Articles

Obstetric and prenatal outcome in menopausal women: a 12-year clinical study

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Abstract

The obstetric and prenatal outcome in postmenopausal women of advanced age in an oocyte donation programme is described in this paper, the oldest being aged 63 years. A total of 2729 candidates were visited up to November 2000. Only 1150 (42%) were accepted, with 1579 being rejected during a rigorous selection procedure. Several excluding clinical conditions were noted, including hypertension of varying severity, cardiovascular disease, smoking, dysfunctions of the hepatic, thyroid and renal systems and diabetes. Overall, 489 (38%) clinical pregnancies were established in 1288 recipient cycles, with 390 healthy babies delivered out of 363 pregnancies (28%), while 126 (25.7%) were lost. In all, 327 (90%) of the pregnancies reached full term, with 36 involving premature deliveries, 24 involving multiple gestation, 21 sets of twins, three sets of triplets (0.9%) and no quadruplets. Antenatal complications arising in 86 patients (23.6% of deliveries) included 33 preterm deliveries, 43 cases of gestational hypertension, four cases of pre-eclampsia, three cases of gestational diabetes and three of abruptio placentae. A total of 272 (75%) of all deliveries were by Caesarean section. Neonatal complications included two cases of growth retardation. There were no neonatal or maternal deaths. The 63-year-old woman reached full term pregnancy in July 1994, with delivery by Caesarean section of a boy in good health. Proper screening for risks has enabled this treatment to be given to a preselected group of patients.

Keywords: *menopause, obstetric outcome, older women, pregnancy-induced hypertension*

Introduction

It has previously been demonstrated that high rates of pregnancy can be achieved in menopausal women if hormonal replacement and endometrial thickness are adequate (Antinori *et al.*, 1993). Edwards *et al.* (1991) report experiences in Cambridge (UK) and Irvine, California (USA) with a model of oocyte donation to ascertain the relative importance of the uterus and embryo in determining pregnancy rates. Their studies confirmed that there was no difference in pregnancy rates when transfer was performed during the natural cycle or during hormone replacement therapy. In both centres, the pregnancy rate in agonadal women was higher than the pregnancy rate in women undergoing IVF and transfer of their own embryos.

Hypertensive disorders of pregnancy continue to be leading causes of fetal, maternal and neonatal morbidity and mortality (Sibai *et al.*, 1986). High blood pressure complicates approximately 10% of all pregnancies (Remuzzi and Ruggenenti, 1991).

Advanced maternal age is a risk indicator rather than a risk factor (Gunning-Schrepers, 1989). It is associated with a number of pregnancy complications, including miscarriage, chromosomal abnormalities, giving birth to twins, uterine fibroids, gestation diabetes, bleeding disorders (including placenta praevia), low birth weight, preterm delivery, ante- and intrapartum fetal loss, neonatal mortality, and hypertensive disorders, including pre-eclampsia (Tuck *et al.*, 1988). However, before the introduction of the oocyte donation programme, most reports of pregnancy outcome in elderly primiparous women have not taken into account influences other than age. These include details of general health, chronic, mild or medium hypertension, diabetes, hepatic and renal dysfunction, obesity, cardiovascular disorders and smoking

habits (Antinori *et al.*, 1995).

It has been suggested that paternal genes (as expressed in the fetus) may contribute to the mother's risk of developing pre-eclampsia (Lie *et al.*, 1998). Long-term sexual cohabitation and previous pregnancies are thought to be protective against the development of hypertensive diseases of pregnancy, although the results of a recent study (Hall *et al.*, 2001) do not support the hypothesis that immunological exposure to semen is associated with a reduced risk of hypertensive disease.

The purpose of the current study was to evaluate the obstetric outcome of risk factors such as hypertensive disorders of pregnancies conceived by women of carefully selected menopausal age through egg donation.

Materials and methods

A total of 2729 candidates were assessed for inclusion in the programme. Only 1150 were admitted, and 1579 were rejected for various reasons (**Table 1**). The majority of the examinations were carried out by external colleagues, and frequently more than one reason was given (especially in the case of mild hypertension) for not admitting a patient to the oocyte donation programme. The medical disorders that these patients exhibited were for the most part not known before the examination and were discovered during investigations performed by this centre.

Recipients underwent complete and strict medical and psychological screenings (the latter conducted by external professionals). These included cardiovascular screening, glycaemia curve, assessment of thromboembolic risk, and serological screening for human immunodeficiency (HIV), hepatitis A, B and C, syphilis, TORCH, including abdominal, pelvic and breast ultrasound and NMR (**Table 2**, **Table 3**, **Table 4**).

