Cost-effective analysis of infertility treatment in women with anovulatory polycystic ovarian syndrome

Michael H. Saad-Naguib, MD, Douglas Timmons, MD, MPH, Kavitha Krishnamoorthy, MD, George R. Attia, MD

Introduction: Polycystic ovarian syndrome (PCOS) is a common cause of female infertility. Clomiphene citrate (CC) is a first line treatment for infertility secondary to PCOS, in addition to Letrozole. After unsuccessful cycles using CC and timed intercourse, pregnancy may be achieved using in-vitro fertilization (IVF), bypassing gonadotropins. We explore the most efficient and cost-effective way to obtain at least 70% live-birth rate in PCOS patients who fail first-line treatment.

Materials and methods: A review of relevant trials using PUBMED was performed to obtain pregnancy rates of women with PCOS undergoing various treatments. Six randomized trials were included in this study. We used 761 cycles from these trials. Four different protocols were structured: protocol 1 consisted of 3 cycles of CC/intrauterine insemination (IUI) followed by 3 cycles of human menopausal gonadotropin stimulation with IUI followed by 2 cycles of IVF/intracytoplasmic sperm injection (ICSI). Protocol 2 involved 3 cycles of CC/IUI followed by 2 cycles of IVF/ICSI. Protocol 3 was comprised of 3 cycles of human menopausal gonadotropin/IUI followed by 2 cycles of IVF/ICSI, and protocol 4 was composed of 2 cycles of IVF/ICSI and 1 cycle of frozen embryo transfer. Each protocol was analyzed for cost per live birth and time to live birth.

Results: Protocol 1 yielded a live-birth rate of 75%, costing $34,923 per live birth achieved over a 10-month period. Protocol 2 yielded a pregnancy rate of 71%, costing $32,172 over 7 months. Protocol 3 yielded a pregnancy rate of 73%, costing $39,812 over 7 months. Lastly, protocol 4 yielded a pregnancy rate of 70%, costing $37,884 per pregnancy over a 5-month period.

Conclusion: Protocol 4 was the most efficient, reaching a 70% live birth rate in a 5-month period. Protocol 2 was the most cost-effective, with a total cost of $32,172 per live birth. These results will assist physicians in counseling PCOS patients with subfertility to determine the optimal treatment method.

Keywords: Polycystic ovarian syndrome, PCOS, Infertility, Clomiphene citrate/IUI, Gonadotropin/IUI, IVF/ICSI
undergoing various forms of treatment. The following keywords were used: polycystic ovarian syndrome, infertility, clomiphene citrate, intrauterine insemination, gonadotropins, in-vitro fertilization, intracytoplasmic sperm injection. No language limitations were applied. On the basis of the 4 protocols that we created, 6 randomized trials were eligible for inclusion [Table 1][15–20]. As 2 protocols included using CC and IUI, we included 2 trials that examined the efficacy of CC/IUI in patients with PCOS. In addition, 2 trials were selected that examined the efficacy of gonadotropins and IUI in PCOS patients. These were included in protocols as our study attempts to achieve the most cost-effective route to pregnancy in patients with PCOS. However, the physical and financial risks of multiple gestation using gonadotropins and IUI are well documented[17]. Lastly, 2 trials involving PCOS patients undergoing IVF with fresh transfer were included. We did not include trials that incorporated frozen embryo transfers (FET) as this would add another cost for the patient and alter our cost-effective analysis. In addition, it is understood that an FET would increase the pregnancy rate achieved in the protocol. While we acknowledge the widespread use and efficacy of FET, we did not include these in our study. This study was exempt from review by institutional review board since all materials studied were obtained from publicly available existing publications.

