Efficacy of natural cycle IVF: a review of the literature

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Since the introduction of IVF treatments, natural cycle IVF has been largely replaced by IVF with ovarian stimulation. However, natural cycle IVF has several advantages. It is associated with a close to zero multiple pregnancy rate, and a zero risk of ovarian hyperstimulation syndrome. Per cycle, natural cycle IVF is less time consuming, physically and emotionally less demanding for patients, and cheaper than stimulated IVF, but also less effective. This systematic literature review addresses the issue of effectiveness of natural cycle IVF. Herein, 20 studies describing natural cycle IVF are presented; 12 case series and eight in which a comparison was made between natural cycle IVF and IVF with ovarian stimulation. Good-quality randomized controlled trials and formal cost-effectiveness analyses are lacking. The 20 selected studies comprised a total of 1800 cycles of natural cycle IVF, resulting in 819 embryo transfers (45.5% per cycle) and 129 ongoing pregnancies (7.2% per cycle and 15.8% per embryo transfer). Efficacy of natural cycle IVF is hampered by high cancellation rates because of premature LH rise and premature ovulations. It is concluded that natural cycle IVF is a low-risk, low-cost and patient-friendly procedure. A randomized controlled trial comparing natural cycle IVF with current standard treatment strategies is warranted.

Key words: IVF/natural cycle/spontaneous cycle/systematic literature review/unstimulated cycle

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Introduction

The first successful IVF treatment was performed in an unstimulated menstrual cycle (Steptoe and Edwards, 1978), since when IVF in natural cycles has been largely replaced by IVF with ovarian stimulation. The use of exogenous gonadotrophins and gonadotrophin-releasing hormone (GnRH) agonists lowers cancellation rates and raises the number of oocytes obtained, thus leading to a higher number of embryos and consequently better results in terms of pregnancy rates.

As a consequence of IVF with ovarian stimulation, two important complications arise, namely multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).

In order to maximize the chance of pregnancy, multiple embryos are usually transferred to the uterus, leading to a 20–30% multiple pregnancy rate in most IVF programmes (Nygren and Andersen, 2001). Compared with naturally conceived pregnancies, the risk for twins in IVF-pregnancies is increased about 20-fold, and the risk for higher-order multiples about 400-fold (Kauma, 1997). Twin and higher-order multiple pregnancies are associated with a high risk of prematurity, causing considerable morbidity and mortality of the neonates (Bergh et al., 1999; Elster et al., 2000). Compared with singletons, twins have a 5- to 6-fold higher perinatal mortality rate (Lieberman, 1998).

Up to 10% of IVF treatments with ovarian stimulation lead to OHSS, which is a severe and sometimes life-threatening condition (Elchalal and Schenker, 1997; Beerendonk et al., 1998). Moreover, although available data are reassuring, the possibility of heightened risk of ovarian cancer after repeated ovarian stimulation remains a matter of concern (Duckitt and Templeton, 1998). The generation of spare embryos also causes ethical and religious dilemmas.

Currently, attention is focused on developing strategies to avoid twin and higher-order multiple pregnancies, as well as strategies to make IVF more ‘patient-friendly’ (Edwards et al., 1996; Olivennes and Frydman, 1998; Olivennes, 2000; Templeton, 2000; Jones and Schnorr, 2001). Strategies proposed to restrict the
incidence of multiple pregnancies include the elective transfer of a single embryo (Vilska et al., 1999; Gerris and Van Royen, 2000; ESHRE Campus Course Report, 2001; Martikainen et al., 2001) or blastocyst (Gardner et al., 2000a,b).

Various regimens of minimal ovarian stimulation for IVF have been proposed as patient-friendly strategies, with no risk of OHSS and pregnancy rates of 17 to 33% per oocyte retrieval, yet still leading to multiple pregnancy rates of 5 to 14% (Fauser et al., 1999; Branigan and Estes, 2000; De Jong et al., 2000; DeVane et al., 2000; Macklon and Fauser, 2000; Ingerslev et al., 2001).

In natural cycle IVF, a low-risk profile is combined with a patient-friendly treatment. Natural cycle IVF is associated with a close to zero multiple pregnancy rate and a zero risk of OHSS. Per cycle, natural cycle IVF is less time consuming, physically less demanding, and also requires far less hormonal medication than stimulated IVF.

In light of the advantages of natural cycle IVF, it seems important to evaluate its effectiveness. The present report is a systematic literature review focusing on the pregnancy rates after natural cycle IVF and its cost-effectiveness.

**Literature search**

**Objectives**

The aim of this review was to determine ongoing pregnancy rates per started cycle of natural cycle IVF. As secondary aims, the wish was to compare results of natural cycle IVF with those of stimulated IVF, and to determine the cost-effectiveness of natural cycle IVF.

**Selection criteria**

Only studies concerning natural cycle IVF or ICSI with no other intervention than the administration of HCG for ovulation triggering were included in the analysis. Studies concerning IVF or ICSI with the use of minimal stimulation by clomiphene citrate (CC) or otherwise, were thus not included. An accurate estimation of the effectiveness of treatments can only be made taking into account the number of started cycles. Therefore, only studies from which the actual ongoing pregnancy rate per started cycle could be calculated were included.

Case series with retrospectively or prospectively collected data were included in the search. Controlled trials with a historical control group, pseudo-randomized and randomized controlled trials were included in the review provided that the natural cycle IVF treatment arm fitted the selection criteria. Case reports and expert opinions were not included.

**Search strategy**

Publications of potential interest were identified through comprehensive searches of the Embase and Medline databases. The following headings were used: IVF, ICSI, spontaneous cycle, natural cycle, and unstimulated cycle. Inclusive dates for the online search were 1989 to July 2001. In addition, bibliographies of retrieved studies were hand-searched for other potentially relevant publications. Abstract books of The American Society for Reproductive Medicine (1989–2000) and European Society for Human Reproduction and Embryology (1989–2001) meetings were hand-searched for potentially relevant publications.

Two independent reviewers (M.J.P. and A.H.) selected the publications to be included in accordance with the above-mentioned criteria.

The studies were analysed to obtain an estimate of the pregnancy rate per started cycle of natural cycle IVF, and an estimate of the cancellation rate per started cycle. No reports were found which dealt primarily with the issue of cost-effectiveness of natural cycle IVF. Three of the studies included in the review provided an estimate of costs of natural cycle IVF (Aboulghar et al., 1995; Daya et al., 1995; Nargund et al., 2001).

