Article

Controlled natural cycle IVF: experience in a world of stimulation

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Abstract

A total of 134 controlled natural IVF (nIVF) cycles were reviewed retrospectively and compared with 370 stimulated IVF (sIVF) cycles. The clinical pregnancy rate per embryo transfer following nIVF was 27% and 47% in sIVF cycles for patients aged less than 35. However, natural cycle patients could attempt consecutive cycles with much less impact on their lives, both medically and financially. In patients under 35 years of age, the choice of controlled nIVF reduces the cost and risk to the patient, permitting her to have multiple, consecutive attempts, and cumulatively offers a clinical pregnancy rate which approaches that of sIVF. The multiple pregnancy rate in nIVF is significantly reduced compared with sIVF treatment cycles. In patients over 35 years of age the benefits of nIVF were much less evident (clinical pregnancy rate: 8% per embryo transfer) and the opportunity to transfer multiple embryos in these patients seems to be advantageous.

Keywords: clinical pregnancy rate, IVF, multiple pregnancies, natural cycle

Introduction

Over recent years, in-vitro fertilization has worked on the principle of stimulation of the ovaries and the production of multiple follicles in order to obtain many oocytes and, hopefully, several embryos. From these embryos, a choice is made as to which ones offer the best developmental potential, and these are then transferred to the patient’s uterus. However, the first IVF baby was conceived following a natural cycle (Steptoe and Edwards, 1978) and indeed natural cycle IVF (nIVF) was the method of choice for the first few years of IVF treatment.

The use of ovarian stimulation allowed an increase in the number of recruited oocytes and an increase in the pregnancy rates associated with IVF (Fishel et al., 1985). It also permits excess embryos to be cryopreserved in the event that the IVF attempt fails to result in a pregnancy or, indeed, to allow the patient to return for additional sibling attempts in the future without a need for further ovarian stimulation. However, due to the additional costs, risks and complexity of ovarian stimulation, there is pressure on both the patient and the care giver to increase the chance of the patient becoming pregnant and therefore it has become standard to transfer more than one embryo. A side effect of this is a dramatic increase in the rate of multiple pregnancies, which has been observed. Although some countries have acted by law to restrict the number of embryos that are permitted to be transferred, such as in the UK with the Human Fertilization and Embryology Authority, many countries leave the decision in the hands of the assisted reproduction professionals and their patients.

Although various different methods have been suggested as to how to choose the best embryos for embryo transfer, such as embryo morphology, nutrient uptake or pronucleus appearance,
there is still no absolute method for determining which embryo has the best chance of developing into a successful pregnancy.

In a natural cycle, several follicles are recruited initially but it is only one that attains dominance and goes on to ovulate. Being able to control ovulation was one of the reasons why natural cycles were replaced with ovarian stimulation cycles, because the first oocyte retrievals had to be performed according to the natural LH surge and resulted in collections at any time of the day or night in order to collect the oocyte before ovulation.

Developments of gonadotrophin-releasing hormone (GnRH) antagonists allowed once again the possibility of using a natural cycle, by preventing the occurrence of a premature LH surge and thereby allowing better control (Rongières-Bertrand et al., 1999). More recently, Trokoudes et al. (2005) published a series of controlled nIVF cycles (CONCIVF) in which he showed that CONCIVF could be a useful tool in the management of some patients presenting for fertility treatment.

Materials and methods

Patients under 39 years of age attending the OVO Fertility Clinic from January 2004 were offered the possibility of having IVF via a controlled natural cycle or stimulated IVF. Those choosing to accept controlled nIVF had a transvaginal ultrasound on day 6 and then serial ultrasounds to measure the leading follicle. It should be noted that patients who had their cycles cancelled before oocyte collection due to premature ovulation or abnormal follicular growth were excluded from the results.

Ultrasound scans were performed using a multifrequency transvaginal probe (Voluson 730 Expert, GE Medical Systems, Saint-Laurent, Quebec, Canada). Assessments were made by measuring the follicle in two perpendicular planes and taking the average diameter. Once the follicle reached 14 mm, GnRH antagonist (Ganirelix, Orgalutran, Organon Pharmaceuticals, Scarborough, Ontario, Canada) was administered (0.25 mg) as a s.c. injection daily until the day of human chorionic gonadotrophin (HCG) administration. Also patients received 150 IU of human menopausal gonadotrophin (HMG) (Repronex, Ferring Canada, North York, Ontario, Canada) daily. The use of HMG was due to the study of Kettel et al. (1991) to prevent an oestradiol drop in response to the GnRH antagonist. No stimulatory effect of HMG was seen: indeed no patient produced more than one follicle and patients only took, on average, two to three days of antagonist and HMG. Once a follicle of 17 mm was seen with an ultrasound scan, patients received an injection of 5000 IU of HCG (Pregnyl, Organon Pharmaceuticals), administered as an i.m. injection, to achieve final follicular maturation and oocyte retrieval took place 34 h later.

