Offering excess oocyte aspiration and vitrification to patients undergoing stimulated artificial insemination cycles can reduce the multiple pregnancy risk and accumulate oocytes for later use

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BACKGROUND: The prevention of multiple pregnancies remains a major challenge in patients treated with ovarian stimulation prior to intrauterine insemination (IUI). The pilot study presented here investigates whether multiple pregnancies can be minimized by a microscopically confirmed aspiration of oocytes from supernumerary follicles immediately before intrauterine insemination and evaluates the benefit of concomitant excess oocyte cryopreservation for future use.

METHODS: Thirty-four aspirations of supernumerary follicles were performed immediately prior to IUI in 31 patients undergoing ovarian stimulation. sIUI was only performed if cumulus-oocyte complexes were microscopically observed in the aspirated follicular fluid. All collected mature excess oocytes were cryopreserved using the vitrification technique.

RESULTS: Only four sIUI procedures had to be cancelled due to failed oocyte retrieval or premature ovulation. IUI treatment resulted in a clinical pregnancy rate of 23.5% per cycle. All were singleton pregnancies. A total of 111 oocytes were cryopreserved. Patients with polycystic ovary syndrome (PCOS) had an average of 6.07 oocytes vitrified, whereas patients without PCOS had 1.3 oocytes vitrified per cycle.

CONCLUSION: Microscopically confirmed collection of excess oocytes prior to stimulated IUI reduced cancellation rates, further reduced the risk for multiple pregnancy and may lead to future additional pregnancies because, based on current information, approximately 5% of the vitrified oocytes could potentially establish a pregnancy.

Key words: intrauterine insemination / oocyte vitrification / excess oocyte / polycystic ovary syndrome

Introduction

The high incidence of multiple pregnancies is the main adverse treatment outcome in assisted reproduction technology (ART) (Bergh et al., 1999). Multiple births are associated with significant neonatal and maternal morbidity (Keith and Oleszczuk, 1999; Ombelet et al., 2005; Luke and Brown, 2008). Although in the context of IVF the wider implementation of a single-embryo transfer (SET) policy reduces the multiple pregnancy rate, the incidence of this complication in ovarian stimulation remains a major concern (Dickey, 2007).

Many studies report a positive correlation between the number of follicles and the pregnancy rate after ovarian stimulation (Tolminson et al., 1996; Nuojua-Huttunen et al., 1999; Stone et al., 1999; Dickey et al., 2002; Ibérico et al., 2004). However, a recent meta-analysis concludes that cycles with three or four follicles result in no substantial gain in pregnancy rate, but result only in an increased multiple pregnancy rate (Van Rumste et al., 2008). A less aggressive stimulation can be an effective method to prevent excessive multifollicular growth and therefore reduce the risk of multiple pregnancies in ovarian stimulation (Dickey, 2009). Other strategies to reduce multiple pregnancies as a result of ovulation stimulation include cycle cancellation, coasting (Urman et al., 1992), aspiration of follicles before hCG administration (Albano et al., 2001), switching to IVF (Lessing et al., 1991; Nisker et al., 1994; Haydardeoglu et al., 2009) and multifetal pregnancy reduction (Ombelet et al., 2007).
Materials and Methods

The pilot study was carried out at the Centre for Reproductive Medicine, UZ Brussels between February and July 2009. The study was approved by the Ethics Committee and all patients gave written informed consent.

The primary end-point was clinical pregnancy rate per patient undergoing an excess oocyte aspiration prior to IUI. Secondary outcomes were the multiple birth rate, IUI cancellation rate, premature luteinization rate and number of retrieved oocytes.

Eligibility inclusion criteria were as follows: (i) female age ≤40 years undergoing OI; (ii) FSH on Day 3 of <12 IU/ml; (iii) more than two follicles of ≥16 mm diameter or more than one follicle of ≥16 mm in combination with two follicles of ≥14 mm; (iii) no more than eight previous OI cycles; (iv) exclusion of tubal factor by hysterosalpingography or laparoscopic tubal patency test in the last 12 months and (v) insemination motile count of >1 x 10^6 spermatozoa.

