

Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy

D.Bodri^{1,3}, V.Vernaev¹, F.Figueras², R.Vidal^{1,2}, J.J.Guillén¹ and O.Coll^{1,2}

¹Clínica EUGIN, c/Entença 293–295, 08029 Barcelona and ²Hospital Clínic, IDIBAPS, University of Barcelona, Spain

³To whom correspondence should be addressed. E-mail: dbodri@euvitro.com

BACKGROUND: Few data are available on pregnancy rate and obstetrical outcome after oocyte donation in Turner's syndrome patients. We conducted a retrospective analysis on the outcome of this subgroup. **METHODS:** Thirty oocyte donation cycles with fresh embryo transfer were performed in 21 patients between 2001 and 2004. **RESULTS:** The mean ($\pm$ SD) age of the recipients was 33.1 ± 1.8 years. The median (range) number of transferred embryos per cycle was two (1–4). Seventeen pregnancies were obtained (57%), of which 12 were clinical (40%). The implantation rate and the ongoing pregnancy rate were 22% (15 out of 68) and 30% (nine out of 30), respectively. Premature delivery was observed in 50% (four out of eight) of the pregnancies and intrauterine growth retardation in 55.5% (five out of nine) of the fetuses. Hypertensive disorders occurred in five out of eight pregnancies (three pre-eclampsias). **CONCLUSIONS:** Turner's syndrome patients achieve acceptable pregnancy rates after oocyte donation. A high rate of pregnancy-associated hypertensive disorders was observed which have led to a high rate of prematurity and intrauterine growth restriction. Although the number of cases in this study is limited, these results call for the need for intensive surveillance of such pregnancies. In order to reduce the risk of hypertensive disorders induced by multiple pregnancies, single embryo transfer should be proposed.

Key words: oocyte donation/pre-eclampsia/Turner's syndrome

Introduction

Turner's syndrome patients are considered sterile, although spontaneous pregnancies have been described, especially in cases with mosaicism. However, a high risk of miscarriages and chromosomal anomalies in the offspring is present (Wray *et al.*, 1981; Baudier *et al.*, 1985; Kohler *et al.*, 1985; Meyer *et al.*, 1989; Swapp *et al.*, 1989; Kaneko *et al.*, 1990; Magee *et al.*, 1998; Tarani *et al.*, 1998). For more than two decades, oocyte donation (OD) has been used successfully as a treatment option for patients with premature ovarian failure including patients with Turner's syndrome (Lutjen *et al.*, 1984). Pregnancy rates of Turner's syndrome patients after OD are reported to be similar to those among other women but, to date, a relatively small number of these cases have been described (Press *et al.*, 1995; Yaron *et al.*, 1996; Khastgir *et al.*, 1997; Foudila *et al.*, 1999). Furthermore, a high number of cardiac anomalies and hypertensive disorders are known to be present among these women (Lippe, 1991), and limited information is available regarding their obstetrical outcome (Foudila *et al.*, 1999). Women with Turner's syndrome have a potentially high risk of death during pregnancy from aortic rupture or dissection. Four fatal cases of aortic dissection have been reported in Turner's syndrome patients following OD pregnancies (Karnis *et al.*, 2003).

Therefore, a retrospective analysis was conducted of our OD programme in order to evaluate the rate of clinical pregnancies and obstetrical complications in this particular group of oocyte recipients.

Materials and methods

Between February 2001 and December 2004, a total of 21 patients with Turner's syndrome had 30 oocyte donation cycles. The chromosomal constitutions were 45X (monosomy) in 13 and other variants such as mosaics or deletions in eight patients. Only one patient had had spontaneous menstruations in the past and her karyotype was a 34% mosaic variant.

Before treatment, careful clinical assessment was carried out including a general physical and gynaecological examination, blood tests (haematology, biochemistry and serology), a Pap smear and a pelvic ultrasound scan. The uterine cavity was assessed by either a hysterosalpingography or hysteroscopy. Cardiological examination was performed by the cardiologist, including echocardiography.

Oral estradiol valerate (Progynova[®], Schering Spain, Madrid, Spain) was used in a constant dose regimen for the endometrial preparation. Patients on standby received up to 6mg a day and the duration of the treatment varied in accordance with the availability of the oocytes, ranging from 12 to 72 days. Endometrial thickness was not routinely measured before the embryo replacement (Remohi *et al.*,

1997a). From the day of the oocyte retrieval, 800mg of micronized vaginal progesterone (Utrogestan®, Laboratorio Seid, Barcelona, Spain) was added.