Table 1. Details of the 1579 patients (58%) not included in the trial.

Condition	*Number of patients(%)*
Hypertension	
Mild	850 (53.8)
Medium	250 (15.8)
Severe	50 (3.1)
Cardiovascular disease	110 (6.9)
Smoking	50 (3.1)
Dysfunction	
Hepatic	42 (2.7)
Thyroid	40 (2.5)
Renal	38 (2.4)
Diabetes	35 (2.2)
Psychological	31 (1.96)
Breast disease (mammography)	20 (1.26)
Endometrial abnormality (by biopsy)	15 (0.94)
Obesity (%)	15 (0.94)
Signs of encephalopathy (NMR) (%)	13 (0.82)
Diffuse uterine leiomyoma (%)	10 (0.63)
Hyperaggregation of platelets (Born test) (%)	10 (0.63)

Recipients were 45–63 years of age, with 998 women being nulligravidae and 152 having experience of one previous pregnancy each at a young age. This study group of 1150 underwent 1288 IVF attempts. Recipients were divided in two groups. Group A were 45–50 years old, and involved 826 patients (925 cycles). Group B were 51–60 years old, and comprised 323 patients (362 cycles), including one 63-year-old woman.

Family history and support

On the basis of family history, the recipients' first-degree relatives (parents or offspring) should be free of cardiovascular disease and thromboembolic risk.

All the couples entering the programme had a good standard of living and had life expectancies of at least 30 more years. The mean ages of the husbands were not very different from those of the wives. In no cases were there marked differences in the spouses' ages.

Table 2. Haematological and radiological screening.

Haematological profile	VDRL
Hepatic profile	Hbsag
Renal function	HIV
Pancreatic function	Rubella, Toxoplasma, Cytomegalovirus, Herpes I, II
Thyroid screening	Cervical smear, vaginal and rectal swab
Abdominal and pelvic echography	Chest radiography
NMR (cranial)	Breast ultrasound and mammography
Plasma concentrations of FSH, LH, oestradiol and progesterone	

Table 3. Cardiovascular evaluation.

Cardiological examination	Basal ECG
Echocardiography	Echo-Doppler
Holter ECG	Blood pressure: dx, sx
BP Holter (24 h)	

Table 4. Coagulation screening and thromboembolic risk for patients.

PT
PTT
Fibrinogen
Platelet aggregation curve
With: ADP1 umolar, ADP3 umolar, collagen

PT = prothrombin; PTT = partial thromboplastin time; ADP = adenosine diphosphate.

Table 5. Results of oocyte donation in 1150 patients aged 45–63 years, percentages in brackets.

Cycles and oocytes	
Cycles	1288
Recovered oocytes	5280
Oocytes per patient	4.1
Embryos	
Resulting embryos	4250
Embryos transferred	4222
Mean embryos per patient	3.3
Pregnancies and deliveries	
Clinical pregnancies	489 (38)
Deliveries	363 (28)
Miscarriages	126 (25)
Term pregnancies	330 (90.9)
Preterm pregnancies	33 (9.1)
Multiple pregnancies	24 (6.6)
Twins	21
Triplets	3

Table 6. Obstetric outcome (percentages in parentheses).

Deliveries	
Term	330 (90.1)
Premature	33 (9.9)
Multiple	20 (6.1)
Single	13 (3.8)
Conditions	
Gestational hypertension related to all deliveries	43 (11.8)
Pre-eclampsia	4 (1.1)
Gestational diabetes	3 (0.8)
Abruptio placentae	3 (0.8)

Exclusions

In this study, approximately 1579 women were excluded from the programme due to rigorous selection criteria (**Tables 1–4**).

Replacement protocol

Oestradiol replacement

This regimen consisted of the daily administration of 2 mg of oestradiol valerate (Progynova; Schering, Milan, Italy) for the first 9 days. The dosage was increased to 6 mg per day on days 10–13. It was then reduced to 2 mg per day on days 14–28.

Progesterone replacement

Progesterone (Prontogest 100 mg ampoule; AMSA, Italy) was administered in a single intramuscular dose of 25 mg daily during days 15–17 and increased to 50 mg daily on days 18–26.

All patients underwent an evaluation cycle in which serum concentrations of oestradiol and progesterone were monitored and an endometrial biopsy was performed on day 21 or 22. The replacement cycle began on day 1 of the new cycle and embryo transfer took place on days 17–19.