The largest group of women undergoing excess oocyte aspiration had anovulation resulting from polycystic ovary syndrome (PCOS), as diagnosed in accordance with the Rotterdam criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). PCOS was the cause of infertility in 12 couples (38.7%). Male subfertility was the indication for OI in 2 couples (6.4%), whereas 12 couples were inseminated with donor sperm. Five couples suffered unexplained infertility (16.1%).

Ovarian stimulation was performed either by clomiphene citrate or gonadotrophins. In 20 of the 34 cycles (58.8%), ovarian stimulation was carried out with 50 mg (16 cycles) or 100 mg (4 cycles) of clomiphene citrate (Clomid®; Hoechst Marion Roussel, Belgium) from Day 3 to Day 7 of the menstrual cycle. In 14 patients (41.2%), hMG (Menopur®, Ferring, Belgium) was administered from Day 2 of the cycle onwards at a daily starting dose of 75 IU. In 10 patients (29.4%), hMG was used for mature oocyte aspiration in our centre. The two largest follicles, preferably one on each side, were left intact. IUI was only performed when the number of excess oocytes retrieved at least equaled the number of follicles of ≥16 mm that had been observed at pelvic ultrasound scan on the day of hCG administration minus two.

Excess oocyte aspiration was immediately followed by IUI with a flexible Frydman catheter (Laboratoire C.C.D, Paris, France). A standard insemination volume of 0.3 ml was generally used. After the oocyte retrieval and IUI, patient rested in their beds for 60 min.

Immediately after cumulus cell removal, all metaphase II (MII) oocytes were vitrified one-by-one using a closed vitrification system. The device used for vitrification was the closed CBS-VIT High Security (HS) straw (Cryo Bio System) in combination with dimethylsulphoxide/ethylene glycol (DMSO-EG)-sucrose as the cryoprotectants (Irvine Scientific® Freeze Kit). The vitrification procedure was carried out in a room at a temperature between 22 and 27°C. The oocyte was incubated for 2 min in a 50 μl droplet of HTF HEPES-buffered culture medium (HTF Heps-buffered medium with gentamycin, Lonza, Verviers, Belgium). Then, the oocyte was put into a 50 μl droplet of equilibration solution containing 7.5% DMSO and 7.5% EG and incubated for 10 min. The oocyte was then transferred sequentially to four 25 μl droplets with vitrification solution (VS) containing 15% DMSO and 15% EG. In the first three VS droplets the oocyte was incubated, respectively, for two times, 5 and 10 s, in the 3rd droplet. The oocyte was then transferred to the last droplet and immediately loaded onto the CBS-HS straw. The straw was heat sealed and plunged into liquid nitrogen.

No luteal support was administered to women undergoing OI with clomiphene citrate, whereas OI with hMG was followed by vaginal progesterone administration. (Urogestan®; Piete, Brussels, Belgium).

Patients can decide to either undergo a warmed oocyte embryo transfer (WOET) cycle immediately following the oocyte retrieval cycle or can continue IUI and accumulate oocytes over several cycles. A SET at blastocyst stage was performed in all WOET cycles.

All data management and statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Student’s t-tests were performed on continuous variables to determine differences in mean scores and standard deviation (SD). Categorical variables were analysed using χ² analysis. A significance level of 0.05 was accepted throughout.

Results

Patient characteristics

The mean age (±SD) of the patients was 31.91 ± 1.53 years (Table I). Women with PCOS were significantly younger than those without (28.71 ± 1.41 versus 34.25 ± 1.84 years). Patients with PCOS had significantly lower FSH levels (5.2 ± 1.16 versus 8.0 ± 0.8 IU/ml). OI was performed more often with hMG in women with PCOS with a significantly higher number of total administered units during stimulation (2164 ± 671 versus 754 ± 267 IU). One of the 32 eligible patients preferred not to participate and cancelled the IUI.

