Human Reproduction Update 1996, Vol. 2, No. 6 pp. 459–468

In-vitro fertilization and embryo transfer in women aged 40 years and over

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TABLE OF CONTENTS

Introduction 459
Results of IVF in women aged ≥40 years 460
Why does fertility diminish with age? 460
How can we identify the subgroup of older women who would benefit most from IVF/embryo transfer? 462
How can we effectively stimulate older patients for IVF? 462
Why are agonadal and post-menopausal women so fertile after oocyte donation? Does a period of amenorrhoea improve subsequent chances of embryo implantation? 463
Transfer of higher numbers of embryos 464
Assisted embryo hatching and co-culture 464
What are the alternatives? 464
What is the pregnancy outcome in women aged ≥40 years? 465
Is treating older women ethical? 465
Conclusions 466
References 466

The decline of fertility with age and its possible causes are discussed; in particular the effect of ageing of oocytes and the uterus, and the effect of the ageing processes on the results of in-vitro fertilization (IVF) and embryo transfer in women aged ≥40 years. The role of prestimulation testing in older women is considered together with the importance of screening and counselling these patients about the likelihood of achieving a live birth. The potential problems that they may face should they become pregnant are reviewed, together with the role of oocyte donation as an alternative treatment for patients with reduced ovarian reserve. Possible ways of improving the chances of achieving a live birth in older women using their own oocytes are reviewed, including the use of more effective stimulation protocols, assisted embryo hatching and co-culture and high order embryo transfer. The outcome of pregnancies in older women and some of the ethical problems relating to their treatment are also discussed.

Introduction

There is an evident decline in female fertility (the ability to achieve a pregnancy) with age. The decline is gradual over the reproductive life span of the woman and is caused by a reduction in the conception rate and an increase in the abortion rate. The decline in normal fecundity (the monthly chance of conception) is particularly noticeable over the age of 30, and accelerates between 35 and 40, so that fertility is almost zero by 45. This decline has been well demonstrated in populations who do not use contraception (Menken and Larsen, 1986).

Male fecundity may also diminish with age, possibly through increased non-dysjunction in the spermatozoa (Griffin *et al.*, 1995), along with a decline in coital frequency, a factor which also tends to be closely related to the age of the woman. A study by CECOS (1982) of 2193 nulliparous women treated by donor insemination because their partners were azoospermic demonstrated a decline in fertility with maternal age. The advantage of this study compared with those using natural fertility is that it removes other variables in spontaneous conception, such as the frequency of intercourse, sperm quality and age of the male partner.

Delayed child bearing is becoming increasingly common in Western societies for a variety of reasons; many couples prefer to rear their children only after establishing a stable relationship and financial security. There are increasing numbers of late and second marriages and more women now wish to finish their education and establish a career before trying to start a family. With the high level of media coverage that in-vitro fertilization

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(IVF) and gamete intra-Fallopian transfer (GIFT) receive, most women are aware that much can be done for infertile couples that was not possible a few years ago.

The impact of ageing on fertility and childbirth has become increasingly relevant. The report on confidential enquiries into maternal deaths in the UK covering the period 1991–1993 showed that one out of 20 British women had her first child after the age of 35, a 25% increase in comparison with the period 1988–1990. The percentage of women aged ≥40 years giving birth to their first child increased from 1% during the period 1988–1990 to 2% during the period 1991–1993. Of all the patients receiving IVF treatment, ~10% are >40 years of age; this proportion varies between countries from 4.9 to 37.5% (World Collaborative Report, 1993).

