Utilization and success rates of unstimulated in vitro fertilization in the United States: an analysis of the Society for Assisted Reproductive Technology database

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Objective: To examine the utilization and outcomes of natural cycle (unstimulated) IVF as reported to the Society of Assisted Reproductive Technology (SART) in 2006 and 2007.

Design: Retrospective analysis.

Setting: Dataset analysis from the SART Clinical Outcome Reporting System national database.

Patient(s): All patients undergoing IVF as reported to SART in 2006 and 2007.

Intervention(s): None.

Main Outcome Measure(s): Utilization of unstimulated IVF; description of patient demographics; and comparison of implantation and pregnancy rates between unstimulated and stimulated IVF cycles.

Result(s): During 2006 and 2007 a total of 795 unstimulated IVF cycles were initiated. Success rates were age dependent, with patients <35 years of age demonstrating clinical pregnancy rates per cycle start, retrieval, and transfer of 19.2%, 26.8%, and 35.9%, respectively. Implantation rates were statistically higher for unstimulated compared with stimulated IVF in patients who were 35 to 42 years old.

Conclusion(s): Unstimulated IVF represents <1% of the total IVF cycles initiated in the United States. The pregnancy and live birth rates per initiated cycle were 19.2% and 15.2%, respectively, in patients <35 years old. The implantation rates in unstimulated IVF cycles compared favorably to stimulated IVF. Natural cycle IVF may be considered in a wide range of patients as an alternative therapy for the infertile couple. (Fertil Steril® 2013;100:392–5. ©2013 by American Society for Reproductive Medicine.)

Key Words: Natural cycle IVF, unstimulated IVF, IVF

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In vitro fertilization remains the treatment of choice for many couples with infertility. It is estimated that nearly 5 million children worldwide have been born after conception with IVF. Although IVF was initially performed in unstimulated reproductive cycles, the limitations of attempting to retrieve an oocyte laparoscopically from a single follicle ultimately led most clinicians to adopt the use of fertility medications (oral and parenteral) to recruit additional ovarian follicles. The introduction of ultrasound-guided transvaginal follicular aspiration also improved the efficiency and success rates of IVF.

However, the use of fertility medications increases the cost of IVF and can result in both direct and indirect complications, such as ovarian hyperstimulation syndrome and multiple pregnancy. Many fertility clinics worldwide have re-examined the use of unstimulated IVF in a wide range of patients, including both good- and poor-prognosis cases.
In the United States, nearly all IVF is performed with the use of fertility medications. The purpose of this study is to examine all unstimulated IVF cycles reported to the Society for Assisted Reproductive Technologies (SART) for 2006 and 2007 with respect to both utilization of unstimulated IVF by individual clinics and the clinical outcomes of those cycles.

Unstimulated IVF (also called natural cycle IVF) is defined by the Centers for Disease Control and Prevention as “an ART cycle in which the woman does not receive drugs to stimulate her ovaries to produce more follicles. Instead, follicles develop naturally.” Current SART clinical reporting standards do not segregate the data from stimulated and unstimulated IVF cycles, so this study represents the first report of actual utilization of natural cycle IVF by fertility clinics in the United States according to SART data.

MATERIALS AND METHODS

The SART Clinical Outcome Reporting System (CORS) database contains information on all IVF cycles performed by reporting assisted reproductive technology (ART) clinics during a given calendar year. All patients are entered into the database by participating clinics without identifying information. All IVF cycles are identified as either unstimulated or stimulated. The SART Research Committee approved this study of utilization of unstimulated IVF, and an exemption from institutional review board approval was obtained. After approval by the SART Research Committee, the desired information regarding all IVF cycles identified as unstimulated in 2006 and 2007 was extracted. Information regarding the total number of IVF cycles and the associated success rates of stimulated cycles performed in the same time period was obtained from the SART Web site (www.sart.org). Statistical analysis was performed using a χ² test with Yates correction.