Oocyte retrieval was performed by vaginal ultrasound guidance using a 17G double lumen needle (Cook, Canada) and flushing of the follicle was performed as necessary (Follicle Flush Buffer, Cook). Oocyte retrieval was performed without sedation or local anaesthetic. Oocytes were collected into fertilization media (Cook) at 37°C and 6% CO₂. Semen was collected by the partner into a sterile container and processed using a gradient system (Puresperm, Nidacon, Sweden). When necessary, spermatozoa was retrieved by percutaneous sperm aspiration, usually performed before the IVF cycle, and cryopreserved (Sperm Maintenance Media, Irvine Scientific, USA) for ease of scheduling and for use on the day of oocyte retrieval (Kadoch et al., 2005).

For stimulated IVF cycles, standard well-known protocols were used. In summary, patients were assessed by ultrasound after 14 days of GnRH agonist (Suprefact, Aventis, Canada) to confirm pituitary suppression. Ovarian stimulation was commenced with daily injections of either recombinant FSH (rFSH) (Puregon, Organon, Canada; Gonad F, Serono, Canada) or HMG (Repronex, Ferring Canada) at a dose dependent on patient age and baseline ultrasound assessment of ovarian reserve. Patients started on 150 IU or 225 IU and adjustment was made following follicular assessment with ultrasound on day 6 of stimulation. Further ultrasound assessment of follicular growth was made as required and gonadotrophins adjusted accordingly. Once three follicles reached an 18 mm average of two perpendicular planes, 10,000 IU of HCG (Pregnyl; Organon Pharmaceuticals) was given and oocyte retrieval was scheduled for 36 h later.

Standard insemination or intracytoplasmic sperm injection (ICSI) was performed according to well-established sperm parameters. Fertilization was verified by the presence of two pronuclei and two polar bodies 18 h after insemination. All fertilized oocytes were transferred into cleavage media (Cook). Embryo transfer was performed under ultrasound guidance using a Wallace Sureview catheter (Smith Medical, UK) on day 2 after oocyte retrieval. Embryo transfer for stimulated IVF cycles was on day 2 or 3 after oocyte retrieval, depending on the numbers of embryos available.

Patients received two injections of HCG (2500 IU), on day 2 and day 4 after collection, and took progesterone intravaginally 600 mg daily (Prometrium, Schering, Pointe-Claire, Quebec, Canada), starting 2 days after oocyte retrieval, and continued until menstruation or for at least the first 8 weeks of pregnancy if the patient became pregnant.

Pregnancy was verified by serum HCG 15 days after oocyte collection and confirmed by the presence of an intrauterine fetal heartbeat by ultrasound at 6 weeks.

Results

Between January 2004 and October 2006, patients attending the clinic for IVF treatment were offered the possibility of sIVF or controlled nIVF. Patients over the age of 35 were counselled and advised to choose IVF in preference, although patients who insisted on trying nIVF were accepted. The data for the results with nIVF are reported in Table 1.

In summary, 134 cycles were performed for patients under 35 years of age, with 75 resulting in an embryo transfer. The clinical pregnancy rate per embryo transfer was 27%. As a comparison, during the same time period, 370 cycles of sIVF were performed for patients under the age of 35 with 355 resulting in an embryo transfer. The clinical pregnancy rate per embryo transfer was 47%. However, in the sIVF group the multiple pregnancy rate was 37% (Table 2).
For those patients over 35 who insisted on attempting nIVF, there were 108 cycles resulting in 52 embryo transfers. The clinical pregnancy rate per transfer was 8%. In sIVF for the same age of patient, there were 240 cycles with 220 embryo transfers and the clinical pregnancy rate per embryo transfer was 37%. The multiple pregnancy rate in this group was 36%.

The cancellation rate or failure to reach embryo transfer was considerably higher in the controlled nIVF groups than in the sIVF groups. For the two treatment groups under 35, 59% of patients under 30 and 54% of patients between 31–35 reached embryo transfer as compared with 96% of patients in sIVF.

The 134 cycles of nIVF were performed for 70 patients. The clinical pregnancy rate per patient undergoing nIVF was 28.5% and 91% of the patients becoming pregnant did so on their first or second attempt, including cycles with no embryo transfer.