Donors

Donors were mostly IVF patients who agreed to donate excess oocytes. In a few cases the donor was a friend or relative of the patient.

Donors' ages ranged from 24 to 34 years old. All donors and family members (first degree) were examined for any medical problems and had not experienced any major malformation of complex cause (multifactorial, polygenic). Such instances include heart malformation, problems with lungs or kidneys, congenital blindness, spina bifida, or any familial disease with a major genetic component, such as severe hypertension, coagulopathy, type I diabetes, inherited hypercholesterolaemia or death from cancer. Donors were also tested psychologically for mental disorders, mental deficiency, schizophrenia and epilepsy and were serologically screened for HIV, hepatitis A, B and C, and syphilis.

The donors were informed of ovarian stimulation treatment and oocyte use, and were requested to sign an informed consent form. Donors then underwent ovarian stimulation and oocyte recovery as previously described.

Recipient–donor synchronization

The recipients began oestradiol replacement 3 days before the donors began human menopausal gonadotrophin (HMG), later starting progesterone supplementation on the morning after human chorionic gonadotrophin (HCG) administration to donors. This day was arbitrarily designated as simulated day 15 (day 1 of progesterone). In this manner, recipients' cycles were synchronized with those of the donors, so that embryo transfer was performed on days 17–19 of the stimulated cycle. Serum oestradiol determinations and endometrial ultrasound were also performed. Oocyte aspiration was scheduled for 36 h after HCG administration. Transvaginal aspiration of the follicles took place under ultrasound guidance with a transvaginal probe. Oocyte recovery, fertilization, embryo culture and subsequent embryo transfer were performed by standard IVF methodology (Belasisch-Alart *et al.*, 1985).

IVF and embryo transfer

After retrieval, oocytes were transferred to dishes containing the culture medium and were inseminated with the spermatozoa of recipients' husbands. Semen was prepared by a 45–90% discontinuous gradient method using PureSperm (Nidacon International, Gothenburg, Sweden). After preparation, the same semen sample was used for both conventional IVF and intracytoplasmic sperm injection (ICSI) (Palermo *et al.*, 1992). The oocytes were examined on the

following day. Fertilized zygotes were transferred to grow the medium and cultured for an additional 24–48 h.

Embryos were then transferred to the recipients approximately 48–72 h after oocyte aspiration on the simulated day 17 (day 3 of progesterone). Up to four cleaving embryos were placed transcervically into the uterine cavity 7–8 mm from the upper limit of the fundus (Antinori *et al.*, 1993). Pregnancies were supported with oral oestradiol and intramuscular progesterone (Prontogest ampoules; AMSA) and only in a few cases with micronized vaginal progesterone given in divided doses for 140 days. After this period, all hormonal supplementation was discontinued (Antinori *et al.*, 1995).

Results

Oocyte donation was performed by IVF and embryo transfer in 1150 women aged 45–63 years (1288 recipient cycles). Of these, 826 were aged 45–50 (group A) and 323 were aged 50–60 years (group B), with one woman being 63 years of age. A total number of 5280 oocytes were donated (mean ± SD number of oocytes per recipient 4.1 ± 0.62) and 4250 were fertilized (80%). In all, 4222 embryos were transferred and the mean number of embryos per patient was 3.3 ± 0.86.

Overall, 489 (38%) clinical pregnancies were established in 1288 recipient cycles, and 390 healthy babies were delivered from 363 pregnancies (28%). A total of 126 (25.7%) were lost and 327 (90%) pregnancies reached full term. Thirty-six (9.9%) were premature deliveries (related to all deliveries). Multiple gestations were not frequent (n = 24; 6.6% of pregnancies) and included 21 (5.7%) sets of twins, three sets of triplets (0.9%) and no quadruplets (**Table 5**, **Table 6**).

Antenatal complications occurred in 86 patients (23.6% of deliveries). The frequencies of preterm deliveries, gestational hypertension, pre-eclampsia, gestational diabetes, and abruptio placentae are shown in **Table 6**. A total of 272 (75%) of all deliveries were by Caesarean section. Neonatal complications included growth retardation in two cases, and there were no neonatal or maternal deaths. The 63-year-old woman reached full term in July 1994 and delivered a boy in good health.