RESULTS

Analysis of the clinics reporting their results to SART revealed that a minority of the clinics performed unstimulated IVF (13% in 2006 and 16% in 2007). Furthermore, the average number of unstimulated IVF cycles at those clinics performing natural cycle IVF was <10 per year and represented <1.5% of the total IVF cycles initiated at those clinics (Table 1).

A total of 795 cycles of unstimulated IVF were reported to SART in 2006 and 2007. The age distribution of patients undergoing natural cycle IVF was skewed compared with the age distribution of patients pursuing stimulated cycle IVF. Patients <35 years old represented 41% of the total stimulated IVF cycles, compared with just 21.5% of the unstimulated IVF cycles (Fig. 1). Nearly half (45.5%) of the unstimulated IVF cycles were performed in patients ≥41 years of age (30% in patients aged >42 years). Conversely, only 15% of stimulated IVF cycles were performed in patients ≥41 years of age (5.8% in patients aged >42 years).

As expected, there was attrition from cycle initiation to ET in the unstimulated IVF cycles (Table 2). In patients <35 years old more than half the initiated cycles (54%) reached ET, with a pregnancy rate per ET (implantation rate) of 35.9%. The implantation rates for unstimulated IVF across the various age groups (<35, 35–37, 38–40, and 41–42 years) were 35.9%, 40.4%, 28.4%, and 19.4%, respectively. The implantation rate was statistically higher in unstimulated IVF cycles compared with stimulated cycle IVF in patients between 35 and 42 years of age, and there was no significant different in patients aged <35 years (Fig. 2). There were no pregnancies from unstimulated IVF in those >42 years of age. For all ages, the clinical pregnancy rates per initiated cycle, retrieval, and transfer were 9.6%, 13.5%, and 26.1%, respectively. Similarly, for all ages (including >42 years) the live birth rates per initiated cycle, retrieval, and transfer were 7.3%, 10.3%, and 19.9% respectively.

DISCUSSION

Although interest in natural cycle IVF remains strong in countries as varied as Japan (1), England (2), Sweden (3), Italy (4), and Cyprus (5), the present study reveals that in the United States <1% of IVF cycles are performed in unstimulated cycles, and only 15% of clinics even offer natural cycle IVF to patients. At the vast majority of those clinics offering unstimulated IVF the percentage of patients undergoing natural cycle IVF represents a fraction of the total IVF volume.
TABLE 2

Outcome of unstimulated IVF by age group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt; 35</th>
<th>35–37</th>
<th>38–40</th>
<th>41–42</th>
<th>&gt; 42</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles initiated (n)</td>
<td>171</td>
<td>101</td>
<td>161</td>
<td>125</td>
<td>237</td>
<td>795</td>
</tr>
<tr>
<td>Oocyte retrievals (n)</td>
<td>123</td>
<td>70</td>
<td>112</td>
<td>84</td>
<td>176</td>
<td>565</td>
</tr>
<tr>
<td>Retrieval attempt/cycle initiated (%)</td>
<td>71.9</td>
<td>69.3</td>
<td>69.6</td>
<td>67.2</td>
<td>61.6</td>
<td>71.1</td>
</tr>
<tr>
<td>ET/cycle initiated (%)</td>
<td>53.8</td>
<td>41.6</td>
<td>41.6</td>
<td>28.8</td>
<td>22.8</td>
<td>36.6</td>
</tr>
<tr>
<td>Pregnancy rate/cycle initiated (%)</td>
<td>19.2</td>
<td>16.8</td>
<td>11.8</td>
<td>5.6</td>
<td>0</td>
<td>9.6</td>
</tr>
<tr>
<td>Live birth/cycle initiated (%)</td>
<td>15.2</td>
<td>14.9</td>
<td>8.7</td>
<td>2.4</td>
<td>0</td>
<td>7.3</td>
</tr>
</tbody>
</table>