Conclusions

Although controlled nIVF does not reach the levels of pregnancy rate that can be obtained by transferring multiple embryos following ovarian stimulation, the authors believe that it can be a useful tool in the treatment of some couples presenting for infertility. The benefits of controlled nIVF are obvious, in that the increasing problem of multiple pregnancy is removed, the patients do not need to inject themselves with expensive medications, and due to the reduced invasive nature of the procedure (no sedation or anaesthesia is used for the oocyte collections), patients can, if they choose, have a cycle each consecutive month. If it is also considered that, as with intrauterine insemination, patients can have three cycles of nIVF consecutively with minimal impact on their life schedules, then the cumulative pregnancy rate will approach that of sIVF cycles. Since it was found that the majority of pregnancies in nIVF occur on the first or second attempt (91%), including cycles with no embryo transfer, most patients are counselled to use sIVF after three unsuccessful attempts with nIVF.

Also it appears that the benefits of transferring more than one embryo are increased in patients over the age of 35, since the pregnancy rate from nIVF was low (8%). In the sIVF group, patients over the age of 35 had a pregnancy rate that was comparable with the younger sIVF groups (37% for patients over 35 versus 53% for patients less than 30, and 44% for patients aged 31–35). It has been suggested that vaginal oestradiol supplementation may improve implantation rate (Wright et al., 2006); however, no benefit in controlled nIVF was seen in this clinic (unpublished data).

While laboratory researchers are trying to find the best method...
to select an embryo or embryos with the best developmental potential for embryo transfer, perhaps the role of natural selection of follicles should be considered. Further research is necessary to verify whether the aneuploidy rate, or perhaps nutrient uptake or output, in natural cycle embryos is improved over embryos resulting from stimulation cycles.

Since there is only one follicle in nIVF, there is a greater risk of cycle cancellation than in stimulated cycles, even in younger patients. This is an area of controlled nIVF that needs more attention and research, since there is certainly less chance of an embryo transfer following the commencement of a controlled nIVF cycle than a sIVF cycle. From the data presented here, slightly over half the cycles in controlled nIVF result in an embryo transfer (59%, 54%) as compared with nearly all cycles in sIVF (96%). The use of non-steroidal anti-inflammatory drugs (NSAID) has been proposed to improve the recuperation of oocytes by reducing the spontaneous ovulation rate (Nargund et al., 2001), and this is an area currently under investigation in the clinic’s programme. In addition, methods to improve fertilization rate with ICSI may provide helpful in ensuring that more patients complete their cycles (Wang et al., 2001; Hazout et al., 2006).

However, the choice to use nIVF can be incorporated into the financial aspect of the programme so that the impact on patients is reduced when an embryo transfer does not occur. For example, in this clinic, patients who do not obtain an oocyte at retrieval pay a much-reduced price simply to cover the costs of the retrieval only, and if the oocyte fails to fertilize, a significant rebate is also given on the cycle price. Patients who have their cycles cancelled before oocyte collection due to premature ovulation or abnormal follicular growth do not pay for their cycle at all, and so they have been excluded from these data. Therefore, only patients who have an embryo transferred pay the total cycle costs, which are still considerably less than a stimulated cycle. It is for this reason that clinical pregnancy rate per embryo transfer is reported, rather than the more traditional clinical pregnancy rate per cycle started. Whilst the authors realise that describing clinical pregnancy rates per embryo transfer may be construed as misleading, they feel that controlled nIVF is sufficiently different to sIVF in terms of impact on the patient’s life to warrant this. Perhaps in a situation where there is no or little financial implication on patients for fertility treatment, this argument is reduced; however, certainly in North America where, unfortunately, the financial burden of assisted reproduction falls on the patients and not governments or insurance companies, the authors feel that it is reasonable to present clinical pregnancy rates per embryo transfer as long as the patients are aware that the chance of failing to reach embryo transfer in a controlled nIVF is higher. During failed cycles, patients will, of course, take very little, if any medication, and undergo two or three vaginal ultrasounds at most, and the costs will be much reduced. Trokoudes et al. (2005) also used clinical pregnancy rates per embryo transfer in their controlled nIVF paper, suggesting that perhaps nIVF should be analysed in a slightly different way to sIVF. Patients initiating controlled nIVF at the centre are counselled about the risk of failing to reach embryo transfer, which may be up to 50% of those starting a cycle, although this rate is expected to improve with research involving NSAID, as mentioned previously, and with potential improvements to the protocol in the future.

The authors believe that, using the method that is described here, that a successful alternative to sIVF can be offered to patients and, in doing so, the various burdens that sIVF places on the patient and health care systems be considerably reduced.

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References


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