**Studies excluded from the review**

Of 33 potentially relevant reports, 13 were not included in the review. Five studies were excluded because the number of started cycles was not mentioned (Monks et al., 1993; Turner et al., 1994; Kumar et al., 1997; Reljic and Vlaisavljević, 1999; Tomažević et al., 1999). Four studies were excluded because the number of ongoing pregnancies was not specified (Ueno et al., 1991; Fahy et al., 1995; Cahill et al., 1996; Reljic et al., 2001). One study was excluded because treatments were performed only in women of advanced age (>44 years) and this was judged not to be representative for the general IVF patient population (Bar-Hava et al., 2000). Another three publications were not included since the presented figures overlapped with subsequent (Paulson et al., 1990; Lindheim et al., 1996) or former (Paulson et al., 1994a) publications by the same authors.

**Studies included in the review**

Of the 20 studies included in the review, 15 were published in peer-reviewed journals (Foulot et al., 1989; Paulson et al., 1992; Claman et al., 1993; MacDougall et al., 1994; Aboulghar et al., 1995; Daya et al., 1995; Seibel et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Zayed et al., 1997; Bassil et al., 1999; Janssens et al., 2000; Ingerslev et al., 2001; Nargund et al., 2001; Ng et al., 2001) and five were published in conference abstract books (Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Tomažević et al., 1996; Feldman et al., 1998).

Of the 20 selected studies, eight were case series of natural cycle IVF with prospectively collected data (Foulot et al., 1989; Hillensjö et al., 1990; Aboulghar et al., 1995; Daya et al., 1995; Feldman et al., 1998; Janssens et al., 2000; Nargund et al., 2001; Ng et al., 2001). Six studies were retrospective case series (Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; Seibel et al., 1995; Lindheim et al., 1997; Zayed et al., 1997). In five studies, a comparison was made with stimulated IVF cycles from the same time period (Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; Lindheim et al., 1997; Ng et al., 2001). One report was a comparative study, in which natural cycle IVF was compared with previous failed cycles of stimulated IVF in the same patients (Bassil et al., 1999). In one study, results of natural cycle IVF were compared with results of simultaneous embryo transfer of cryopreserved embryos together with embryos obtained after natural cycle IVF (Kim et al., 1996). One study was a randomized controlled trial comparing two embryo transfer policies (Tomažević et al., 1996). Two studies were randomized controlled trials comparing natural cycle IVF with IVF in CC-stimulated cycles (MacDougall et al., 1994; Ingerslev et al., 2001). One study was a randomized controlled trial with cross-
over design comparing natural cycle IVF with stimulated IVF (Levy et al., 1991).

The 20 selected studies comprised 1800 natural cycle IVF treatment cycles. The total number of participating patients remained uncertain because two trials did not mention this number.

The results of natural cycle IVF of the above-mentioned studies are presented in Tables I and II.

Case series

All case series, as well as the natural cycle IVF treatment arms of the controlled trials included in the review, were analysed together.

Patient selection and inclusion criteria

Indications for IVF

In 10 studies, the indications for IVF were tubal infertility (Hillensjö et al., 1990; Svalander et al., 1991; Claman et al., 1993; Aboulghar et al., 1995; Tomazević et al., 1996; Janssens et al., 2000; Nargund et al., 2001), unexplained infertility (Zayed et al., 1997), or both (Paulson et al., 1992; Ng et al., 2001). In one study, indications for IVF were tubal infertility, unexplained infertility, endometriosis or cervical factor infertility (Foulot et al., 1989). In one study, indications for IVF were tubal infertility, endometriosis or male factor infertility (Bassil et al., 1999). In one study, indications for IVF were tubal infertility, unexplained infertility or failed donor insemination (MacDougall et al., 1994). In one study, indications for IVF were tubal infertility, unexplained infertility or male factor infertility (Ingerslev et al., 2001). In one study, indication for IVF was not specified, but fertilization in a previous IVF treatment cycle was an inclusion criterion (Daya et al., 1995). In one study, the indication for IVF was not specified, but male factor infertility was an exclusion criterion (Kim et al., 1996). In four studies, the indication for IVF was not specified at all (Levy et al., 1991; Seibel et al., 1995; Lindheim et al., 1997; Feldman et al., 1998).

In 11 of the 20 studies, normal semen quality was an inclusion criterion (Foulot et al., 1989; Hillensjö et al., 1990; Levy et al., 1991; Paulson et al., 1992; Claman et al., 1993; MacDougall et al., 1994; Aboulghar et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Nargund et al., 2001; Ng et al., 2001). In one study, a total motile sperm count of \( >5 \times 10^6 \) was required (Daya et al., 1995).

In two studies, ICSI was performed where applicable (Bassil et al., 1999; Ingerslev et al., 2001), whilst in one study, ICSI was performed in all cases (Feldman et al., 1998).

Previous IVF treatments

In several studies, the included patients had undergone previous stimulated IVF treatments.

In five studies, all included patients had undergone IVF treatment before enrollment (Daya et al., 1995; Tomazević et al., 1996; Lindheim et al., 1997; Feldman et al., 1998; Bassil et al., 1999), and in three of these, poor response in previous cycles was an inclusion criterion (Lindheim et al., 1997; Feldman et al., 1998; Bassil et al., 1999).

In three studies, some of the included patients had undergone IVF treatment before enrollment (Foulot et al., 1989; Paulson et al., 1992; Nargund et al., 2001). In two of these, some of the patients had been poor responders in previous IVF cycles (Paulson et al., 1992; Nargund et al., 2001).

In 11 studies, it was not specified whether patients had undergone IVF treatment before inclusion (Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Claman et al., 1993; MacDougall et al., 1994; Aboulghar et al., 1995; Seibel et al., 1995; Kim et al., 1996; Zayed et al., 1997; Janssens et al., 2000; Ng et al., 2001).

In one study, none of the patients had undergone IVF treatment before enrollment (Ingerslev et al., 2001).

Assessment of ovulatory function

Clearly, an ovulatory cycle is required to be able to perform natural cycle IVF.

All patients included in the studies were judged to have ovulatory menstrual cycles, based on regularity of the cycle (Foulot et al., 1989; Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Aboulghar et al., 1995; Daya et al., 1995; Zayed et al., 1997; Bassil et al., 1999; Ingerslev et al., 2001; Nargund et al., 2001), biphasic basal body temperature charts (Claman et al., 1993; Seibel et al., 1995; Janssens et al., 2000), elevated midluteal progesterone values (Paulson et al., 1992; MacDougall et al., 1994; Kim et al., 1996; Ng et al., 2001) or in-phase endometrial biopsies (Claman et al., 1993; Janssens et al., 2000). In three studies, this was not specified (Tomazević et al., 1996; Lindheim et al., 1997; Feldman et al., 1998).

Patient age

The mean, median and range of age of the study patients are presented in Table I.

Cycle monitoring and timing of oocyte retrieval

In almost all studies, cycle monitoring was performed with ultrasound, either starting on cycle day 6–11 or 2–4 days before anticipated ovulation (Foulot et al., 1989; Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; MacDougall et al., 1994; Aboulghar et al., 1995; Daya et al., 1995; Zayed et al., 1997; Bassil et al., 1999; Ingerslev et al., 2001; Nargund et al., 2001; Ng et al., 2001). In one study, monitoring was carried out by serial measurements of serum estradiol (E_2) and LH, without ultrasound (Zayed et al., 1997).

