pregnancy outcomes.
- It is unknown if the aggregation of embryos from multiple mild-stimulation cycles as compared with a single traditional-dose IVF cycle is more effective or costly.
- Future studies should evaluate if there are other potential benefits of mild-stimulation protocols, such as improved neonatal outcomes or lower complication rates.
- Future studies need to compare cumulative pregnancy rates between traditional- and mild-stimulation protocols.

- Future studies should include the outcome of live birth.

SUMMARY

- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing mild ovarian-stimulation protocols using low-dose gonadotropins (≤ 150 IU/day) to conventional-gonadotropin protocols, but there are no data about live-birth rates. From two Level-I, good- to high-quality (Grade A, B) studies. Grade B.
- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing mild ovarian-stimulation protocols using a combination of oral agents and low-dose gonadotropins (≤ 150 IU/d) to conventional-gonadotropin protocols. Data about oocyte yield are mixed. From two Level-I, good- to high-quality (Grade A, B) and several low-quality studies (Grade C). (Grade B).
- In women considered to be poor responders, there is insufficient evidence to recommend for or against IVF with mild ovarian stimulation using oral agents alone over conventional gonadotropin stimulation. From one Level-I and two Level-II, low- to good-quality (Grade B and C) studies. Grade C.
- In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing natural-cycle protocols to conventional-gonadotropin protocols. From two small RCTs and several Level-II, low- to good-quality (Grade B and C) studies. Grade B.
- In women considered to be poor responders, there is fair evidence to support the recommendation that mild ovarian stimulation is cost-effective, though live-birth rates are extremely low in both groups. From one Level-I, good-quality (Grade B) study. Grade B.

RECOMMENDATIONS

- In patients who are classified as poor responders and pursuing IVF, strong consideration should be given to a mild ovarian-stimulation protocol (low-dose gonadotropins with or without oral agents) due to lower costs and comparable low pregnancy rates compared with traditional IVF-stimulation protocols.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate,

taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The Practice Committee acknowledges the special contribution of Jennifer Mersereau, M.D., Silvina Bocca, M.D., Ph.D., Jennifer Eaton, M.D., Jason Franasiak, M.D., Samantha Pfeifer, M.D., Aimee Seungdamrong, M.D., and Eric Widra, M.D., in the preparation of this document.

No external funding was received for the development of this document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Alan Penzias, M.D.; Kristin Bendikson, M.D.; Samantha Butts, M.D., M.S.C.E.; Christos Coutifaris, M.D., Ph.D.; Tommaso Falcone, M.D.; Susan Gitlin, Ph.D.; Clarisa Gracia, M.D., M.S.C.E.; Karl Hansen, M.D., Ph.D.; Sangita Jindal, Ph.D.; Jennifer Mersereau, M.D.; Randall Odem, M.D.; Robert Rebar, M.D.; Richard Reindollar, M.D.; Mitchell Rosen, M.D.; Jay Sandlow, M.D.; Peter Schlegel, M.D.; Dale Stovall, M.D., Michael Vernon, Ph.D.

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