Results of IVF in women aged ≥40 years

The lower IVF pregnancy rates achieved in women ≥40 years of age have been universally recognized and are entirely consistent with the progressive decline in natural fecundity with age. Tan *et al.* (1992) reported a cumulative conception rate of 54% and a live birth rate of 45% after five IVF treatment cycles for women aged 20–34 years compared with rates of 20.2 and 14.4% respectively, in patients aged >40 years. Data from the report of the Human Fertilisation and Embryology Authority (HFEA, 1995) for the year 1993 show pregnancy and live birth rates of 9.5 and 6.3% respectively for women aged 40–44 years, of 3.1 and 2.3% for the group of women aged ≥45 years, and of 21.2 and 17.2 % for women aged <25 years. Data from the French National IVF Registry (FIVNAT, 1990) for the period 1986–1990 showed a pregnancy rate of 20% in women aged <35 years compared with 9% for women aged ≥40 years. Data from the US and Canada IVF registry for 1993 (Society for Assisted Reproductive Technology/American Society for Reproductive Medicine, 1995) showed a live birth rate per retrieval of 8.6% in women aged ≥40 years compared with 21.5% for women <40 years old.

Age is associated with poor IVF outcome at every step of the procedure, with increasingly poor responsiveness to ovarian stimulation drugs and increased rates of cycle cancellation. Approximately one third of these older women undergoing IVF will not reach the stage of oocyte retrieval, and if they do, fewer oocytes are retrieved. Furthermore, there are fewer embryos available for transfer, a decrease in egg and embryo quality, a lower implantation rate and a higher rate of abortion, which varies between 41 and 62.5%. The rate of fertilization and embryo cleavage, however, is not affected by age (Edwards *et al.*, 1984; Romeu *et al.*, 1987; FIVNAT, 1990; Wood *et al.*, 1992).

Hull *et al.* (1996), reported results from an IVF/embryo transfer programme which was controlled for confounding variables, including the cause and duration of infertility, history of previous pregnancy, hormonal treatment, rank cycle of treatment and number of embryos transferred and available. Embryo implantation and live birth rates dropped from 18.2 and 15.7% respectively at age 25–29 years to 6.1 and 3.5% respectively for the group aged 40–44 years.

Why does fertility diminish with age?

Older women are at an increased risk of suffering from a number of problems that affect fertility: tubal disease may result from pelvic infection; deciliation of the Fallopian tubal endothelium may increase with age (Crow *et al.*, 1994); reduced vascular perfusion of the uterus may be shown by Doppler ultrasound scan studies (Goswamy *et al.*, 1988); endometriosis and fibroids are common in older women and there is also an increase in ovulatory dysfunction (Doring, 1969).

Certainly, the reproductive system is not immune to the chronological ageing which affects all cells and tissues. Starting before birth, there is a constant and unrelenting reduction in the number of oocytes, from about 7×10^6 oocytes at midgestation to 2×10^6 at birth, and only ~300 000 at the menarche. The rate of follicle disappearance subsequently increases at age 37.5 years until the menopause (Gougeon *et al.*, 1994; Faddy *et al.*, 1992; Faddy and Gosden, 1996). Concomitant with the decline in ovarian reserve, there is an increase in the incidence of oocyte aneuploidy, a significant factor in the high spontaneous abortion rate found in older women (Richardson and Nelson, 1990). Increasing age is associated with a decrease in embryo viability (Chetkowski *et al.*, 1991; Hull *et al.*, 1996). Generally, the occurrence of any implantation indicates uterine receptivity, whereas multiple implantation reflects oocyte and embryo quality.

The fact that very satisfactory pregnancy rates can be achieved in older women using oocytes donated by younger women has led to the conclusion that reproductive ageing of the human female is solely due to a decline in oocyte quality rather than uterine ageing (Navot *et al.*, 1994). However, further evidence has shown that both oocyte and uterine factors are involved. Navot *et al.* (1991) reported the results of an oocyte donation programme in which the donors and recipients shared oocytes from the same cohort of follicles from the same donor. A total of 35 patients aged ≥40 years, who had failed to conceive following IVF using their own oocytes received oocytes donated from 29 women undergoing IVF. Pregnancy and delivery rates were 33 and 23% respectively in the donors