In most studies, the timing of oocyte retrieval was done by ovulation triggering with HCG, with cancellation or advancement of oocyte retrieval in case of an LH surge (Table I). HCG was administered when the follicle size was 15–20 mm. In two studies, the follicle size at which ovulation was triggered was not mentioned (Tomazević et al., 1996; Lindheim et al., 1997). The interval between HCG injection and oocyte retrieval ranged from 31 to 36 h. In one study, oocyte retrieval was planned on the basis of spontaneous LH surges only (Zayed et al., 1997). Patients were requested to draw blood samples twice to five times daily. The interval between the onset of the spontaneous LH surge and oocyte retrieval was 34–36 h.
Table I. Selected studies of natural cycle IVF

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>No. of cycles</th>
<th>No. of cancelled cycles/reason for cancellation</th>
<th>Timing of oocyte retrieval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LH surge/ovulation</td>
<td>Other</td>
</tr>
<tr>
<td>Foulot et al. (1989)</td>
<td>71</td>
<td>32; NA; 24–40</td>
<td>80</td>
<td>7 (8.8)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Hillensjö et al. (1990)</td>
<td>18</td>
<td>30.8; NA; NA</td>
<td>48</td>
<td>12 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Levy et al. (1991)</td>
<td>22</td>
<td>NA</td>
<td>22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Svalander et al. (1991)</td>
<td>44</td>
<td>34; NA; NA</td>
<td>51</td>
<td>7 (13.7)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>Paulson et al. (1992)</td>
<td>46</td>
<td>33.9 ± 3.2; NA; 28–39</td>
<td>101</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Claman et al. (1993)</td>
<td>NA &lt;38</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MacDougall et al. (1994)</td>
<td>14</td>
<td>32.1 ± 0.9; NA; NA</td>
<td>14</td>
<td>8 (57.1)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Aboulghar et al. (1995)</td>
<td>58</td>
<td>32 ± 4.1; NA; 23–39</td>
<td>229</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Daya et al. (1995)</td>
<td>NA</td>
<td>34.5 ± 3.0; NA</td>
<td>240</td>
<td>56 (23.3)</td>
<td>28 (11.7)</td>
</tr>
<tr>
<td>Seibel et al. (1995)</td>
<td>48</td>
<td>32.8; NA; 26–38</td>
<td>64</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al. (1996)</td>
<td>45</td>
<td>32.2 ± 2.8; NA; NA</td>
<td>80</td>
<td>13 (16.3)</td>
<td>0</td>
</tr>
<tr>
<td>Tomazevic et al. (1996)</td>
<td>73</td>
<td>33.9 ± 3.6; NA; NA</td>
<td>110</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lindheim et al. (1997)</td>
<td>30</td>
<td>&lt;40</td>
<td>35</td>
<td>5 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Zayed et al. (1997)</td>
<td>117</td>
<td>NA; NA; 24–44</td>
<td>162</td>
<td>10 (6.2)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Feldman et al. (1998)</td>
<td>22</td>
<td>NA; NA; NA</td>
<td>44</td>
<td>8 (18.2)</td>
<td>8 (18.2)</td>
</tr>
<tr>
<td>Bassil et al. (1999)</td>
<td>11</td>
<td>36.6 ± 6.0; NA; NA</td>
<td>16</td>
<td>2 (12.5)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Janssens et al. (2000)</td>
<td>50</td>
<td>NA; NA; 22–38</td>
<td>81</td>
<td>13 (16.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Nargund et al. (2001)</td>
<td>52</td>
<td>NA; 34; 24–40</td>
<td>202</td>
<td>7 (3.5)</td>
<td>21 (10.4)</td>
</tr>
<tr>
<td>Ingerslev et al. (2001)</td>
<td>64</td>
<td>30.7 ± 2.5; NA; NA</td>
<td>114</td>
<td>34 (29.8)</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Ng et al. (2001)</td>
<td>19</td>
<td>NA; 32; 25–40</td>
<td>32</td>
<td>17 (54.2)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Total</td>
<td>1800</td>
<td>199/1199 (16.6)</td>
<td>94/1199 (7.8)</td>
<td>490 (28.9)</td>
<td></td>
</tr>
</tbody>
</table>

aValues are mean ± SD; median; range.

bValues in parentheses are percentages per cycle.

CT IU given.

dTomazevic et al. (1996) not included.

NA = not available.

In eight studies, E2 levels were used together with follicle size to determine the optimal time for ovulation triggering (Foulot et al., 1989; Levy et al., 1991; Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; Seibel et al., 1995; Kim et al., 1996; Ng et al., 2001).

Cancellation of oocyte retrieval

One of the disadvantages of natural cycle IVF is a high cancellation rate because of premature LH surges or premature ovulation.

There are two approaches in planning oocyte retrieval. The first is to plan oocyte retrieval by ovulation triggering with HCG and to cancel the cycle in case a spontaneous LH surge occurs. In the studies where this approach was applied, oocyte retrieval was performed in 28.6 to 86.1% per started cycle (Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; MacDougall et al., 1994; Aboulghar et al., 1995; Daya et al., 1995; Seibel et al., 1995; Lindheim et al., 1997; Feldman et al., 1998; Janssens et al., 2000; Nargund et al., 2001; Ng et al., 2001). The total number of oocyte retrievals in these studies was 367 out of 452 started cycles (80.6%).

One study reports on the successful use of the cyclooxygenase inhibitor indomethacin to postpone follicle rupture, with 3.5% cancellations because of ovulation and 10.4% for other reasons (Nargund et al., 2001).

Reasons for cancellation of oocyte retrieval were specified in 14 studies, in which a total of 1199 cycles was described (Table I). Oocyte retrieval was cancelled because of premature LH surge or ovulation in 199 out of 1199 cycles (16.6%). Ninety-four out of 1199 cycles (7.8%) were abandoned because of poor follicular growth, ovarian cyst formation or for other reasons.

Follicle aspiration and oocyte recovery rate

In seven studies, the aspiration needle which was used for transvaginal oocyte retrieval was specified. In two studies, single-lumen needles were applied without flushing of the follicle, and with successful oocyte recovery rates of 83% and 83.6% respectively (Tomazevic et al., 1996; Janssens et al., 2000). In four studies, either single- or double-lumen needles were applied with flushing of the follicle. The successful oocyte recovery rate was 60.0 to 95.2% in these studies (Claman et al., 1993; Zayed et al., 1997; Ingerslev et al., 2001; Ng et al., 2001). The total number of successful oocyte retrievals in these studies was 240 out of 271 procedures (88.6%). In one study, both single- and double-lumen needles were used (Daya et al., 1995); in this study, the successful oocyte recovery rate rose from 68.5% with single-
lumen needles to 91.2% after the introduction of double-lumen needles with flushing of the follicle. Oocyte recovery was successful in 57.1 to 100% of retrievals in studies where the choice of needle was not specified (Foulot et al., 1989; Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; Paulson et al., 1992; MacDougall et al., 1994; Aboulghar et al., 1995; Seibel et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Feldman et al., 1998; Bassil et al., 1999; Nargund et al., 2001).

