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Cumulative conception and live birth rates in natural (unstimulated) IVF cycles

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IVF treatment, which involves ovarian stimulation, poses significant health problems such as ovarian hyperstimulation and is associated with a high incidence of multiple pregnancy and premature birth. In this paper, we demonstrate how natural cycle IVF is an effective and potentially cost-effective alternative treatment option for certain groups of infertile couples. The study was conducted in the Assisted Conception Unit at King's College School of Medicine, London. Fifty-two women with regular menstrual cycles whose partners had normal semen parameters were offered a total of 181 cycles of treatment (average 3.49 per couple). Life table analysis was used to calculate cumulative success rates after successive cycles of treatment. After four cycles, the cumulative probability of pregnancy was 46% with an associated live birth rate of 32%. To achieve maximal effectiveness, natural cycle IVF should be offered as a series of treatment cycles, for it is safer, less stressful and can be offered over consecutive cycles. Moreover, the avoidance of expensive drugs and reduced intensity of monitoring make natural cycle IVF less expensive than conventional treatment involving stimulation. We calculate that this treatment can be offered at ~23% of the cost of a stimulated cycle, suggesting that it may be a cost-effective alternative to conventional assisted conception techniques.

Key words: cumulative success rate/IVF/natural cycle/unstimulated cycle

Introduction

IVF and embryo transfer is now an established method of treating female infertility (Hull *et al*., 1992). The first successful pregnancy resulting from IVF and embryo transfer occurred during an unstimulated normal menstrual cycle (Steptoe and Edwards, 1978) but natural cycle treatment has been abandoned following the extensive use of ovarian stimulation by exogenous FSH in an attempt to obtain more oocytes. This has resulted in fewer abandoned cycles and improved pregnancy rates, especially when down-regulation with gonadotrophin-releasing hormone analogues prior to ovarian stimulation is employed (Hughes *et al*., 1992).

Such ovarian stimulation regimens, however, pose significant problems for the couple, medical staff and society in general. Most cycles of treatment in the United Kingdom are not funded by the National Health Service (NHS) and the additional drug bill for ovarian stimulation can add significantly to the cost to the patient. The disposal of the extra embryos generated can cause ethical and religious dilemmas while problems related to the generation of high order multiple gestations still occur and add significantly to the number of premature births and costs to the NHS for neonatal care. Data from all Swedish IVF clinics demonstrate an incidence of multiple births of 27% compared with 1% born in the normal population (Bergh *et al*., 1999). This has led the Royal College of Obstetricians and Gynaecologists (RCOG), London to recommend that no more than two embryos are transferred in view of the unacceptably high rate of multiple births. Equally importantly, ovarian stimulation leads to up to 5% of women developing ovarian hyperstimulation syndrome (OHSS) which is a life-threatening condition (Beerendonk *et al*., 1998). Finally, there is anxiety that the long-term effects of repeated ovarian stimulation may increase the risk of ovarian, endometrial and breast cancer (Duckitt and Templeton, 1998).

With this background, it seems an opportune time to re-evaluate natural cycle IVF, especially as improvements in embryology may have increased the success rate of the technique. Previous studies on natural cycle IVF have reported live birth rates of between 3.8 and 18.1% per treatment cycle (Daya *et al*., 1995) but none of these studies attempted to estimate on cumulative pregnancy and live birth rates. We report here the results of a study conducted in a teaching hospital where selected groups of women were recruited to a natural cycle IVF programme so that cumulative pregnancy and live birth rates could be analysed.

Materials and methods

The study was conducted at the Assisted Conception Unit of King's College School of Medicine and Dentistry between 1993 and 1996. All couples on the waiting list for ovulation induction IVF–embryo transfer were offered immediate treatment with natural cycle IVF if they had regular menstrual cycles and if the male partner had normal semen parameters. Women who opted to receive natural cycle treatment fell into three main categories. (i) Thirty-two women with primary infertility and tubal damage who found it difficult to afford ovulation induction and IVF–embryo transfer. These women had a total of 116 cycles. (ii) Three women with secondary infertility and tubal damage who did not wish to risk a multiple pregnancy. These women had a total of 15 cycles. (iii) Seventeen women with primary infertility and poor ovarian reserve whose previous IVF cycle was abandoned prior to oocyte collection either due to no response or poor response (less than two follicles recruited) to standard ovarian stimulation on two occasions. These women had a total of 50 cycles.

A total of 202 cycles were initiated, but in 21 cycles there was no follicular recruitment as seen on ultrasound scan. Fifty-two couples who underwent 181 natural (unstimulated) cycles for IVF were included in the study.

Treatment cycles were monitored with a transvaginal scan on day 8 or 9 of the cycle to measure follicular structures within the ovary and endometrial thickness and morphology. Depending on the size of the follicle, a second scan was performed and human chorionic gonadotrophin (HCG) 5000 IU was administered i.m. when the follicular diameter was predicted to be 16–18 mm.