compared with 40 and 30% in the recipients, suggesting that the age-related decline in female fertility is not attributable solely to oocyte quality. Sauer *et al.* (1990) reported the results of oocyte donation in seven women aged 40–44 years with ovarian failure who received oocytes donated by young women and compared the result with women <40 years of age with ovarian failure who also received donor oocytes. He found no significant difference in the rates of implantation or ongoing pregnancy. Abdalla *et al.* (1993) also evaluated the relative contribution of oocyte and uterine factors to the decline in female fecundity with age. They analysed retrospectively the results from 241 patients who received donated oocytes and compared the pregnancy and miscarriage rates with those of women undergoing IVF and GIFT using their own oocytes. They reported significantly higher pregnancy and live birth rates, and significantly lower miscarriage rates, in the group receiving donated oocytes compared with the group using their own oocytes and suggested that the age-related decline in fecundity is associated with the age of the oocytes rather than the age of the uterus. However, there was no control group of younger women receiving donated oocytes from the same cohort of follicles in these studies; also the study by Sauer *et al.* (1990) contained only seven patients. Although the effect of ageing oocytes on declining fecundity with age is generally accepted, the role of uterine receptivity in implantation is still controversial.

There are two ways to test the effect of endometrial receptivity on implantation: (i) transfer oocytes from older women into two groups of recipients <40 and ≥40 years; and (ii) transfer oocytes from younger women to two groups of recipients aged <40 and ≥40 years. However the first option is difficult to enact for medical and ethical reasons. Levran *et al.* (1991) reported significantly lower pregnancy rates in recipients aged >33 years in 169 oocyte donation cycles. This study, and that of Abdalla *et al.* (1993) showed that the age of the donor was directly related to the miscarriage rate. Yaron *et al.* (1993) retrospectively analysed the results of standard IVF and oocyte donation in recipients aged ≥40 and <40 years. In standard IVF cycles, the clinical pregnancy rates were significantly lower in older women (12.9 versus 23.8%). In oocyte donation cycles the clinical pregnancy rates were also significantly lower in recipients aged ≥40 years compared with <40 (21.2 versus 29.3%). Because the pregnancy rate in women aged ≥40 years was higher using donated oocytes than their own oocytes (21.2 versus 12.9%) the data suggest an effect of ageing of the oocytes as well as the uterus. There is increasing evidence that uterine receptivity plays an important role in implantation. Recent studies have compared the clinical pregnancy rates of women aged <40 and ≥40 years of age who received oocytes from the same cohort of follicles with transfer of embryos of similar number and quality. Meldrum (1993) reported significantly lower ongoing pregnancy and delivery rates in women aged >40 years compared with women aged <40 years; the difference between them was corrected by the administration of progesterone 100 mg i.m. daily. Cano *et al.* (1995) reported similar embryo implantation rates but significantly higher abortion rates in women age >40 years despite an appropriate action of progesterone on the endometrium and the transfer of embryos of similar quality and number. They concluded that there is an increase in age-related pregnancy losses after implantation is completed and suggested that uterine ageing is a factor responsible for the poor reproductive performances of women of advancing age. Flamigni *et al.* (1993) compared the outcome of oocyte donation between recipients from different age groups. They found pregnancy and implantation rates of 45 and 23% in women aged 21–35 and of 23 and 10% in women aged 41–49 years; the difference being statistically significant. Borini *et al.* (1996a) investigated the role of uterine ageing as regards pregnancy, implantation and abortion rates using the oocyte donation model. A total of 114 women aged 21–49 years of age underwent 114 oocyte donation cycles. The recipients were divided into two groups: those aged <39 years and those aged 40–49 years. The clinical pregnancy rates were 47.3% for the first group compared with 24.5% for the second group. It was concluded that fertility does not depend merely on oocyte age and quality but also on uterine age.

Note Added At Proof

Templeton *et al.*, (1996) analysed the factors that affect the outcome of in-vitro fertilization. They used the HFEA data base of all treatment cycles between August 1991 and April 1994 and found that at all ages >30 years, use of donor eggs was associated with a significantly higher livebirth rate than use of the woman's own eggs. But there was also a downward trend in the success rate with increasing age ($P=0.04$), which suggests decreasing uterine receptivity with age.