Four protocols were designed to yield similar outcomes. Each scenario was created using a balance of different treatment options (CC/IUI, HMG/IUI, and IVF/ICSI) to obtain a pregnancy rate of at least 70% as previously described (Fig. 1). Each protocol was preceded by failed attempts at conception with CC and timed intercourse. Protocol 1 consisted of women undergoing 3 cycles of CC with IUI, followed by 3 cycles of HMG with IUI, followed by a maximum of 2 cycles of IVF/ICSI if pregnancy was not achieved at that point. Protocol 2 was comprised of 3 cycles CC/IUI with 2 cycles of IVF/ICSI as needed. Protocol 3 consisted of women undergoing 3 cycles of HMG/IUI followed by 2 cycles of IVF/ICSI if no pregnancy was achieved. Protocol 4 consisted of 2 cycles of IVF/ICSI and 1 cycle of FET as needed. Cycle length was set at 1 month for CC/IUI and HMG/IUI. For IVF/ICSI, cycle length was determined to be 2 months as there is 1 month of oral contraceptive use prior to starting IVF stimulation. FET was also set for 1 month.

For each treatment method, the pregnancy rate and miscarriage rate were calculated by taking the total average from the appropriate studies. These rates were comparable to the national average[14,21]. During each cycle, the total number of live births calculated was based on miscarriage rate subtracted from pregnancy rate for each respective treatment. This model assumed the pregnancy rate was the same during each cycle performed and that natural conception did not occur.

The data regarding the cost per cycle was obtained from UHealth Fertility Center at the University of Miami (Table 2).

### Materials and methods

A review of relevant trials was performed using PUBMED as a search engine to obtain pregnancy rates of women with PCOS who fail the first-line treatment for infertility with CC and timed intercourse. We believe that a 70% live birth rate is an acceptable mark and thus each protocol below was designed with the goal of providing a 70% rate by the final intervention.

### Table 1

| References | Trial Characteristics | Baseline Characteristics | Interventions |
|------------|-----------------------|--------------------------|---------------|
| Abu Hashim et al[13] | Randomized trial to compare the efficacy of IUI vs. timed intercourse with CC as a first-line treatment for anovulatory infertility associated with PCOS | Rotterdam Criteria 2003 | CC/IUI, CC/ timed intercourse |
| Deveci et al[16] | Randomized controlled trial to compare traditional CC use vs. stair-step CC use | Rotterdam Criteria 2003 | CC/IUI |
| Ertunc et al[17] | Prospective randomized study performed on infertile patients with PCOS | Rotterdam Criteria 2003 | HMG/IUI |
| Gerli et al[18] | Prospective, randomized trial to compare urinary FSH (uFSH) and recombinant FSH (rFSH) in ovarian stimulation for IUI cycles in PCOS patients | Diagnostic criteria for the evaluation of PCOS used: clinical and/or biochemical hyperandrogenism, chronic anovulation, and exclusion of related disorders. At least 2 y of infertility | HMG/IUI |
| Kim et al[19] | Prospective randomized study of 211 infertile women with PCOS who underwent IVF/ICSI | Rotterdam Criteria 2003 | IVF/ICSI |
| Tang et al[20] | Randomized, placebo-controlled double-blinded study. Women with PCOS between 20 and 39 y of age underwent IVF/ICSI cycles | Rotterdam Criteria 2003 | IVF/ICSI |

CC indicates clomiphene citrate; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; NF, in-vitro fertilization; PCOS, polycystic ovarian syndrome.

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The time to pregnancy and the cost per pregnancy in each arm. The outcome measured was the number of pregnancies in each arm. The outcome measured was the number of cycles for each treatment method. The cost per arm was calculated by multiplying the cost per treatment cycle by the number of cycles for each treatment method. The cost per pregnancy was calculated by dividing the total cost by the total number of pregnancies in each arm. The outcome measured was the time to pregnancy and the cost per pregnancy in each arm.

### Results

A total of 761 cycles were included in our study. Of this 289 cycles were performed using CC and IUI. A total of 318 were performed using gonadotropins and IUI, and 154 cycles were performed using IVF/ICSI.