Distribution of follicular size and excess oocyte yield

Patients with PCOS typically had more small follicles as compared with patients without PCOS (Table II). Both groups had a similar number of follicles that reached 16 mm; 3.54 in PCOS patients versus 3.39 in individuals without PCOS. However, significantly
more cumulus-oocyte complex (COCs) and mature oocytes were retrieved in women with PCOS. An average of 6.07 follicles per cycle were vitrified in the PCOS group, whereas the average number of follicles in the group without PCOS was 1.3.

Premature LH surge and luteinization

Eleven patients had an elevated LH level of >10 IU/ml on the day of hCG administration (11/34; 32.3%). Premature luteinization was observed during seven treatment cycles (7/34; 20.6%). Two of the four patients with a cancelled IUI cycle owing to a failed oocyte retrieval experienced premature luteinization. A third cancellation was preceded by an elevated LH (12.9 IU/ml), combined with a non-elevated progesterone level (0.85 ng/ml) on the day of hCG administration. The fourth IUI was cancelled because follicle aspiration failed to retrieve an adequate number of COCs and possibly leaving more than two oocytes for fertilization after IUI. Although IUI was cancelled in 3 of the 11 IUI cycles with a premature LH surge, another three of cycles with a premature LH surge did result in a pregnancy. None of the inseminations in cycles with premature luteinization was successful.

Outcome of IUI

Insemination was cancelled in four patients, as follicle aspiration did not yield the number of oocytes to allow ‘safe’ insemination (Table III). The overall clinical pregnancy rate was 23.5% per initiated cycle and 26.7% per IUI. All pregnancies were singletons. Clinical pregnancy rate in women with PCOS was 35.7% as compared with 18.7% in patients without PCOS. No statistically significant differences were detected.

Age-related IUI outcome and excess oocyte yield

We compared the IUI outcome and the excess oocyte yield between women younger or older than 36 years of age (Table IV). There was a significantly higher IUI cancellation rate in patients more than 36 versus less than 36 years of age (0% versus 40%; P < 0.05). The prevalence of premature LH rise, premature luteinization and pregnancy rates between the two age groups was not different. PCOS patients under the age of 36 years had an average of 6.07 vitrified oocytes per cycle as compared with 1.5 in the non-PCOS group. The patients with an IUI not resulting in a pregnancy had a similar average number

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### Table I Characteristics of patients and ovarian stimulation modalities (mean with SD).

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PCOS</th>
<th>No PCOS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>12</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No. of excess oocyte retrieval cycles</td>
<td>34</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>31.91 (1.53)</td>
<td>28.71 (1.41)</td>
<td>34.25 (1.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.42 (1.02)</td>
<td>21.92 (1.76)</td>
<td>22.73 (1.25)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous</td>
<td>1.62 (0.58)</td>
<td>1.21 (0.87)</td>
<td>1.9 (0.76)</td>
<td>NS</td>
</tr>
<tr>
<td>OI cycles (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3 FSH (IU/ml)</td>
<td>6.9 (0.9)</td>
<td>5.2 (1.16)</td>
<td>8.0 (0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CC 5 × 50 mg (%)</td>
<td>16 (47)</td>
<td>4 (29)</td>
<td>12 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CC 5 × 100 mg (%)</td>
<td>4 (12)</td>
<td>–</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>hMG (%)</td>
<td>14 (41)</td>
<td>10 (71)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Average total units of hMG (IU)</td>
<td>1651 (597)</td>
<td>2164 (671)</td>
<td>754 (267)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E₂ (pg/ml)⁺</td>
<td>1293 (242)</td>
<td>1468 (378)</td>
<td>1164 (299)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*On the day of hCG administration.
PCOS, polycystic ovary syndrome; CC, clomiphene citrate; OI, ovulation induction (comparison of PCOS with non-PCOS using Student’s t-test).

### Table II Distribution of follicle size on the day of hCG administration, and excess oocytes on the day of oocyte retrieval.