In eight studies, more than one oocyte was obtained on some occasions (Paulson et al., 1992; Aboulghar et al., 1995; Daya et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Ingerslev et al., 2001; Nargund et al., 2001). Almost all oocyte retrievals were transvaginal and ultrasound-guided. In one case, a laparoscopy was performed for oocyte retrieval because of anatomical reasons (Foulot et al., 1989).

**Analgesia during oocyte retrieval**

In three studies, analgesia was standard for oocyte retrieval (Paulson et al., 1992; Claman et al., 1993; Ingerslev et al., 2001), whilst in two studies analgesia was only given on patient request (Daya et al., 1995; Janssens et al., 2000). In three studies, all oocyte retrievals were performed without analgesia (Aboulghar et al., 1995; Tomážević et al., 1996; Feldman et al., 1998), whilst in 12 studies it was not mentioned whether analgesia was used (Foulot et al., 1989; Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; MacDougall et al., 1994; Seibel et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Zayed et al., 1997; Bassil et al., 1999; Nargund et al., 2001; Ng et al., 2001).

**Luteal phase support**

It is not clear whether luteal phase support is necessary in natural cycle IVF. In 10 studies, luteal phase support was given after embryo transfer (Foulot et al., 1989; Paulson et al., 1992; Claman et al., 1993; Aboulghar et al., 1995; Daya et al., 1995; Kim et al., 1996; Tomážević et al., 1996; Zayed et al., 1997; Bassil et al., 1999; Ng et al., 2001), and from a total of 535 embryo transfers, 79 ongoing pregnancies resulted (14.8%). In two studies, no luteal phase support was given (Janssens et al., 2000; Ingerslev et al., 2001), and 12 ongoing pregnancies resulted from a total of 70 embryo transfers (17.1%). In eight studies, it was not mentioned whether luteal phase support was given (Hillensjö et al., 1990; Levy et al., 1991; Svalander et al., 1991; MacDougall et al., 1994; Seibel et al., 1995; Lindheim et al., 1997; Feldman et al., 1998; Nargund et al., 2001), and among a total of 214 embryo transfers, 38 ongoing pregnancies resulted (17.8%).

**Fertilization rate and embryo transfer rate**

In treatment cycles where IVF was applied, fertilization rate per inseminated oocyte was 44.2 to 100%. In treatment cycles where ICSI was applied, fertilization rate per injected oocyte was 56.3 to 62.5% (Table II).

Triploidy was observed in from 0 to 18.2% of the fertilized oocytes (Paulson et al., 1992; MacDougall et al., 1994; Daya et al., 1995; Kim et al., 1996; Tomážević et al., 1996; Bassil et al., 1999; Janssens et al., 2000).

The percentage of embryo transfers per started cycle was 22.7 to 80.0%, whilst the percentage of embryo transfers per attempted oocyte retrieval was 35.7 to 100.0% (Table II).

Although in eight studies on some occasions more than one oocyte was obtained, in most cases only one embryo was available for transfer (Paulson et al., 1992; Aboulghar et al., 1995; Daya et al., 1995; Kim et al., 1996; Lindheim et al., 1997; Ingerslev et al., 2001; Nargund et al., 2001). In 12 studies, all transfers were of a single embryo (Foulot et al., 1989; Levy et al., 1991; Svalander et al., 1991; Claman et al., 1993; MacDougall et al., 1994; Kim et al., 1996; Zayed et al., 1997; Feldman et al., 1998; Bassil et al., 1999; Janssens et al., 2000; Ingerslev et al., 2001; Nargund et al., 2001). In four studies, in some patients two embryos were transferred (Paulson et al., 1992; Aboulghar et al., 1995; Daya et al., 1995; Lindheim et al., 1997), whilst in another four studies the number of embryos per transfer was not specified (Hillensjö et al., 1990; Seibel et al., 1995; Tomážević et al., 1996; Ng et al., 2001).

**Implantation rate and pregnancy rate**

Fourteen studies provided sufficient data to calculate the clinical implantation rate per transferred embryo (Table II). The clinical implantation rate per transferred embryo in these studies ranged from 0 to 50% (Table II).

Eighteen studies provided sufficient data to calculate the clinical pregnancy rate per started cycle and per embryo transfer (Table II). The clinical pregnancy rate per started cycle was 0 to 21.3% (Table II); in one study it was not specified how pregnancy was defined (Nargund et al., 2001).

In two studies, intraperitoneal or intrauterine insemination was performed in cycles where oocyte retrieval was either cancelled or unsuccessful, and two pregnancies were obtained (Foulot et al., 1989; MacDougall et al., 1994). These pregnancies were not included in the calculation of pregnancy rate per cycle.

All studies provided sufficient data to calculate the ongoing pregnancy rate per started cycle and per embryo transfer (Table II). The ongoing pregnancy rate per started cycle and per embryo transfer was 0 to 18.8% and 0 to 50.0% respectively (Table II).

Of 129 ongoing clinical pregnancies, one was a monozygotic twin (Seibel et al., 1995) and 128 were singleton. Of these, spontaneous abortion of the twin pregnancy occurred at 20 weeks gestation, 56 were reported as ongoing, and 72 as live births.

**Cumulative pregnancy rates**

In three studies, life-table analysis was performed. In two of these studies (Paulson et al., 1992; Aboulghar et al., 1995), the analysis was performed on those cycles where follicle aspiration was performed; in one study (Nargund et al., 2001), the analysis was performed on the total number of started cycles. Cumulative pregnancy rates were 43.0% and 41.7% after three (Paulson et al., 1992) and five (Aboulghar et al., 1995) follicle aspirations respectively. A 46.0% cumulative pregnancy rate and a 32% probability of live birth after four cycles was calculated in one study (Nargund et al., 2001).

