Efficacy of natural cycle IVF: a review of the literature
Pelinck M J, Hoek A, Simons A H, Heineman M J

Authors' objectives
To evaluate the effectiveness of natural cycle in vitro fertilisation (IVF) on pregnancy rates, to compare it with stimulated IVF, and to determine its cost-effectiveness.

Searching
EMBASE and MEDLINE were searched from 1989 to July 2001 using the search terms 'IVF', 'ICSI', 'spontaneous cycle', 'natural cycle' and 'unstimulated cycle'. The bibliographies of retrieved studies, and abstract books of The American Society for Reproductive Medicine (1989 to 2000) and the European Society for Human Reproduction and Embryology (1989 to 2001), were checked for additional references.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), controlled trials and case series (retrospective or prospective) were included in the review. Case reports and expert opinions were not included.

Specific interventions included in the review
Studies examining natural cycle IVF or intracytoplasmic sperm injection (ICSI) with no intervention other than the administration of human chorionic gonadotropin (HCG) for ovulation triggering were included in the review. Studies examining IVF or ICSI with minimal stimulation by clomiphene citrate or otherwise, were excluded from the review.

Participants included in the review
The participants were women undergoing IVF treatment. However, the authors do not explicitly state the inclusion criteria for the participants. The authors excluded one study where the treatments were performed on women older than 44 years.

Outcomes assessed in the review
Only studies where the actual pregnancy rate per started cycle could be calculated were included in the review. The other outcomes assessed included fertilisation and embryo transfer rate, implantation rate per transferred embryo and the clinical pregnancy rate per started cycle. Cumulative pregnancy rates and multiple pregnancy rates were also considered.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies to be included in the review.

Assessment of study quality
No formal validity checklist was used. However, the authors briefly discussed methods of randomisation, power calculations and drop-out rates for each of the controlled studies.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The authors presented the data using a descriptive synthesis. The studies were described within two sections. The first
section presented an overview of the case series as well as the natural cycle IVF treatment arms of the controlled trials. The second section described the results from studies that compared natural cycle IVF and stimulated IVF.

How were differences between studies investigated?
Differences between the studies were described for the following variables: indications for IVF, previous IVF treatments, assessment of ovulatory function, cycle monitoring and timing of oocyte retrieval, cancellation of oocyte retrieval, follicle aspiration and oocyte recovery rate, analgesia during oocyte retrieval, luteal phase support, and ovarian stimulation.

Results of the review
Twenty studies were included in the review, comprising 1,800 natural cycle IVF treatment cycles. Four of the studies were RCTs (260 treatment cycles), eight were case series with prospectively collected data (956 treatment cycles), six were retrospective case series (488 treatment cycles) and two were non-randomised controlled studies (96 treatment cycles).

The 20 studies comprised a total of 1,800 cycles of natural cycle IVF. This resulted in 819 embryo transfers (45.5% per cycle) and 129 ongoing pregnancies (7.2% per cycle and 15.8% per embryo transfer).

Using data from 18 studies, the clinical pregnancy rate per started natural cycle IVF ranged from 0 to 21.3%. Based on all 20 studies, the ongoing pregnancy rate per started cycle and per embryo transfer ranged from 0 to 18.8% and from 0 to 50%, respectively.

Eight studies compared natural cycle IVF and stimulated IVF. Seven studies provided sufficient data to calculate the clinical pregnancy per started cycle; this ranged from 0 to 12.5%. Based on all eight studies, the ongoing pregnancy rate per started cycle and per embryo transfer ranged from 0 to 14.3% and from 0 to 50.0%, respectively, for natural cycle IVF.

For gonadotrophin-stimulated IVF cycles, the clinical pregnancy rate per started cycle ranged from 7.4 to 23.1% (based on five studies). Based on three studies, the ongoing pregnancy rate per started cycle and per embryo transfer ranged from 7.4 to 15.6% and from 9.5 to 21.8%, respectively.

For clomiphene citrate-stimulated IVF cycles, the clinical pregnancy rate per started cycle was 12.5 to 17.1%. The ongoing pregnancy rate per started cycle and per embryo transfer ranged from 12.5 to 16.2% and from 18.2 to 30.5%, respectively.

Cost information
No reports were found that dealt primarily with the issue of the cost-effectiveness of natural cycle IVF. Three of the studies included in the review provided an estimate of the costs of natural cycle IVF.

Authors' conclusions
Natural cycle IVF is a low-risk and patient-friendly procedure.

CRD commentary
The inclusion criteria were clear for the study design, intervention and primary outcome, but were less clear for the participants. The authors did not state whether non-English publications or unpublished data were sought. It is possible, therefore, that this could have introduced publication or language bias into the review. While the authors did address some aspects of the quality of the controlled studies, a systematic approach to the quality assessment was not taken. Without an assessment of the quality of all of the included studies, it is difficult to determine the reliability of the results. The authors described the studies in some detail, demonstrating the heterogeneous nature of the data set. As such, a narrative summary of the studies appears to have been appropriate. Given the paucity of studies comparing natural cycle IVF and IVF with ovarian stimulation, the authors have not attempted to draw any firm conclusions from this data.
Implications of the review for practice and research
Practice: The authors state that, given its many potential advantages, natural cycle IVF should be considered in the wide range of possible fertility treatments.

Research: The authors state that a RCT comparing natural cycle IVF with current standard treatments is warranted. In addition, the study should include a cost-effectiveness analysis and focus on cumulative pregnancy rates.

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