Animal studies in which embryos of young donors are flushed and transferred to older recipients also indicate decreased uterine receptivity to be the main factor responsible for declining fertility with advanced age (Blaha, 1964).

How can we identify the subgroup of older women who would benefit most from IVF/embryo transfer?

Prestimulation testing

The ability of the ovaries to respond to gonadotrophins with adequate follicular development has been referred to as ovarian reserve. Although it declines with age, it is a biological and not just a chronological function. The most important aspect of diminished ovarian reserve is that the timing of its onset is highly variable (Mosher and Pratt, 1991).

Assessing the ovarian reserve may help to identify women in whom IVF would be most appropriate, so that women with reduced ovarian reserve could be offered oocyte donation. There is a subtle age-related rise in follicle stimulating hormone (FSH) that precedes the onset of menopause by many years (Sharman *et al.*, 1976), while luteinizing hormone (LH) concentrations remain normal until 3–4 years before the menopause (Lenton *et al.*, 1988).

There is no doubt that there is a need for a screening test for ovarian reserve that is easily measurable, minimally invasive, inexpensive and has a good predictive value; none of the current tests provides a 100% prognostic reliability. The available tests include: estimation of the basal FSH concentration, the clomiphene citrate challenge test (CCT) and gonadotrophin-releasing hormone (GnRH) agonist stimulation test (GAST). Scott *et al.* (1989) reported that pregnancy rates decreased markedly as FSH concentrations rose. The ongoing pregnancy rates were highest in those women with FSH <15 mIU/ml and fell to <5% in those whose basal FSH values were >25 mIU/ml. Toner *et al.* (1991) measured the relative values of basal day 3 FSH and maternal age in 1478 consecutive IVF cycles and found that basal FSH had a superior predictive value for pregnancy when compared with age alone. Scott *et al.* (1995) studied the impact of age and ovarian reserve status on cumulative pregnancy rates and reported that women with evidence of diminished ovarian reserve have uniformly poor pregnancy rates independent of their age, but that age remains an important prognostic factor among those with a normal ovarian reserve. Paired analysis of high and low FSH values in treatment cycles of patients with reduced ovarian reserve showed no differences in the numbers of oocytes retrieved or in fertilization rates, all the patients having poor responses in both cycles (Scott *et al.*, 1990). This suggests that serial screening of basal FSH concentrations to select the optimal cycle for stimulation would be of limited clinical value. There are certain practical problems associated with the use of basal FSH concentrations to determine biological age and ovarian reserve, as there is cycle-to-cycle fluctuation in the concentration of FSH. An elevated oestradiol concentration on day 3 of menstruation may reflect follicular recruitment, thus masking what otherwise would be a high FSH value (Corson, 1994). There is marked variation between different laboratories in what is considered to be the normal range of FSH concentrations. Scott *et al.* (1995) reviewed the literature on normal and abnormal FSH values and found that the normal range varied between 10 and 26 mIU/ml. A normal FSH value does not guarantee good response to ovarian stimulation.

Navot *et al.* (1987) first described the clomiphene citrate (CC) challenge test to assess ovarian reserve in 51 patients aged ≥35 years with unexplained infertility. All of them had normal basal FSH concentrations and regular menstrual cycles; 18 had a high FSH of ≥26 mIU/ml (>2 SD above control values) after CC administration; however, only one out of the 18 patients in this group conceived (6%). In contrast, out of 33 patients with an adequate reserve, 14 (42%) conceived. Tanbo *et al.* (1992) demonstrated that the CC challenge test is prognostically more efficient than the basal FSH value. They studied 91 women aged >35 years and found abnormal CC challenge tests in 37; 20 out of the 37 patients also had an elevated basal FSH on day 3; only one patient had an abnormal value on day 3 with a normal value on day 10. The predictive value of an abnormal test was 85% for cancellation due to poor ovarian response and 100% for failing to conceive, in contrast to a 31.5% cancellation rate and pregnancy rate of 11% in those with normal tests. Loumaye *et al.* (1990) defined an abnormal test by adding day 3 FSH and day 10 FSH together and reported that no pregnancies resulted when the sum of the two amounts was >26 mIU/ml.