Women who had a follicle of ⩾16 mm and those who had a spontaneous LH surge on a Friday were asked to take tablets of indomethacin 50 mg three times a day orally starting on Friday until Monday morning. This was done to delay follicle rupture and oocyte retrieval at the weekend (Nargund and Wei, 1996). All women who took indomethacin tablets received HCG 5000 IU i.m. 36 h before transvaginal ultrasound-guided oocyte retrieval. A total of 27 women received indomethacin in 42 cycles.

Results

Fifty-two women took part over a total of 181 cycles, 3.49 cycles per woman. Thirty-two women underwent three or more cycles, the maximum number of cycles being 10. The median age was 34 years, range 24–40, interquartile range 33–37 years.

There were 174 oocyte retrieval procedures undertaken, of which 142 resulted in at least one oocyte being retrieved (81.6%). Two oocytes were retrieved in 10 cycles, (5.7%). Where two oocytes were collected, only one was fertilized and the other oocyte was immature. Seven patients had ovulated spontaneously. Of the 142 successful collections, 100 (70%) were fertilized and 96 embryos were transferred. Of these transfers, 23 (24.0% per embryo transfer) resulted in pregnancies and 16 (16.7% per embryo transfer) in live births.

Thus there were 23 pregnancies and 16 live births from the 181 treatment cycles, giving success rates of 12.7 and 8.8% per cycle respectively. The rates for the 174 oocyte retrieval procedures were 13.2 and 9.2% per oocyte retrieval respectively.

Life table analysis was used to estimate the cumulative probabilities of pregnancy and live birth with succeeding cycles. Figure 1 shows the cumulative probabilities for pregnancy. After four cycles the cumulative probability of a pregnancy was 46%. Figure 2 shows the corresponding probabilities for a live birth, which was 32% after four cycles. The final cumulative probability of pregnancy is less than for birth, because two women had two pregnancies. The first pregnancy did not result in a birth and they had further IVF. Only the first pregnancy is included in the pregnancy table, and the total time to birth is included in the birth table.

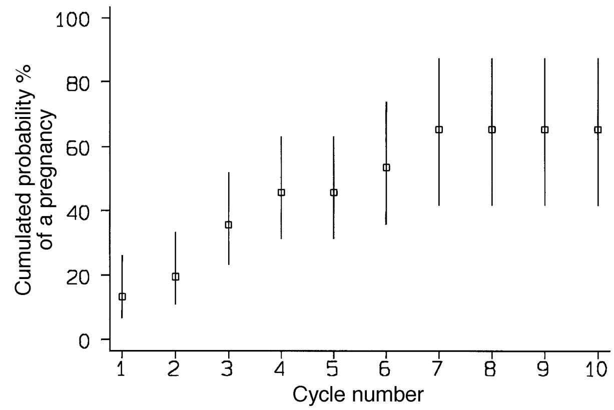

Figure 1. Cumulative probability of pregnancy in natural cycle IVF.

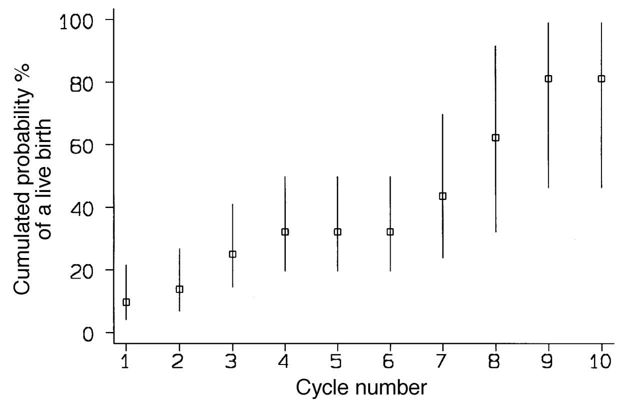

Figure 2. Cumulative probability of a live birth in natural cycle IVF.

In 42 cycles, oocyte collection was delayed for a maximum of 72 h following indomethacin administration. In this group, only one follicle ruptured prior to the oocyte retrieval procedure. A total of 38 oocytes were retrieved and fertilization occurred in 27 (71%). Four pregnancies occurred and none miscarried, so the pregnancy and live birth rate was 9.6% per cycle. The live birth rate in this group was thus very similar to that in cycles in which indomethacin was not administered.

Discussion

The results of this analysis indicate that natural cycle IVF is an effective method of treatment for ovulatory women undergoing assisted conception. The cumulative live birth rates after four cycles of treatment is 32% which is comparable with the value of 34% for women having conventional IVF treatment (Tan *et al.*, 1992). There is, however, an absence of

Table I. Estimated costs for a hypothetical cohort of 100 couples

	Natural cycle IVF	Stimulated cycle IVF[a]
Cumulative pregnancy after four consecutive cycles (%)	46	44–65
Cost per cycle (£)	396.92	1717.35
Cost per couple (£)	1315	5599–4879
Cost per pregnancy (£)	2864	12 721–7633

[a]Ranges represent results for severe to mild tubal factor.

recent data on cumulative live birth rates following conventional IVF and it is likely that current cumulative rates for IVF will be higher than quoted above. The comparative costings analysis was, therefore, made on the basis of recent data on cumulative clinical pregnancy rates per cycle.