The pregnancy rate did not differ significantly in the two groups; group A, n = 354 (38.2%), group B, n = 134 (37%). Additionally, regarding preterm pregnancies, there were 26 out of 268 deliveries in group A (9.7%) compared with 10 out of 94 deliveries in group B (10.6%). There was no difference between the groups in multiple pregnancies, including 18 out 268 deliveries in group A (6.7%), and six out 94 deliveries in group B (6.4%).

A slightly higher number of abortions occurred in group B (n = 40; 29.8%) as compared with group A (n = 86; 24.2%).

No differences in gestational hypertension were observed (group A, n = 32; 11.9%; group B, n = 12; 11.7%).

Discussion

Primary attention must concentrate on the outcome of gestation in postmenopausal women up to the age of 62. In order to investigate pregnancy risks such as hypertension, pre-eclampsia/eclampsia, renal and hepatic disease, diabetes, abruptio placentae, haemorrhage, cardiovascular disorders and premature deliveries, an analysis was performed in this series of recipients (45–63 years old), in which 489 clinical pregnancies were achieved and 369 delivered, with 126 lost. The data with regard to hypertension and pre-eclampsia/eclampsia were very similar to the rates of hypertensive disorders of pregnancy (12%) previously reported in menopausal women (Sauer *et al.*, 1996).

In contrast, Blanchette (1993) reported that two of five patients (40%) developed pregnancy-induced hypertension (PIH). Pados *et al.* (1994) also found that PIH occurred in one-third of the women in their series. Serhal and Craft (1989) discovered nearly 40% of their pregnancies were complicated by pre-eclampsia. Among other investigators, Borini *et al.* (1995) found moderate and severe pre-eclampsia occurred in five (27.7%) out of 18 pregnancies in postmenopausal women aged >50 years. More recently, PIH was noted in 31% of oocyte recipients compared with 14% in IVF pregnancies (Soederstroem-Antilla *et al.*, 1998) and, in another study (Salha *et al.*, 1999), 33% of pregnancies developed hypertension after oocyte donation. However, in all these groups the cases studied numbered only a few women and no information was available regarding the selection criteria of recipients admitted to the oocyte donation programme. As far as is known, this is the largest retrospective analysis of 1288 recipient cycles out of 2729 women visited. To date, only in one study of 232 ovum donation pregnancies (Abdalla *et al.*, 1998) was it noted that 23% of all pregnancies were complicated by hypertension.

Multiple pregnancy is associated with greater risk for both mother and fetus when compared with a single pregnancy. Maternal risks include increased miscarriage, preterm labour/delivery, anaemia, hydramnios, hypertension, antepartum haemorrhage, antepartum fetal death, and other minor disorders of pregnancy. Miscarriage occurs more frequently in multiple pregnancies than in single pregnancies. Preterm delivery (before 37 weeks gestation) occurred in 20 (83.3%) out of all multiple pregnancies, compared with 3.8% in single pregnancies.

The incidences of pregnancy-induced hypertension and pre-eclampsia are increased in multiple pregnancies. Primigravida women with pregnancies involving twins have a 5 times greater risk of severe pre-eclampsia than in the case of single pregnancies; the risk for multigravida women is 10 times greater (MacGillivry *et al.*, 1988). The risk of hypertension is reported to be greater with monozygotic twins (McMullan *et al.*, 1984).

In conclusion, postmenopausal women do not have a greater risk associated with pregnancy if they do not exhibit any medical disorders. The risks in pre-menopausal women would be much lower than those known overall in the normal population if those groups had also received similar correction for pre-existing medical disorders that complicate pregnancy. Many risks to the fetuses and mothers are related to multiple pregnancy. It is concluded that proper screening for other risks such as pre-existing hypertension, coagulatory pathologies or

cardiological pathologies should be carried out to allow access to treatment only to a preselected group of menopausal women, with the intention of reducing ante-, intra- and postpartum complications. Without such rigorous selection, the complications could well have been greater.

A longitudinal assessment of prenatal outcomes is currently being performed, as well as neurological, social and behavioural development of children and their parents in this cohort.

While the events of pregnancy in these patients must be the primary concern, some interest attaches to the high rates of loss of implanted embyros in the two groups (29.8 and 24.4%). This stands in contrast with the age of the oocyte donors, who were only 24–34 years old. This is far less than the average age of IVF patients, who nevertheless have a higher implantation rate. These estimates could indicate that good-quality embryos are less able to implant in very old mothers, a suggestion confirmed by the low rate of multiple births in relation to the numbers of transferred embryos. This possibility should be followed up in later studies, in relation to matters such as the site of implantation and fetal survival.

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