<table>
<thead>
<tr>
<th>Distribution of follicle sizes on the day of hCG administration (mm)</th>
<th>Aspirated follicles</th>
<th>Intact follicles/cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;14</td>
</tr>
<tr>
<td>All cycles (n = 34)</td>
<td>8.76</td>
<td>7.14</td>
</tr>
<tr>
<td>PCOS (n = 14)</td>
<td>13⁺</td>
<td>10⁺</td>
</tr>
<tr>
<td>No PCOS (n = 20)</td>
<td>6.17a</td>
<td>5.39⁺</td>
</tr>
</tbody>
</table>

⁺PCOS > non-PCOS; P < 0.001. 
⁻Non-PCOS > PCOS; P < 0.05.

IUI, intrauterine insemination; MII, metaphase II; COC, cumulus-oocyte complex (comparison of PCOS with non-PCOS using Student’s t-test).
Level of these patients had premature luteinization defined by a progesterone had an elevated LH on the day of hCG administration. Two of three of these patients were likely to be post-ovulatory, as they licsles resulted in the cancellation of four insemination procedures.

IUI may further reduce the incidence of multiple pregnancies. Failure to detect the expected number of oocytes in the fluid of aspirated follicles after aspiration of supernumerary follicles before IUI to reduce the multiple pregnancy rate while cancellations may have been prevented by the implementation of half of these would have resulted in 32% (11/34) fewer IUIs and 37.5% (3/8) fewer pregnancies in our excess oocyte population. However, half of these cancellations may have been prevented by the implementation of

De Geyter et al. (1996 and 1998) demonstrated the feasibility of aspirating oocytes before IUI to reduce the multiple pregnancy rate while achieving excellent pregnancy rates; however, the incidence of multiple pregnancies remained relatively high at 9.3% (11/118), including two triplets. Our findings indicate that additional microscopical confirmation of oocytes after aspiration of supernumerary follicles before IUI may further reduce the incidence of multiple pregnancies. Failure to detect the expected number of oocytes in the fluid of aspirated follicles resulted in the cancellation of four insemination procedures. Three of these patients were likely to be post-ovulatory, as they had an elevated LH on the day of hCG administration. Two of these patients had premature luteinization defined by a progesterone level of >1.2 ng/ml. In our series, simply cancelling IUI in the cycles with an elevated LH without prior attempt of excess follicle aspiration would have resulted in 32% (11/34) fewer IUIs and 37.5% (3/8) fewer pregnancies in our excess oocyte population. However, half of these cancellations may have been prevented by the implementation of

Discussion

De Geyter et al. (1996 and 1998) demonstrated the feasibility of aspirating oocytes before IUI to reduce the multiple pregnancy rate while achieving excellent pregnancy rates; however, the incidence of multiple pregnancies remained relatively high at 9.3% (11/118), including two triplets. Our findings indicate that additional microscopical confirmation of oocytes after aspiration of supernumerary follicles before IUI may further reduce the incidence of multiple pregnancies. Failure to detect the expected number of oocytes in the fluid of aspirated follicles resulted in the cancellation of four insemination procedures. Three of these patients were likely to be post-ovulatory, as they had an elevated LH on the day of hCG administration. Two of these patients had premature luteinization defined by a progesterone level of >1.2 ng/ml. In our series, simply cancelling IUI in the cycles with an elevated LH without prior attempt of excess follicle aspiration would have resulted in 32% (11/34) fewer IUIs and 37.5% (3/8) fewer pregnancies in our excess oocyte population. However, half of these cancellations may have been prevented by the implementation of