**Controlled trials**

The studies in which a comparison was made between natural cycle IVF and stimulated IVF were analysed separately and are presented in Table III.
Table II. Selected studies of natural cycle IVF

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (n)</th>
<th>Successful OR (n)</th>
<th>Fertilization rate (%/oocyte)</th>
<th>Embryo transfer (n)</th>
<th>Implantation rate (n)</th>
<th>Clinical PR (n)</th>
<th>Ongoing PR (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IVF</td>
<td>(%)/cycle; %/OR</td>
<td>(%)/embryo; %/cycle</td>
<td>(%)/cycle; %/ET</td>
<td>(%)/cycle; %/ET</td>
</tr>
<tr>
<td>Foulot et al. (1989)</td>
<td>68 (85.0)</td>
<td>63 (92.6)</td>
<td>NA</td>
<td>53 (66.3; 77.9)</td>
<td>17 (32.1)</td>
<td>17 (21.3)</td>
<td>13 (16.3; 24.5)</td>
</tr>
<tr>
<td>Hillensjö et al. (1990)</td>
<td>36 (75.0)</td>
<td>30 (83.3)</td>
<td>NA</td>
<td>20 (41.7; 55.6)</td>
<td>NA</td>
<td>2 (4.2)</td>
<td>2 (4.2; 10.0)</td>
</tr>
<tr>
<td>Levy et al. (1991)</td>
<td>16 (72.7)</td>
<td>13 (81.3)</td>
<td>84.6</td>
<td>11 (50.0; 68.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Svalander et al. (1991)</td>
<td>32 (62.7)</td>
<td>31 (96.9)</td>
<td>64.5</td>
<td>20 (39.2; 62.5)</td>
<td>6 (30.0)</td>
<td>6 (11.8)</td>
<td>6 (11.8; 30.0)</td>
</tr>
<tr>
<td>Paulson et al. (1992)</td>
<td>78 (77.2)</td>
<td>NA</td>
<td>71.7</td>
<td>63 (62.4; 80.8)</td>
<td>11 (13.4)</td>
<td>11 (10.9)</td>
<td>9 (8.8; 14.3)</td>
</tr>
<tr>
<td>Claman et al. (1993)</td>
<td>40 (53.3)</td>
<td>24 (60.0)</td>
<td>NA</td>
<td>18 (24.0; 45.0)</td>
<td>2 (11.1)</td>
<td>2 (2.7)</td>
<td>2 (2.7; 11.1)</td>
</tr>
<tr>
<td>MacDougall et al. (1994)</td>
<td>4 (28.6)</td>
<td>4 (100.0)</td>
<td>100.0</td>
<td>4 (28.6; 100.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aboulghar et al. (1995)</td>
<td>112 (48.9)</td>
<td>98 (87.5)</td>
<td>NA</td>
<td>86 (37.6; 76.8)</td>
<td>11 (12.1)</td>
<td>11 (4.8)</td>
<td>11 (4.8; 12.8)</td>
</tr>
<tr>
<td>Daya et al. (1995)</td>
<td>156 (65.0)</td>
<td>130 (83.3)</td>
<td>80.0</td>
<td>92 (38.3; 58.9)</td>
<td>NA</td>
<td>11 (4.6)</td>
<td>9 (3.8; 9.8)</td>
</tr>
<tr>
<td>Seibel et al. (1995)</td>
<td>48 (75.0)</td>
<td>36 (75.0)</td>
<td>69.4</td>
<td>25 (39.1; 52.1)</td>
<td>NA</td>
<td>8 (12.5)</td>
<td>7 (10.9; 28.0)</td>
</tr>
<tr>
<td>Kim et al. (1996)</td>
<td>67 (83.8)</td>
<td>64 (95.5)</td>
<td>97.0</td>
<td>61 (76.3; 91.0)</td>
<td>10 (16.4)</td>
<td>10 (12.5)</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>Tomazěvič et al. (1996)</td>
<td>NA</td>
<td>NA</td>
<td>77.0</td>
<td>59 (53.6; NA)</td>
<td>13 (22.0)</td>
<td>13 (11.8)</td>
<td>11 (10.0; 18.6)</td>
</tr>
<tr>
<td>Lindheim et al. (1997)</td>
<td>30 (85.7)</td>
<td>30 (100.0)</td>
<td>89.1</td>
<td>28 (80.0; 93.3)</td>
<td>NA</td>
<td>NA</td>
<td>5 (14.3; 17.9)</td>
</tr>
<tr>
<td>Zayed et al. (1997)</td>
<td>145 (89.5)</td>
<td>138 (95.2)</td>
<td>73.4</td>
<td>89 (54.9; 61.4)</td>
<td>12 (13.5)</td>
<td>12 (7.4)</td>
<td>9 (5.6; 10.1)</td>
</tr>
<tr>
<td>Feldman et al. (1998)</td>
<td>28 (63.6)</td>
<td>16 (57.1)</td>
<td>62.5</td>
<td>10 (22.7; 35.7)</td>
<td>2 (20.0)</td>
<td>2 (4.5)</td>
<td>2 (4.5; 20.0)</td>
</tr>
<tr>
<td>Bassil et al. (1999)</td>
<td>13 (81.3)</td>
<td>11 (84.6)</td>
<td>83.3</td>
<td>6 (37.5; 46.2)</td>
<td>3 (50.0)</td>
<td>3 (18.8)</td>
<td>3 (18.8; 50.0)</td>
</tr>
<tr>
<td>Janssens et al. (2000)</td>
<td>67 (82.7)</td>
<td>56 (83.6)</td>
<td>89.3</td>
<td>41 (50.6; 61.2)</td>
<td>10 (24.4)</td>
<td>10 (12.3)</td>
<td>8 (11.1; 19.5)</td>
</tr>
<tr>
<td>Nargund et al. (2001)</td>
<td>174 (86.1)</td>
<td>142 (81.6)</td>
<td>65.8</td>
<td>96 (47.5; 55.2)</td>
<td>NA</td>
<td>NA</td>
<td>16 (7.9; 16.7)</td>
</tr>
<tr>
<td>Ingerslev et al. (2001)</td>
<td>74 (64.3)</td>
<td>68 (91.9)</td>
<td>44.2</td>
<td>29 (25.4; 39.2)</td>
<td>4 (13.8)</td>
<td>4 (3.5)</td>
<td>4 (3.5; 13.8)</td>
</tr>
<tr>
<td>Ng et al. (2001)</td>
<td>12 (37.5)</td>
<td>10 (31.3)</td>
<td>80.0</td>
<td>8 (25.0; 66.7)</td>
<td>NA</td>
<td>4 (12.5)</td>
<td>4 (12.5; 50.0)</td>
</tr>
<tr>
<td>Total</td>
<td>819 (45.5)</td>
<td>NA</td>
<td>819 (45.5; NA)</td>
<td>129 (7.2; 15.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aPregnancy after intraperitoneal or intrauterine insemination after cancelled or unsuccessful oocyte retrieval: not included in calculation of clinical PR
NA = not available; ET = embryo transfer; OR = oocyte retrieval; PR = pregnancy rate.