The average age in patients undergoing CC + IUI, HMG + IUI, IVF was 25.9, 29.3, and 31.84, respectively. There were no statistically significant differences between the different groups regarding body mass index, duration of infertility or baseline follicle-stimulating hormone (Table 3).

### Discussion

Our study assessed the cost and time to live birth of different treatment scenarios for women with anovulatory PCOS who do not conceive after CC and timed intercourse. Protocol 4 (2 cycles of IVF/ICSI and 1 cycle of FET as needed) achieved at least a 70% live birth rate in the shortest time at 5 months. Protocol 2 (3 cycles of CC/IUI followed by 2 cycles of IVF/ICSI) provided the most cost-efficient method of obtaining a live birth, with a total cost of $32,172 per live birth achieved.

There are 2 other studies reporting long-term treatment scenarios for women with PCOS. Eijkemans and colleagues compared favorable ovulation induction methods in normogo-

### Table 2

| Treatment          | Cost of Medication ($) | Cost of Procedure ($) | Total Cost ($) |
|--------------------|------------------------|-----------------------|---------------|
| CC/IUI cycle       | CC 100 mg/d x 5 d: $26.19 Ovidrel: $100 | 1000 | 1126.19 |
| Gonadotropin/IUI cycle | Follistim AQ 900U: $762 Follistim AQ 300U: $254 Ovidrel: $100 | 2500 | 3616 |
| IVF cycle          | 37 vials of bravelle for each patient (37 x 55): $2035 11 vials menopur (11 x 70): $770 Lupron 1 kit: $150 Progesterone 1 mL/d (2 vials x 10 mL x 100): $200 HCG 10000U: $80 | 10,500 | 13,735* |

* Those who became pregnant received progesterone support for the first 12 weeks of pregnancy (extra 5 vials of 10 mL each 5 x 10 x 10): $500.

CC indicates clomiphene citrate; IUI, intrauterine insemination; IVF, in-vitro fertilization.

### Table 3

| Demographic characteristics. | Study 1 (CC/IUI), N = 30 (30 Cycles) | Study 2 (CC/IUI), N = 93 (259 Cycles) | Study 3 (rFSH/IUI), N = 88 (197 Cycles) | Study 4 (rFSH/IUI), N = 47 (121 Cycles) | Study 5 (IVF/ICSI), N = 105 (105 Cycles) | Study 6 (IVF/ICSI), N = 49 (49 Cycles) |
|------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Age (y)                      | 24.9                               | 26.3                               | 29.1                               | 29.7                               | 32.2                               | 31.1                               |
| BMI                          | 27.1                               | 25.1                               | 23.7                               | 24.9                               | 22.7                               | 26.9                               |
| Duration of infertility (y)  | 2.25                               | 2.2                                | 2.3                                | 5.6                                | 4.3                                | 5.0                                |
| FSH (mIU/mL)                 | 5.7                                | 5.7                                | 5.7                                | 8.9                                | 7.2                                | 6.8                                |
| LH (mIU/mL)                  | 9.7                                | 12.8                               | 12.8                               | 8.9                                | 7.2                                | 6.8                                |
| Estradiol (pg/mL)            | 43.7                               |                                    |                                    |                                    |                                    |                                    |

BMI indicates body mass index; CC indicates clomiphene citrate; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; NF, in-vitro fertilization; LH, luteinizing hormones; rFSH, recombinant FSH; uFSH, urinary FSH.

### Table 4

| Pregnancy outcomes.        | CC/IUI       | HMG/IUI       | IVF/ICSI      | FET          |
|-----------------------------|--------------|--------------|---------------|--------------|
| Pregnancy rate              | 9.25%        | 11.65%       | 38%           | 35%          |
| Miscarriage rate             | 15%          | 15%          | 10%           | 11%          |
| Cost per cycle              | $1130        | $4,000       | $15,000       | $3,500       |
| Time per cycle              | 1 mo         | 1 mo         | 2 mo          | 1 mo         |

CC indicates clomiphene citrate; FET, frozen embryo transfer; HMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization.