GnRH antagonist administration in all IUI cycles as that would effectively prevent premature luteinization (Kosmas et al., 2008). The use of GnRH-antagonists in OI treatment cycles in patients with PCOS is believed to favour a more monofollicular growth, but the cost is an important drawback as it does not increase the overall pregnancy rate (Ertunc et al., 2009). It is encouraging that no multiple pregnancies have occurred in this pilot study. However, multiple pregnancies cannot be ruled out in a larger series, as two follicles are kept intact after each aspiration procedure. The cutoff value for the number of follicles and their size is important in the light of occurrence of multiple pregnancies (Van Rumste et al., 2008). The American College of Obstetricians and Gynaecologists (ACOG, 2002) and the Royal College of Obstetricians and Gynaecologists (RCOG, 1998) of the UK recommend cancelling IUI cycles or withholding hCG when there are more than three follicles of ≥15 mm (ACOG) or ≥16 mm (RCOG), as a precautionary measure. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Workshop Group (2008) advises withholding hCG administration for sIUI cycles which have more than two follicles of ≥16 mm, or more than one follicle of ≥16 mm and two additional follicles of ≥14 mm in women with PCOS under the age of 38 years with no other infertility factors. To our surprise, we were able to vitrify more mature oocytes than we would have expected from the follicular count on the day of hCG administration (Table II). The sum of the vitrified oocytes (3.26 per cycle) with the two oocytes left for insemination equalled the number of follicles of ≥14 mm on the final ultrasound scan (3.10 per cycle). These findings confirm the conclusion of Gleicher et al. (2000) stating that the total number of follicles is an independent predictor of the risk of high-order pregnancy, whereas the number of follicles of 16 mm or more is not. This also suggests that although large follicles are believed to contain the most mature follicles, guidelines based on the number of large follicles may be inadequate for reducing the incidence of high-order multiple pregnancies.

A major advantage of aspiration of supernumerary follicles 36 h after hCG administration is the retrieval of mature oocytes. A total of 111 MII oocytes were vitrified with an average of 3.26 oocytes per cycle. The average number of live births per 100 oocytes warmed after vitrification is reportedly around 4.6 (Oktay et al., 2006). Extrapolation of these success rates to our patient population

### Table III Outcome of OI and IUI.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PCOS</th>
<th>No PCOS</th>
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<tbody>
<tr>
<td>IUI</td>
<td>30</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Cancellation rate</td>
<td>4/34 (11.7)</td>
<td>0/14 (0%)</td>
<td>4/20 (20%)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>8/34 (23.5)</td>
<td>5/14 (35.7)</td>
<td>3/20 (15)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>8/30 (26.7)</td>
<td>5/14 (35.7)</td>
<td>3/16 (18.7)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>0/8 (0)</td>
<td>0/5 (0)</td>
<td>0/3 (0)</td>
</tr>
</tbody>
</table>

No differences were observed using χ² analysis at a significance level of 0.05.

### Table IV Outcome of OI and IUI and excess oocyte yield in patients, by age.

<table>
<thead>
<tr>
<th></th>
<th>&lt;36 years old</th>
<th>≥36 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/cycles</td>
<td>21/24</td>
<td>9/10</td>
</tr>
<tr>
<td>IUI cancellation (%)</td>
<td>0/24* (0)</td>
<td>4/10* (40)</td>
</tr>
<tr>
<td>Premature LH rise (%)</td>
<td>7/24 (29.1)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>Premature luteinization (%)</td>
<td>5/24 (20.8)</td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>Pregnancy rate /cycle (%)</td>
<td>6/24 (25)</td>
<td>2/10 (20)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>No PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes vitrified (oocytes retrieved)</td>
<td>85 (110)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Oocytes vitrified /cycle</td>
<td>6.07* (85/14)</td>
<td>1.5* (15/10)</td>
</tr>
<tr>
<td>Oocytes vitrified after failed IUI</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>Oocytes vitrified after failed IUI /cycle</td>
<td>6.22* (56/9)</td>
<td>1.5* (14/9)</td>
</tr>
</tbody>
</table>

*Comparison of categorical variables with χ² analysis. Comparison of PCOS with non-PCOS using Student’s t-test. A significance level of 0.05 was accepted throughout.
would add three pregnancies (4.6 × 0.7 = 3.2) to the eight pregnancies resulting from IUI. However, significant differences are noted in the number of oocytes available in patients with PCOS versus those without PCOS. As the average patient with PCOS appears to have 6.22 vitrified oocytes after a failed IUI, one additional pregnancy can be expected per four subsequent warming cycles. The oocyte yield per cycle among patients without PCOS is significantly lower. However, oocyte vitrification allows supernumerary oocytes from several ovarian stimulation cycles to be accumulated.