(Table 1). Given the large percentage of unstimulated cycles attempted in patients >41 years old (Fig. 1), it seems likely that natural cycle IVF is used by many US clinics primarily in poor prognosis older patients with diminished ovarian reserve and poor egg quality, for whom stimulated cycle IVF is no longer an option. Lack of interest in natural cycle IVF has been suggested by Heng (6) to result from [1] diminished profits compared with stimulated cycle IVF, [2] reduction in success rates as published in “league tables,” and [3] inability to create supernumerary embryos for future use or donation. Some authors have criticized natural cycle IVF as a form of “patient friendly IVF” that is more about marketing than effective therapy (7). However, those who argue against natural cycle IVF often quote a per-cycle pregnancy rate (7) that is half the rate actually reported to SART (19%) for patients < 35 years old.

In a recent survey of ART clinics in the United States, physicians were asked to identify their reasons for deciding against offering natural cycle IVF (8). The most often cited reasons were poor success rates, lack of cost effectiveness, and lack of patient interest. However, these reflect physician opinions, which may be very different from patient motivations. One study found that some patients have such a strong preference for natural cycle IVF over stimulated cycle IVF that pregnancy rates per initiated cycle of 10%–15% would be readily viewed as reasonable (9). Compared with stimulated IVF, there is an increased rate of cycle cancellation with natural cycle IVF because of premature LH surge, ovulation, failure to retrieve an oocyte, fertilization failure, or embryo arrest. Although the majority of initiated cycles result in oocyte retrievals (71.1%), the present study found that the percentage of cycles that result in ET ranged from 54% in the youngest patients to 23% in the patients >42 years old. Proponents of unstimulated IVF have suggested that natural cycle IVF be considered as a series of treatments to obtain a successful cumulative pregnancy rate (10–12). Many patients have a strong preference for natural cycle IVF over stimulated IVF and are willing to undergo a greater number of simpler treatments to obtain a successful pregnancy (9, 13). However, there is no doubt that establishing a natural cycle IVF program will adversely impact a clinic’s pregnancy statistics as reported to SART for clinics in the United States. Currently SART combines stimulated and unstimulated IVF cycle results when reporting a clinic’s success rates. Given the lower pregnancy rates per initiated cycle for natural cycle IVF any clinic that offers natural cycle IVF will be adversely impacting its published IVF success rates. In fact, almost 40% of ART clinics responding to a survey concerning unstimulated IVF indicated that they would likely or definitely consider offering unstimulated IVF if the reporting procedures were changed so that stimulated and unstimulated IVF results were segregated (8).

Comparison of the implantation rates between unstimulated and stimulated IVF cycles demonstrated a statistically higher implantation rate in several age categories. This finding may support the observation of improved endometrial receptivity in unstimulated cycles (as has been recently suggested in a randomized controlled trial by Shapiro et al. [14]). Unstimulated IVF also represents the ultimate example of physiologic egg/embryo selection using the normal reproductive cycle, avoiding the production of supernumerary eggs/embryos in a stimulated cycle. If there is a selective bias in favor of the dominant follicle recruited in an unstimulated cycle then this selectivity could lead to an embryo that is more likely to implant compared with those produced as a result of controlled ovarian hyperstimulation. Perhaps the selection of the dominant follicle represents a more discriminatory process than we previously assumed, leading to an embryo with improved implantation potential.

Limitations of the present study include the retrospective nature of such an analysis, the aggregation of data from
multiple ART clinics whose inclusion criteria for unstimulated IVF is unknown and variable, and the assumption that the data reported include all initiated unstimulated IVF cycles. We believe that many patients would consider unstimulated IVF as a valid treatment option if presented with the choice. However, only a small percentage of the ART clinics reporting to SART CORS currently offer this treatment. Looking at the pregnancy rates across all ages, it would seem appropriate to consider unstimulated IVF in younger patients instead of relegating this option to older patients in whom all other treatments have failed. Changes in the reporting system may encourage more clinics to attempt unstimulated IVF if results from stimulated and unstimulated cycles were segregated.

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REFERENCES