Padilla *et al.* (1990) investigated the prognostic value of early serum oestradiol concentrations in response to GnRHa administration (GAST). They reported pregnancy rates of 37% in the group with rising oestradiol concentrations compared with 6% in the group with no rise. Winslow *et al.* (1991), however, found no significant correlation between the early oestradiol rise and pregnancy rate.

How can we effectively stimulate older patients for IVF?

Initially GnRH agonists combined with human menopausal gonadotrophins (HMG) were given to patients who had responded poorly to combined treatment with clomiphine citrate and HMG in previous cycles and better results were achieved (Fleming and Coutts, 1986; Howles *et al.*, 1987; Serafini *et al.*, 1988; Smitz *et al.*, 1988; Belaisch-Allart *et al.*, 1989; Macnamee *et al.*, 1989). Further studies (Rutherford *et al.*, 1988; Macnamee *et al.*, 1989) have

shown that the combination of GnRH agonist with HMG results in higher rates of pregnancy and live birth and reduced cancellation rates due to poor follicular response or premature luteinizing hormone surges. Marcus *et al.* (1993) analysed the outcome of IVF treatment in 312 patients with tubal infertility in a prospective randomized study comparing two regimens of ovarian stimulation with GnRH agonist and HMG. Half the patients were given an ultra-short GnRHa treatment protocol, administered on days 2, 3 and 4 of menstruation; the other half were given a long GnRHa protocol with the agonist administered from the midluteal phase of the cycle preceding the treatment cycle. Patients who received the long protocol had significantly more supernumerary embryos cryopreserved and successful deliveries. The effect of increasing the dose of gonadotrophins for ovarian stimulation in poor responders is controversial. Most researchers have observed no beneficial effect (Ben-Rafael *et al.*, 1987; Benadiva *et al.*, 1988; Karande *et al.*, 1990; Land *et al.*, 1996). Other authors have found a positive effect, with a significantly lower cancellation rate and higher pregnancy rate when higher doses were used (Hofmann *et al.*, 1989). Van Hooff *et al.* (1993) in a prospective randomized study reported that doubling the dose of gonadotrophins from 225 IU to 450 IU daily in the course of IVF treatment for poor responders had no effect on ovarian response.

Why are agonadal and post-menopausal women so fertile after oocyte donation? Does a period of amenorrhoea improve subsequent chances of embryo implantation?

There is increasing evidence of an improvement in clinical pregnancy rates after a natural or induced period of amenorrhoea. Edwards *et al.* (1991) studied the comparative fertility of acyclic and cyclic women aged <50 years after IVF/embryo transfer or oocyte donation and found that, age for age, acyclic women were more fertile than those cyclic women who received their own oocytes. The embryo implantation rates were significantly higher for acyclic women when all patients were analysed. In contrast, pregnancy rates were identical in the two groups of women when analysis was performed on pregnant women only. In a group of women with severe endometriosis, Marcus and Edwards (1994) reported high pregnancy rates in women who had amenorrhoea for ≥4 months before IVF treatment. Amenorrhoea was induced in these cyclic patients with a long acting GnRH agonist. The pregnancy rate was 47.6% for the group treated with a long GnRH agonist compared to 10.5% in the control group treated with standard busereline regimen. The data also showed that own oocytes were as effective as donated oocytes following a period of amenorrhoea.