Although aspiration of excess oocytes and their vitrification increases treatment cost, the main alternative approaches may also be costly. Cycle cancellation, especially those with clomiphene citrate resistant polycystic ovaries, may be preceded by weeks of costly gonadotrophin stimulation. Moreover, the latter group remains at risk of having the same difficulty in achieving monofollicular development in subsequent cycles. However, cancellation may be the only option in non-IVF centres lacking the skill and infrastructure to perform oocyte retrieval and vitrification.

A move from IUI after OI with excessive follicular development to IVF holds the advantage of a low multiple pregnancy rate when using a SET policy. However, the average number of oocytes retrieved in the trials advocating the success of IUI to IVF conversion cycles range from 11.1 to 16.7 oocytes per cycle. (Nisker et al., 1994; Antman et al., 2002; Quaas et al., 2009; Haydardeoglu et al., 2009). Intriguingly, the average number of oocytes retrieved per cycle in our series is much lower (4.2 COCs), which suggests that patients with only a limited number of excess oocytes are underrepresented in these studies or that higher follicular count cutoffs for ‘safe’ IUI were applied. The excellent pregnancy rates reported in these trials need to be confirmed for the large group of women with only a few surplus follicles (Antman et al., 2002; Haydardeoglu et al. 2009). We therefore assume that in the case of a limited number of supernumerary follicles, vitrification of oocytes and accumulation over consecutive cycles may be a cost-effective strategy for generating material that can be used for a subsequent transfer.

Alternatively, selective follicular reduction can be followed by immediate fertilization and embryo cryopreservation (Belaisch-Allart et al., 1988; Zusterzeel et al., 1996). Although embryo cryopreservation is a more established technique, oocyte vitrification holds important benefits. Fertilization can be postponed until a larger number of supernumerary oocytes have been retrieved over several treatment cycles. Fertilization can even become obsolete if pregnancy is achieved by IUI. Oocyte cryopreservation therefore constitutes an organizational tool which may possibly limit the total costs of the laboratory procedures. Patients undergoing OI may temporarily prefer to refrain from more advanced ART or they may have moral or ethical issues with the creation of possibly unnecessary embryos for cryopreservation.

Ovarian stimulation followed by IUI has become a questionable approach owing to its associated risk of multiple pregnancy, especially at a time of widespread use SET in IVF. Despite the extensive literature on the subject, controversy remains about the effectiveness of stimulated IUI in relation to IVF and ICSI (The ESHRE Capri Workshop Group, 2009). Several trials conclude that ovarian stimulation plus IUI is more cost-effective than IVF (Karande et al., 1999; Goverde et al., 2000). Unfortunately, these trials did not include the cost of neonatal care following preterm birth and multiple pregnancy. The application of excess oocyte retrieval and vitrification may further improve the cost-effectiveness of stimulated IUI as it effectively reduces the multiple pregnancy rates while offering additional chances of pregnancy.

A paper by Collins (2003) reviewing different approaches for unexplained infertility concludes that the best evidence continues to support the long-established clinical strategy based on a progression from low-tech IUI to high-tech IVF treatment. Although we acknowledge that oocyte vitrification is part of a high-tech approach, the actual use of these vitrified oocytes can be postponed until the couple is faced with the limitations of the conventional low-tech IUI approach.

Although IVF is the most effective per treatment cycle for infertility, IUI is cheaper and less demanding for the patient. Performing aspiration of supernumerary follicles in patients with excessive ovarian response may prove to be an effective method in limiting the two major drawbacks of ovarian stimulation, by reducing the risk of multiple pregnancy and increasing the overall pregnancy rate by later use of vitrified oocytes. Future effectiveness trials need to evaluate whether reduced multiple pregnancy and cancellation rates and the expected augmented pregnancy rates through oocyte vitrification achieved after stimulated IUI will balance out the increased cost and burden for those patients undergoing the oocyte aspiration and vitrification. Prospective randomized trials also need to evaluate the cost-effectiveness of the accumulation of vitrified excess oocytes over consecutive cycles after ovarian stimulations versus conversion to IVF. We conclude that the excess oocyte vitrification in ovarian stimulation is a valid technique offering additional chances of pregnancy as compared with a simple pre-ovulatory follicular reduction. However, the technique should not become a substitute for carefully monitored OI.

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