Description of the studies

One study (Levy et al., 1991) was a series of 22 cycles of natural cycle IVF compared with 26 cycles of stimulated IVF. This study was randomized with a cross-over design, though the method of randomization was not mentioned. There was no mention of either the sample size estimation by power calculation or the drop-out rate (Levy et al., 1991). Four studies reported on series of natural cycle IVF that were retrospectively compared with stimulated IVF cycles of the same time period (Svalander et al., 1991; Paulson et al., 1992; Claman et al., 1993; Ng et al., 2001). In three of these studies, drop-out rates were not mentioned (Svalander et al., 1991; Claman et al., 1993; Ng et al., 2001). In one study, it was possible to extrapolate drop-out rates after one, two and three cycles. The reasons for drop-out were not specified in this study (Paulson et al., 1992). Others (Lindheim et al., 1997) reported on 35 natural cycle IVF cycles in 30 patients and retrospectively compared these with 27 cycles of stimulated IVF. The 30 patients in the natural cycle IVF group were patients whose oocyte retrieval was cancelled in a former treatment cycle because of poor response to ovarian stimulation. The 27 patients in the stimulated IVF group were patients with a poor response to ovarian stimulation who proceeded with oocyte aspiration (Lindheim et al., 1997). Two studies were randomized controlled trials comparing natural cycle IVF with IVF in CC-stimulated cycles (MacDougall et al., 1994; Ingerslev et al., 2001). In the former study (MacDougall et al., 1994), randomization was performed using computer-selected random numbers. There was no mention of sample size estimation by power calculation, and drop-out rates were not mentioned (MacDougall et al., 1994). In the latter study (Ingerslev et al., 2001), block randomization was performed by a sealed envelope method. Power calculation was not done in this study, and although drop-out rates were mentioned for the total group of patients, they were not specified for the natural cycle arm (Ingerslev et al., 2001).

Ovarian stimulation

For stimulated IVF, luteal phase-initiated down-regulation with GnRH agonists and ovarian stimulation with human menopausal gonadotrophins (HMG) was used in three studies (Levy et al., 1991; Claman et al., 1993; Lindheim et al., 1997). In one study, either a down-regulation protocol with a GnRH agonist and HMG or HMG alone was used for ovarian stimulation (Paulson et al., 1992). In one study, ovarian stimulation was performed with a CC/HMG protocol (Svalander et al., 1991), while in another study the stimulation protocol was not specified (Ng et al., 2001). In two studies, ovarian stimulation was performed with CC (MacDougall et al., 1994; Ingerslev et al., 2001).

Embryo transfer rate

For natural cycle IVF, the proportion of embryo transfers per started cycle was 24 to 80%. For gonadotrophin-stimulated IVF cycles, the proportion of embryo transfers per started cycle was...
cycles, 20 were ongoing; of these, two were twin pregnancies (Levy et al., 1991; Svalander et al., 1991; Claman et al., 1993; MacDougall et al., 1994; Ingerslev et al., 2001). In two studies, some transfers were of two or three embryos (Paulson et al., 1992; Lindheim et al., 1997). In one study, the number of embryos per transfer was not specified (Ng et al., 2001). For gonadotrophin-stimulated IVF cycles, a mean of 1.14 to 3.35 embryos were transferred in three studies where this was specified (Svalander et al., 1991; Claman et al., 1993; Lindheim et al., 1997). In three studies, the number of embryos per transfer was not specified (Levy et al., 1991; Paulson et al., 1992; Ng et al., 2001). For CC-stimulated cycles, the number of embryos per transfer was not mentioned in one study (MacDougall et al., 1994), and was 1.44 in another (Ingerslev et al., 2001).

**Implantation rate and pregnancy rates**

For natural cycle IVF, seven studies provided sufficient data to calculate clinical implantation rate per transferred embryo (Table III), and this ranged from 0 to 33.0%. For gonadotrophin-stimulated IVF cycles, two studies provided sufficient data to calculate clinical implantation rates per transferred embryo of 7.0–9.0% (Table III). For CC-stimulated IVF cycles, clinical implantation rate per transferred embryo was 24.7% in the only study where this was specified (Ingerslev et al., 2001).

For natural cycle IVF, seven studies provided sufficient data to calculate clinical pregnancy rate per started cycle (Table III), and this ranged from 0 to 12.5%. All studies provided sufficient data to calculate ongoing pregnancy rate per started cycle and per embryo transfer (Table III). Ongoing pregnancy rates per started cycle and per embryo transfer were 0 to 14.3% and 0 to 50.0% respectively. For gonadotrophin-stimulated IVF cycles, clinical pregnancy rate per started cycle could be calculated from five studies (Table III), and ranged from 7.4 to 23.1%. Three studies provided data which enabled the calculation of ongoing pregnancy rate per started cycle and per embryo transfer (Table III). Ongoing pregnancy rate per started cycle and per embryo transfer was 7.4 to 15.6% and 9.5 to 21.8% respectively. For CC-stimulated IVF cycles, the clinical pregnancy rate per started cycle was 12.5 to 17.1%. Ongoing pregnancy rate per started cycle and per embryo transfer was 12.5 to 16.2% and 18.2 to 30.5% respectively (Table III).

**Multiple pregnancy rate**

Of 32 clinical pregnancies reported from natural cycle IVF, 30 were ongoing. All pregnancies were singleton. Of 139 clinical pregnancies reported from gonadotrophin-stimulated IVF, 104 were ongoing. In two studies, the number of ongoing pregnancies was not mentioned for the stimulated IVF group (Levy et al., 1991; Ng et al., 2001). In only one study was the multiple pregnancy rate specified; in this study, of 48 ongoing pregnancies, eight were twins, four were triplets, and one was a quadruplet (Claman et al., 1993). In the other studies, multiple pregnancy rates were not specified (Svalander et al., 1991; Paulson et al., 1992; Lindheim et al., 1997). Of 21 clinical pregnancies reported from CC-stimulated cycles, 20 were ongoing; of these, two were twin pregnancies (MacDougall et al., 1994; Ingerslev et al., 2001).

**Cost-effectiveness**

Although in almost all studies, low costs of natural cycle IVF are mentioned as an advantage, formal cost-effectiveness analyses are lacking.

One group (Aboulghar et al., 1995) stated that in their centre the total costs of one complete trial of unstimulated IVF treatment including average costs of cancelled cycles, was 20% of that of a stimulated cycle. Others (Nargund et al., 2001) reported that in their experience the per treatment cost of natural cycle IVF was 23% of that of stimulated IVF, with costs related to OHSS included. These authors also stated that natural cycles offer savings of between £4796 and £9857 per pregnancy as compared with stimulated cycles (Nargund et al., 2001). A cost per cycle for natural cycle IVF of $1200 was also mentioned (Daya et al., 1995); considering a live birth rate of 6.8%, these authors concluded that costs per live birth were $17 650 for natural cycle IVF. They also assumed costs of IVF with ovarian stimulation of $5680 per cycle (one transfer of cryopreserved embryos included). Assuming a live birth rate of 14.3% from fresh embryo transfers plus 1.8% from cryopreserved embryo transfers, it was concluded that costs per live birth were $35 000 after stimulated IVF (Daya et al., 1995).