Borini *et al.* (1995) studied the effect of long-term down-regulation on pregnancy and implantation rates in 122 cyclic patients who received donor oocytes. Recipients were divided into three groups according to whether they were menopausal (group A) or cyclic and treated with short- (group B) or long-term (group C) GnRH agonist. Oocyte donors were aged 21–35 years and were equally distributed between the different recipients. The pregnancy and implantation rates were 30.8 and 16.1% respectively in group A, 30.6 and 17.7% respectively in group C and 10.4 and 5.6% respectively in group B; these differences being statistically significant. Apart from the improved pregnancy and implantation rates after long-term down-regulation, these data not only demonstrate an important role of the endometrium in implantation, but also suggest that a period of amenorrhoea improves the pregnancy rate. The cause of this is unknown, but it is possible that a period of uterine rest may restore full function to steroid-sensitive structures such as the pinopodes (Psychoyos, 1993; Nikas *et al.*, 1995) after a prolonged period of constant menstrual cycling (Edwards, 1992; Edwards and Marcus, 1995). There is a need for a larger randomized prospective trial to assess the effects of long-term down-regulation on the fertility of women aged ≥40 years with tubal damage.

Long-term down-regulation may also reduce the rate of depletion of the human follicular pool, as in rats (Ataya *et al.*, 1989). Lowering FSH concentrations by long-term down-regulation or long-term use of contraceptive pills may reduce migration by acting directly on the oocyte pool or indirectly by removing any stimulatory effects of primary follicles on migration rates. Because age-related aneuploidy in humans occurs as a direct or indirect result of follicle depletion, long-term use of oral contraceptive pills or GnRH agonist may protect against abortion due to aneuploidy by preserving the number of follicles (Ford and MacCormac, 1995). Although the use of GnRH agonists generally improves outcome in IVF, they may lead to over-suppression in women with reduced ovarian reserve, and increased doses of gonadotrophins may be required, with little improvement in ovarian response (McKenna *et al.*, 1989; Droesch *et al.*, 1989; Muasher, 1993). The 'flare' GnRH agonist protocol seems to have a place in the treatment of poor responders. Muasher (1993) reported a 5% cancellation rate and 21.3% pregnancy rate when using the flare protocol combined with high doses of FSH (450–600 IU daily). Garcia *et al.* (1990) also reported better outcomes when using the flare protocol.

Transfer of higher numbers of embryos

The number of embryos that should be transferred in IVF/embryo transfer is still a controversial issue. There is no doubt that transferring a higher number of embryos increases the chance of pregnancy (Edwards *et al.*, 1984; Balen *et al.*, 1993; Nijs, 1994; Azem *et al.*, 1996; Antinori *et al.*, 1996b; Walters, 1996; Wildra *et al.*, 1996). Transfer of a high number of embryos is also associated with increased risk of higher order of multiple pregnancy, with its associated risks to both the mother and fetuses. Due to the low rates of embryo implantation in older patients when using their own oocytes, many authors recommend the transfer of higher numbers of embryos/oocytes to compensate for this, and hence improve the clinical pregnancy rates (Craft *et al.*, 1988; Qasim *et al.*, 1995; Azem *et al.*, 1996; Antinori *et al.*, 1996b). There are only limited data available on the incidence of multiple pregnancy in women aged ≥40 years who received higher numbers of their own embryos; these studies lack the statistical power to detect substantial differences in the incidence of multiple pregnancy in the older women (Azem *et al.*, 1996; Walters, 1996). However, it appears from a review of the literature that, if a higher number of embryos are transferred in IVF or oocytes in GIFT to women aged >40 years when using their own oocytes, the chance of pregnancy will be improved with only a small risk of multiple pregnancy. This is in contrast to older patients receiving higher numbers of donated oocytes or embryos, when the increased risk of higher order of multiple pregnancy may not be acceptable. Since 1991, The HFEA Code of Practice in the UK states that the maximum number of embryos that may be transferred is three, whether they are own or donated gametes.