A total of 123 patients underwent a total of 289 CC/IUI cycles, with an average pregnancy rate of 9.25% per cycle and miscarriage rate of 15% [15,16]. One hundred thirty-five patients underwent 318 HMG + IUI cycles and had an average pregnancy rate of 11.65% with miscarriage rate of 15% [17,18]. IVF patients had a pregnancy rate of 36.1% and miscarriage 10% [19,20] (Table 4).

We used a group of 100 hypothetical patients from these studies, which we were able to do as there were no statistically significant differences in the parameters above. We then applied each protocol to this group of 100 patients to obtain the following results. Patients in protocol 1 achieved a pregnancy rate of 75% within 10 months, and the average cost of a live of birth was $34,923. In protocols 2 and 3, patients achieved a pregnancy rate of 71% and 73%, respectively, in an average of 7 months. Protocol 2 was the most cost-effective plan at an average of $32,172, while protocol 3 was an average of $39,812. Protocol 4 achieved a pregnancy rate of 70% in 5 months, which was the shortest time by 2 months needed to obtain a 70% pregnancy rate; however, the average cost per live birth was $37,884 in this protocol (Table 5).
nagadotropic anovulatory women based on age, duration of infertility, and insulin: glucose ratio. The primary outcome studied was the overall live birth rates using CC and gonadotropins without exploring other methods of ovulation induction in women with normogonadotropic anovulation. In this study, patients were exposed to the “classical” ovulation induction method. Patients who did not ovulate within three treatment cycles of CC with increasing dosages and those who did ovulate with CC, but did not conceive within 6 cycles, underwent gonadotropin induction using a step-down dose regimen. This study determined that classical ovulation induction protocols produce good live birth rates, and it is a benefit to the patient if the physician continues with the classic protocol instead of changing methods after the first or second cycle does not result in conception. Moolenaar and colleagues performed a similar study analyzing cost-effacy of treatments for women who do not conceive after 6 ovulatory cycles with CC and timed intercourse. They outlined 6 protocols of various combinations of continuing CC with timed intercourse, HMGs, and IVF. The group concluded that after 6 failed cycles of CC, continuation using 6 more cycles of CC, followed by 6 or 12 cycles with HMGs and IVF is potentially cost-effective. This study did not consider the time to live birth and the potential emotional difficulties couples may face enduring that many failed cycles. While parts of that study are comparable to ours, differences among costs between infertility care in the study country of the Netherlands and the United States make our current study distinctive[23].

Four protocols were designed with the patient’s expectations of efficient and cost-effective treatments in mind. After unsuccessful attempts at CC stimulation with timed intercourse, couples seek more effective methods of achieving pregnancy; however, the European Society of Human Reproduction and Embryology (ESHRE) consensus guideline considers 12 cycles of CC before using more aggressive protocols[7]. We want to note that a protocol for achieving 70% life birth rate without the use of IVF/ICSI was considered; however, the time and cost for a live birth in this scenario would exceed all other protocols studied, thus making a protocol without the use of IVF/ICSI unlikely in a real-life setting. To eliminate any assumptions drawn from this study and validate these conclusions made, a randomized clinical trial is essential.

Comparing all the available treatment options for ovulation induction, CC remains the lowest cost. One may assume that continuing CC for additional cycles than the protocols defined would be more cost-effective[23]. However, additional cycles may lead to patient intolerance with continued feelings of anxiety and despair after each failed attempt at conception.

Most studies regarding pregnancy or live birth rates in women with PCOS concentrate on rates per cycle or outcomes in the first few cycles. Data on long-term treatment strategies is lacking[23]. This study is a stepping stone to analyzing PCOS treatment strategies to achieve a well-desired live birth rate. Bypassing the use of gonadotropins in ovulation induction for women with PCOS is a unique finding not identified in previous studies. A balance between costs and effectiveness of treatment is crucial for mutual satisfaction.