**Discussion**

In the studies included in this review, 129 ongoing pregnancies out of 1800 started cycles are described (7.2%).

In these studies, natural cycle IVF and ICSI is described for all causes of infertility. Some authors have proposed natural cycle IVF as a valuable alternative to stimulated IVF in poor responders (Lindheim et al., 1997; Feldman et al., 1998; Bassil et al., 1999). Moreover, patient characteristics and protocols for monitoring of IVF treatment cycles also vary considerably, and as a consequence the outcome of the IVF treatments is variable.

In natural cycle IVF, results are hampered by high (28.9%) cancellation rates per started cycle.

The timing of oocyte retrieval is usually performed after ovulation triggering with HCG. In case an LH rise is found before ovulation triggering, oocyte retrieval is either cancelled or advanced. Although, in studies where oocyte retrieval was performed in case of an LH rise, the number of oocyte retrievals per started cycle was higher and there seemed to be little impact on overall results. The ongoing pregnancy rate per started cycle was 6.8% and 8.2% respectively in those studies where oocyte retrieval was or was not cancelled in case of an LH rise. Two groups (Foulot et al., 1989; Kim et al., 1996) found similar fertilization and cleavage rates in patients with or without an LH surge. The pregnancy rate, however, was higher in patients without an LH surge (32.0% and 15.9% per cycle) than in those with an LH surge (11.5% and 8.3% per cycle). The planning of oocyte retrieval based on an LH rise requires intensive monitoring, and an almost round-the-clock service—which most laboratories cannot provide.

One study reported on the successful use of indomethacin to postpone follicular rupture (Nargund et al., 2001). An interesting strategy to lower cancellation rates because of LH rise or ovulation is the use of GnRH antagonists, which are given after...
Table III. Comparison of natural cycle IVF with stimulated IVF

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>No. of cycles</th>
<th>Embryo transfer (%)/cycle</th>
<th>Implantation (%)/embryo</th>
<th>Clinical PR (%)/cycle</th>
<th>Ongoing PR (%)/cycle</th>
<th>Multiple PR (%)/ET</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levy et al. (1991)</td>
<td>22</td>
<td>NA</td>
<td>22</td>
<td>11 (50.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Randomized</td>
</tr>
<tr>
<td>Natural cycle</td>
<td>26</td>
<td>NA</td>
<td>26</td>
<td>23 (88.5)</td>
<td>NA</td>
<td>6 (23.1)</td>
<td>NA</td>
<td>NA</td>
<td>Cross-over</td>
</tr>
<tr>
<td>Svalander et al. (1991)</td>
<td>44</td>
<td>34; NA; NA</td>
<td>51</td>
<td>20 (39.2)</td>
<td>6 (30.0)</td>
<td>6 (11.8)</td>
<td>6 (11.8; 30.0)</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>CC/HMG</td>
<td>121</td>
<td>35; NA; NA</td>
<td>122</td>
<td>87 (71.3)</td>
<td>NA</td>
<td>27 (22.1)</td>
<td>19 (15.6; 21.8)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Paulson et al. (1992)</td>
<td>46</td>
<td>33.9 ± 3.2;</td>
<td>101</td>
<td>63</td>
<td>11 (13.4)</td>
<td>11 (10.9)</td>
<td>9 (8.9; 14.3)</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Natural cycle (GnRHa)/HMG</td>
<td>NA &lt;40</td>
<td>NA</td>
<td>NA</td>
<td>66 (9.0)</td>
<td>49 (NA)</td>
<td>35 (NA)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Claman et al. (1993)</td>
<td>NA &lt;38</td>
<td>NA</td>
<td>75</td>
<td>18 (24.0)</td>
<td>2 (11.1)</td>
<td>2 (2.7)</td>
<td>2 (2.7; 11.1)</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>GnRHa/HMG</td>
<td>NA</td>
<td>NA</td>
<td>450</td>
<td>298 (66.2)</td>
<td>NA</td>
<td>65 (14.4)</td>
<td>48 (10.7; 16.1)</td>
<td>13 (20.0)</td>
<td></td>
</tr>
<tr>
<td>MacDougall et al. (1994)</td>
<td>14</td>
<td>32.1 ± 0.9;</td>
<td>14</td>
<td>4 (28.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Randomized</td>
</tr>
<tr>
<td>Natural cycle CC</td>
<td>16</td>
<td>32.8 ± 1.1;</td>
<td>16</td>
<td>11 (68.8)</td>
<td>NA</td>
<td>2 (12.5)</td>
<td>2 (12.5; 18.2)</td>
<td>0</td>
<td>Controlled</td>
</tr>
<tr>
<td>Lindheim et al. (1997)</td>
<td>30</td>
<td>&lt;40</td>
<td>35</td>
<td>28 (80.0)</td>
<td>NA (33.0)</td>
<td>NA</td>
<td>5 (14.3; 17.9)</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Natural cycle CC</td>
<td>27</td>
<td>&lt;40</td>
<td>27</td>
<td>21 (77.8)</td>
<td>NA (7.0)</td>
<td>2 (7.4)</td>
<td>2 (7.4; 9.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ng et al. (2001)</td>
<td>64</td>
<td>30.7 ± 2.5;</td>
<td>114</td>
<td>29 (25.4)</td>
<td>4 (13.8)</td>
<td>4 (3.5)</td>
<td>4 (3.5; 13.8)</td>
<td>0</td>
<td>Randomized</td>
</tr>
<tr>
<td>Natural cycle CC</td>
<td>68</td>
<td>30.2 ± 2.9;</td>
<td>111</td>
<td>59 (53.2)</td>
<td>21 (24.7)</td>
<td>19 (17.1)</td>
<td>18 (16.2; 30.5)</td>
<td>2 (10.5)</td>
<td>Controlled</td>
</tr>
<tr>
<td>Ng et al. (2001)</td>
<td>19</td>
<td>32; NA; 25–40</td>
<td>32</td>
<td>8 (25.0)</td>
<td>NA</td>
<td>4 (12.5)</td>
<td>4 (12.5; 50.0)</td>
<td>0</td>
<td>Retrospective</td>
</tr>
<tr>
<td>‘Stimulated’</td>
<td>268</td>
<td>NA</td>
<td>301</td>
<td>278 (92.4)</td>
<td>NA</td>
<td>63 (20.9)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

aValues are mean ± SD; median; range.
bPregnancies ensuing from 178 oocyte retrievals; number of started cycles and number of embryo transfers not available.

cImplantation rate mentioned in the text; number of implantations not available.

CC = clomiphene citrate; ET = embryo transfer; GnRHa = gonadotrophin-releasing hormone agonist; HMG = human menopausal gonadotrophin; NA = not available; PR = pregnancy rate.
follicular dominance has developed and for a few days only. There are three reports on this approach (Meldrum et al., 1994; Paulson et al., 1994b; Rongieres-Bertrand et al., 1999); in these studies the cancellation rates because of ovulation ranged from 0.0 to 9.0%.