Assisted embryo hatching and co-culture

Normal embryo hatching is accomplished predominately, if not entirely, by zona lysis and not by pressure exerted by the expanding blastocyst (Gordon and Dapunt, 1993). Cohen *et al.* (1990) introduced a micromanipulation procedure to promote embryo hatching and reported a significant difference in embryo implantation rates, which were 23% after assisted hatching compared with 11% in the control group. Cohen *et al.* (1992) reported two groups of patients for whom assisted hatching statistically improved the pregnancy rates: patients whose embryos had a zona pellucida thickness of ≥15 μm and women aged >38 years. Schoolcraft *et al.* (1994) assessed the effects of assisted hatching in the treatment of poor prognosis patients and reported a higher implantation rate of 33% in the assisted hatching group compared with 6.5% in the control group. Recently, Schoolcraft *et al.* (1995) assessed the impact of assisted hatching on IVF outcome in women aged 40 and older and reported a significantly higher delivery rate per oocyte retrieval in the assisted hatching group; 13/38 (48%), compared with three out of 28 (11%) in the control group ($P = 0.003$). Antinori *et al.* (1996a) analysed the outcome of laser-assisted hatching in patients with repeated IVF failure (group A) and in patients undergoing IVF treatment for the first time (group B); both groups were compared with control groups (A′ and B′) whose embryos were transferred with intact zonae pellucida. The pregnancy rates were 42.7 and 39.6% in groups A and B compared with 23.1 and 19% in the control groups A′ and B′ ($P < 0.05$). The implantation rates were 12.2% in group A and 11.8% in group B compared with 7.3 and 7.1% in the control groups A′ and B′.

Culture conditions have been implicated as a major factor in reducing embryo viability (Rogers *et al.*, 1986). Co-culture is the culture of embryos on monolayers of somatic cells. Various cell types have been used, including oviduct cells, uterine cells and monkey (Vero) kidney epithelial cells. Wiemer *et al.* (1993) noted that embryo development and implantation rates were improved after co-culture for 1 day on virus-screened bovine oviductal epithelial cells. Also, Freeman *et al.* (1995) reported improved embryonic development and pregnancy rates using granulosa cell co-culture. The mechanisms by which the feeder cells promote embryonic growth and development during co-culture is not known, but possible mechanisms include the removal of toxic elements such as free oxygen radicals from the culture medium and the secretion of embryotrophic factors by the feeder cells (Wiemer *et al.*, 1994). Other researchers have not observed any significant difference (Sakkas *et al.*, 1994). Wiemer *et al.* (1994) and Tucker *et al.* (1994) reported improved pregnancy rates with combined selective assisted hatching and co-culture in women either with high basal serum FSH concentrations or following repeated failures at IVF (Wiemer *et al.*, 1994). It has also been reported that assisted hatching is associated with increased risk of monozygotic twin formation (Alikani *et al.*, 1994).

What are the alternatives?

Older patients undergoing IVF should receive thorough counselling about their likelihood of achieving a clinical pregnancy and live birth. Those patients with reduced ovarian reserve should be offered alternative options including the use of donated oocytes or embryos. It is felt by many that there may be a beneficial effect if these

women undergo a 'cleansing cycle'. This is a cycle in which older women who have been given a poor prognosis feel nevertheless that they must make at least one attempt using their own oocytes in order to purge themselves emotionally of the need to at least try. Many women will feel that, if they have a chance at treatment before being advised to give up, they have done everything they can do and will be able to accept their childlessness much more easily in the years that follow.

Oocyte donation is now a well established treatment option in assisted conception (Edwards *et al.*, 1991). It is 12 years since Lutjen *et al.* (1984) reported the first pregnancy after oocyte donation in a woman with premature ovarian failure. Ever since, a number of authors have reported higher pregnancy and delivery rates, as well as lower abortion rates, with the use of donated oocytes (Serhal and Craft, 1989; Navot *et al.*, 1991; Edwards *et al.*, 1991; Abdalla *et al.*, 1993; Remohi *et al.*, 1993; Sauer *et al.*, 1995; Borini *et al.*, 1996a). These authors have shown that patients in their early and late 50s and older can establish pregnancies with donor oocytes and that their uteri can respond to steroid therapy and implant embryos as efficiently as young uteri. Most assisted conception programmes have difficulty in recruiting sufficient ovum donors, but there is a significant number of patients who can benefit from this treatment. Embryo donation also has a place in selected cases when the male partner suffers from primary testicular failure or genetic disorder and the female partner is menopausal. As with oocyte donation, embryo donation results in high pregnancy and delivery rates (Asch, 1992; Marcus *et al.*, 1996).