The cost implications of natural versus stimulated cycle IVF were estimated using local cost data and results (Philips *et al*., 2000). Table I details the costs per cycle, per pregnancy and per couple for a hypothetical cohort of 100 couples undergoing either natural or stimulated cycle IVF for four consecutive cycles. The cost for natural cycles are based on three ultrasound scans (£105) and an ultrasound-guided oocyte collection (£150), the cost of embryo transfer (£100) and drug costs [HCG 5000 IU (£3.75), indomethacin 50 mg (£2.55 per 10 tablet course)]. The cost and outcome (probability of pregnancy) data for IVF are taken from Philips *et al*. and are based on the tubal model, where reported success rates were 15–25% per cycle depending on severity. The expected cost of treatment for IVF is based on 2 ampoules (75 IU) of gonadotrophins administered daily for 2 weeks (£625.38), buserelin (£58), pessary costs (£8.85), HCG 10 000 IU (£6.65), monitoring costs and the fertilization procedure (£1009). The expected costs of complication due to OHSS is also included in the overall procedure cost. Based on these estimates, natural cycle IVF can be offered at 23% of the cost of stimulated IVF based on similar success rates. Natural cycles offer savings of between £4769 and £9857 per pregnancy compared with stimulated cycles. These savings are likely to be higher as our estimates do not take account of factors such as the knock-on consequences due to multiple births or the couples' personal costs such as travel and time off work. A more detailed cost-effectiveness study, which takes these factors into account, will be the subject of further research.

An important question is whether the selection of patients in this study biased the results towards more favourable success rates. We do not believe this is so. The median age of women in the series was 34 years, and 24 patients (48%) were above the age of 35 years. Indeed, 67 cycles (37%) were in women aged >38 years. Furthermore, one-third of all cycles in the series were in women who previously responded poorly to ovarian stimulation. Overall, then, the patients in this series would probably not be regarded as being in a favourable category for successful treatment.

Apart from the avoidance of complications of ovulation induction treatment such as OHSS and high order multiple pregnancy outlined above, there are significant practical advantages to natural cycle IVF. The avoidance of expensive drugs and the reduced intensity of monitoring involving only two or three ultrasound scans makes the treatment far less expensive and stressful for the patient and less demanding on the assisted conception unit. Also, repeated cycles of ovulation induction treatment are frequently eschewed by couples because of cost and complications. Repeat cycles are also spread out over several months or years because of the need for the ovaries to recover between cycles of stimulation. On the other hand, natural cycle treatment is usually regarded on the basis of a series of treatment cycles, for the treatment is less stressful for the couple, and, as ovarian 'recovery' is not a factor, the cycles can be compressed over consecutive cycles.

One of the advantages of modern ovulation induction treatment with down regulation is that by suppressing the LH surge there is little requirement to perform oocyte collection procedures at weekends. To maintain this advantage in the natural cycle group, we decided to delay the follicular rupture by prescribing the cyclooxygenase inhibitor indomethacin to women likely to require oocyte collection at the weekend as we had previously found indomethacin effective in this respect (Nargund and Wei, 1996; Athanasiou *et al*., 1998). Although the effects of indomethacin can only be assessed on the basis of a randomized trial, the fact that indomethacin cycles in this study were similar in terms of fertilizing ability of oocytes, live birth rates to non-indomethacin cycles is reassuring. Probably the strongest advantage of ovulation induction treatment is that several embryos can usually be frozen for transfer in subsequent cycles. This reduces the need for further oocyte collections, but down-regulation and hormone replacement treatment are still often required. The success rates for frozen embryo transfer, however, are very variable (Human Fertilisation and Embryology Authority, 1999). Although some units achieve high success rates, the average live birth rate for frozen embryo transfer in the UK is 12.3%, so the advantages of frozen embryo transfer compared with repeated natural cycle treatments are not clear-cut.

There are also persuasive physiological reasons for preferring natural cycle IVF. Ovulation induction therapy has been reported to be associated with an increased rate of mosaicism in embryos which fail to implant (Munné *et al*., 1997). Stimulation can also disturb the maturational matching of embryo and endometrium which may be detrimental to successful implantation (Paulson *et al*., 1990; Lass *et al*., 1998). However, proof as to whether these theoretical advantages are real can only be proved if natural cycle treatment is compared with conventional IVF treatment in which only one embryo is transferred. Recently, there has been a move towards the transfer of only two embryos in conventional IVF treatment to avoid the possibility of high order multiple pregnancy, as it has been shown that there are no significant advantages to transferring more than two embryos if more than four eggs were fertilized (presumably reflecting normal ovarian function) (Templeton and Morris, 1998). In view of this trend towards reducing the number of embryos transferred with ovulation induction IVF (Royal College of Obstetricians and Gynaecologists, 2000), the results of this study must open the debate as to whether a series of natural cycle IVF treatments in terms of cost and convenience and the avoidance of short- and long-term risks of ovarian stimulation should make it a mainstream assisted conception technique for female factor infertility. Its role in treating couples with male infertility needs to be evaluated.

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