Another factor contributing to low success rates of natural cycle IVF is a rather low percentage of successful oocyte retrievals (57.1 to 100.0%). Flushing of the follicle during oocyte retrieval might raise the efficacy of the procedure, but makes the procedure less comfortable for patients.

Implantation rates per embryo after natural cycle IVF are quite acceptable up to 50.0%. The studies with lower implantation rates included poor responders and patients with a history of several unsuccessful IVF treatments. Implantation rates of embryos obtained after IVF with ovarian stimulation are rather low in the controlled trials included in this review (7.0–9.0%), though considering that these studies are not very recent, this may partly reflect poor laboratory skills (Paulson et al., 1992; Lindheim et al., 1997).

It is possible that, compared with stimulated IVF cycles, the endometrium in natural cycle IVF is more receptive. Some reports claim a diminished endometrial receptivity caused by supraphysiological levels of steroid hormones after ovarian stimulation for IVF (Fossum et al., 1989; Simón et al., 1998; Basír et al., 2001). Physiological levels of steroid hormones as present in unstimulated IVF cycles may theoretically lead to better endometrial receptivity. On the other hand, implantation rates per embryo may be lowered by the fact that usually no selection of embryos is possible as only one is obtained.

In natural cycle IVF, multiple embryos are available for transfer in some cases, after aspiration of secondary follicles. In one study (Paulson et al., 1992), a lower fertilization rate was found in oocytes derived from secondary follicles compared with oocytes derived from dominant follicles (41.0 versus 100.0%), but a higher pregnancy rate after multiple embryo transfer than after transfer of a single embryo (31.2 versus 13.0% per embryo transfer). This suggests that embryos ensuing from secondary oocytes are able to produce a pregnancy, or alternatively, that the production of multiple embryos is a marker of pregnancy success of the dominant follicle (Paulson et al., 1992).

In theory, the depletion of granulosa cells by follicle fluid aspiration might cause corpus luteum dysfunction, making luteal support necessary (Garcia et al., 1981). This could not be concluded from the included studies however, as ongoing pregnancy rates were comparable in studies where luteal support was and was not given (14.8 and 17.1% per embryo transfer respectively).

For accurate assessment of efficacy of natural cycle IVF, cumulative pregnancy rates are more useful than pregnancy rates per started cycle only. Life-table analysis in three studies included in this review showed cumulative pregnancy rates of 43.0 and 41.7% after three and five oocyte aspirations (Paulson et al., 1992; Aboughar et al., 1995), and 46.0% after four started cycles (Nargund et al., 2001).

Natural cycle IVF has many potential advantages. In the studies included in this review, in the majority of cases a single embryo was transferred and the multiple pregnancy rate was close to zero. In controlled trials included herein, for the stimulated IVF groups the multiple pregnancy rate was not mentioned in most studies, but it was very high (13 out of 48 pregnancies were multiple) where this was mentioned (Claman et al., 1993). In studies where minimal ovarian stimulation with CC was applied, the multiple pregnancy rate was 9.5% (MacDougall et al., 1994; Ingerslev et al., 2001). Clearly, multiple pregnancies are a consequence of embryo transfer policy, and not of ovarian stimulation in itself, and so can be avoided by replacing a single embryo. This strategy still allows for the selection of good-quality embryos, which raises pregnancy rates while leading to singleton pregnancies. Reports on this subject show excellent pregnancy rates of 27.0 to 48.3% per single embryo transfer (Gerris et al., 1999; Vilska et al., 1999; ESHRE Campus Course Report, 2001; Martikainen et al., 2001). The addition of pregnancies after transfer of frozen–thawed spare embryos raises the delivery rate per oocyte retrieval even further (Tiitinen et al., 2001). However, so far, elective single embryo transfer is only proposed for selected, good-prognosis patients and is far from standard in most IVF centres (Nygren and Andersen, 2001).

When natural cycle IVF is applied, there is no risk of OHSS. Although the cryopreservation of spare embryos and their subsequent transfer contribute to pregnancy rates of stimulated IVF, legal, ethical and religious dilemmas caused by the generation of spare embryos after stimulated IVF are avoided by applying natural cycle IVF.

Per cycle, natural cycle IVF is physically less demanding than stimulated IVF and probably less emotionally so (Højgaard et al., 2001).

Per cycle, natural cycle IVF is cheaper than stimulated IVF, as it is less time consuming for laboratory and medical personnel as well as patients, and requires less hormonal medication. The per-cycle costs of natural cycle IVF are 20–23% of those of stimulated IVF (Aboughar et al., 1995; Nargund et al., 2001).

Controlled trials comparing natural cycle IVF with stimulated IVF are lacking. For a correct comparison, pregnancy rates after transfer of cryopreserved embryos should be included in the pregnancy rates of stimulated IVF. Considering the lower costs and shorter duration of a natural cycle IVF treatment, it seems logical to compare a number of natural cycle IVF treatments with one cycle of stimulated IVF, either with or without elective single embryo transfer. In such a study, the cumulative pregnancy rates of natural cycle IVF should be compared with the pregnancy rate of one cycle of stimulated IVF, frozen embryo transfers included. The complication rate of both strategies should also be taken into account.

From a cost-effectiveness point of view, the costs per live birth should be reported, and the costs related to complications should also be included in such an analysis. Since the total birth costs of a twin pregnancy are 4- to 10-fold higher than those of a singleton pregnancy (Callahan et al., 1994; Luke et al., 1996), the prevention of twin pregnancies by applying natural cycle IVF will lead to huge savings. The prevention of OHSS will also lead to a reduction in costs. On the other hand, more cycles of natural cycle IVF are needed to obtain pregnancy rates comparable with those of stimulated IVF, and therefore direct treatment-related costs per pregnancy may be higher with natural cycle IVF than with stimulated IVF. The cost-effectiveness of either strategy will thus depend on their efficacy.
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Conclusions

Natural cycle IVF is a low-risk and patient-friendly procedure with a ongoing pregnancy rate of about 7% per started cycle and about 16% per embryo transfer. The success rates of natural cycle IVF are hampered by high cancellation rates because of premature LH rise and premature ovulations. Recent reports using GnRH antagonists to prevent such a LH rise, or indomethacin to prevent rupture of the follicle before planned oocyte retrieval, appear promising in this respect.

Improvements in laboratory conditions and fertilization techniques such as ICSI may increase the success rate of natural cycle IVF. In light of the many potential advantages of natural cycle IVF, it seems advisable to re-evaluate its place in the wide range of possible fertility treatments. A randomized controlled trial, comparing natural cycle IVF with current standard treatments, is warranted. Such a study should include a cost-effectiveness analysis and focus on cumulative pregnancy rates.

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References


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