What is the pregnancy outcome in women aged ≥40 years?

The risks of pregnancy for women increase considerably with maternal age. In the UK, the maternal mortality rate during the period 1991 to 1993 was 5.5 per 100 000 pregnancies in women aged 20–24 years compared with 20.6 in those aged >40 years (Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1996). Such risks might be acceptable to women who have a strong desire to have a baby. Thorough medical screening is essential to reduce to a minimum the obstetric risks in this group of patients. Maternal complications are also increased by multiple pregnancies. The factors affected by age include increased rate of chromosomal anomalies, hypertension, diabetes, placenta praevia, a higher incidence of Caesarean section, maternal and fetal mortality and morbidity. Spellacy *et al.* (1986) compared the outcome of pregnancy in 511 women whose age was ≥40 years at delivery with that of 26 759 women whose age at delivery was 20–30 years. They concluded that older women of low parity and normal weight, when managed by modern obstetric methods, can expect a good pregnancy outcome. Borini *et al.* (1996b) summarized the obstetric outcome of 43 pregnancies obtained in post-menopausal women after oocyte donation; there were 38 singletons, four twins and one triplet; two women miscarried during the second trimester, and all except two were delivered by Caesarean section. In total, 14 women developed hypertension (34%) and 11 of these progressed to pre-eclampsia; two developed diabetes. The gestational age ranged from 33–40 weeks, and birth weight ranged from 885–4310 g. The results of this study showed a high incidence of obstetric complications, despite pre-screening examination. Sauer *et al.* (1995) also reported the obstetric outcome of 22 women aged ≥50 years after oocyte donation; these included three preclinical pregnancies, two ended in spontaneous abortion and there were 17 viable pregnancies. Nine of the 17 pregnancies were multiple pregnancies. All pregnancies delivered beyond 32 weeks. Complications occurred in eight patients; gestational hypertension (n = 7), preterm labour (n = 3), gestational diabetes (n = 3) and pre-eclampsia (n = 1). One infant was trisomy 21.

Is treating older women ethical?

Flamigni (1993), Benagiano (1993) and Edwards (1993) have all addressed the important ethical considerations and social issues related to ovum donation in post-menopausal women. Generally, there are three main objections related to this issue: (i) the physical risk to the women; (ii) the rights of the children born to older women; and (iii) the use of scarce health care resources that might deprive younger patients of treatment. Other issues which have been raised against treating older patients include the views of donors about using their oocytes for treating older women, and the psychological effect of giving birth beyond the age of 50, which is unknown at present. Those who are in favour of treating older patients argue that, by careful selection of patients, the risk of complications is reduced to a minimum and most older women wanting children are quite willing to accept the small risk of complications. There is also argument about the definition of what constitutes advanced maternal age. There is also discussion of whether there should be any difference between men and women and whether men should have the right to procreate late in life and not women. It is also known that there are many children who have been raised by their grandparents and who do very well, and it is also a fact that the life

expectancy of both men and women has increased very considerably recently.

Conclusions

Although ovarian reserve declines with age, it is a biological and not just a chronological function. Age alone should no longer be a reason for not treating infertile women older than 40. IVF/embryo transfer does have an important place in the management of older infertile patients. Prestimulation testing for ovarian reserve will identify women who would benefit most from treatment. These women and their partners should receive careful medical and psychological assessment and counselling both about the likelihood of achieving a live birth as well as the potential problems that they may face should they become pregnant. Many suggestions have been made to help to improve the results of IVF in these patients, including more effective ovarian stimulation protocols, assisted hatching and co-culture, and the transfer of three or more embryos where it is acceptable and legal. Patients with poor ovarian reserve should be offered alternative treatment such as oocyte or embryo donation and they should be informed about the better success rates of these treatments. Thorough medical screening is essential to reduce to a minimum the obstetric risks in these patients and, if pregnancy is otherwise uncomplicated, both mother and baby can anticipate a good outcome.

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Received on September 13, 1996 accepted on November 25, 1996