For the purpose of our study, we used CC as our first line treatment, and we acknowledge the 2014 study by Legro et al[23] stating that Letrozole is associated with a higher live-birth rate and ovulation among infertile women with PCOS. A review of the literature did not demonstrate a study that directly compares the cost-effacy of Letrozole versus CC in a setting like ours. Thus, we propose a future study in which cost-effacy of Letrozole is compared with CC or is the primary intervention used. In addition, FET cycles were not included in our analysis as this adds an additional cost and would alter our cost-effective analysis.

While our review did not include enough studies to qualify as a meta-analysis, it shares some of the same inherent weaknesses of a meta-analysis. The quality of the meta-analysis is determined by the data obtained from the original studies, and a sufficient number of eligible studies to perform the analysis must be available[24]. Another weakness of the study is that we created hypothetical models that were designed to achieve the desired pregnancy rate, and we did not take into consideration common complications of assisted reproductive technology (ART) and pregnancy, such as ovarian hyperstimulation, cycle cancellation, and twins, among other complications. We did not take multiple gestations into consideration as the main outcome of the study was the birth of at least one child contributing to the live birth rate, thus a twin pregnancy was considered one successful pregnancy.

As per guidelines from the 2008 Consensus on Infertility Treatment related to PCOS, the protocols for using gonadotropin therapy for ovulation induction have become restrictive such that 25% of potential cycles are cancelled due to an excessive response. While we did not incorporate the cost of these cycles in our study, this is certainly a cost that would need to factored into the physician’s decision making[7].

Another limitation of our study is the lack of an absence to treat arm. In any set of patients enrolled in a trial, not all patients would be subject to the treatment that they were scheduled to receive, thus resulting in a deviation from protocol. As noted above, some cycles undergoing gonadotropin therapy will be cancelled to avoid ovarian hyperstimulation syndrome. Lack of an intent to treat arm can introduce attrition bias into our group as the groups of patients being compared may no longer have similar characteristics.

This study assumed the same pregnancy rate for each cycle; however, if pregnancy is not achieved in early cycles, the live birth rate declines at an unknown rate with each subsequent cycle after 3 cycles[27,28]. Similarly, the effectiveness of gonadotropins in repeated cycles is uncertain as most studies only report the first few cycles[23,29]. As this study included the use of gonadotropins for up to 3 cycles, the same live birth rate per cycle was assumed.

There are several well-known complications of ART, such as ectopic pregnancy, multiple gestation, etc. We did not incorporate the cost of the complications associated with ART as these are relatively unpredictable and unexpected outcomes that would not be expected to significantly affect the overall average cost of the treatments provided in our studies. Complications such as multiple gestation are now better avoided by the implementation of single embryo transfers.

### Table 5

| Protocol | Live Birth Rate (%) | Total Cost ($) | Cost/Live Birth rate ($) | Time (mo) |
|----------|---------------------|----------------|--------------------------|-----------|
| Protocol 1 | 75 | 2,619,225 | 34,923 | 10 |
| Protocol 2 | 71 | 2,284,212 | 32,172 | 7 |
| Protocol 3 | 73 | 2,906,276 | 39,812 | 7 |
| Protocol 4 | 70 | 2,651,880 | 37,884 | 5 |
We believe that this is the first study in the United States looking to maximize the efficiency and cost-efficacy of treatment for anovulatory PCOS patients.

After unsuccessful attempts at CC with timed intercourse, proceeding directly to IVF/ICSI will yield a 70% live birth rate in a 5-month period—the shortest amount of time among all the protocols studied. The most cost-effective method of obtaining pregnancy was 3 cycles of CC/IUI followed by 2 cycles of IVF/ICSI, with a total cost of $32,172 per live birth achieved. This will help physicians counsel patients to determine the optimal method to obtain at least a 70% live birth rate in anovulatory females with PCOS who fail CC with timed intercourse.

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**Conflict of interest disclosures**

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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