OD was performed according to the Spanish Act on Reproduction. Donation was anonymous and altruistic, and donors were required to be between the ages of 18 and 35. A conventional clinical and psychological work-up was performed, including karyotype analysis.

The ovarian stimulation of the donors was performed using recombinant FSH, and hypophysary suppression was obtained using either agonists or antagonists in a short stimulation protocol. Oocyte–cumulus complexes (OCCs) were recovered 36h after the administration of recombinant HCG. After the surrounding cumulus and corona cells were removed, the nuclear maturation of the oocytes was assessed under an inverted microscope. Only metaphase II oocytes were injected with motile spermatozoon into the ooplasm. These procedures have been described previously (Van Steirteghem *et al.*, 1993; Joris *et al.*, 1998). The ICSI procedure was performed routinely in order to ensure that immature oocytes were not given to the recipients and to enhance the fertilization rate. In the majority of the cycles (25 out of 30), frozen–thawed sperm, obtained during the first appointment, was used for convenience purposes for the patients living abroad, avoiding the need for them to be present on the day of oocyte retrieval.

Further culture of injected oocytes was performed in 25µl drops of culture medium under lightweight paraffin oil. Fertilization was confirmed after 16–18h by the observation of two distinct pronuclei under an inverted microscope. Developing embryos were classified according to their morphological appearance. Cleaving embryos with <50% of their volume filled with nucleate fragments were considered eligible for transfer. Cleaving embryos were transferred into the uterine cavity 2 or 3 days after the ICSI procedure.

A rise in serum HCG levels on two consecutive occasions from 14 days after transfer indicated pregnancy. In the case of pregnancy, hormonal replacement therapy was continued during 100 days following the embryo replacement. Each pregnancy with at least one intrauterine sac revealed by ultrasonography ~5 weeks after transfer was considered as a clinical pregnancy. The implantation rate was defined as the ratio of gestational sacs to the number of embryos transferred. Ongoing pregnancy was defined as a viable pregnancy confirmed on an ultrasound scan performed at 12 weeks. Pregnancy rates were defined per embryo transfer.

Pregnancy-induced hypertension (PIH) was defined as new onset of hypertension with two readings at least 6h apart of >140mmHg systolic or >90mmHg diastolic during gestation after 20 weeks of pregnancy. Pre-eclampsia (PE) was defined as PIH together with at least 1+ proteinuria (0.1g/l) on dipstick confirmed with >300mg/24h urine collection (Walker, 2000). Pregnancy-associated hypertensive disorder was defined as the occurrence of either PIH or PE. Fetal death was considered as an intrauterine fetal death after 22 weeks of pregnancy.

Results

The mean (±SD) age (range) of the recipients and donors was 33.1±1.8 (26–42) and 25.5±3.9 (19–32) years, respectively. The recipient's mean body mass index was 22.3±6.7 kg/m².

The median number of mature oocytes received was six (range: 3–17). The median number (range) of fertilized oocytes per patient was four (1–14). The median number of cleavage embryos (day 2–3) and transferred embryos (range) was three (1–7) and two (1–4), respectively. Cryopreservation of super-numerary embryos was performed in five treatment cycles (one or two embryos).

During the study period, no recipient candidate with Turner's syndrome was refused due to a cardiac anomaly. Only

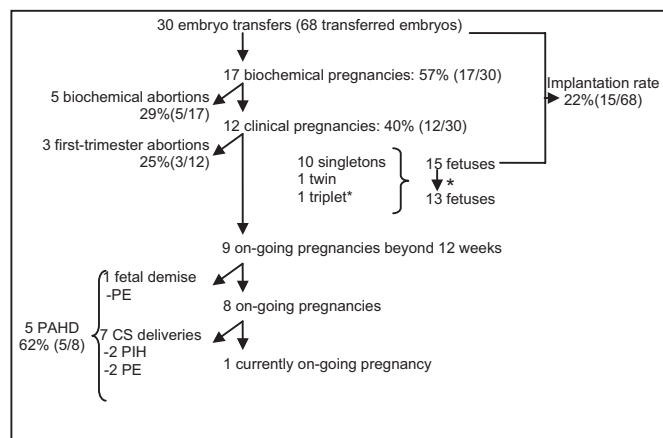


Figure 1. Flow of events for the studied cases. PE = pre-eclampsia; PIH=pregnancy-induced hypertension; PAHD = pregnancy-associated hypertensive disorders; CS=Caesarean section; (*)=embryo reduction.

one patient had a mild aortic insufficiency which did not contraindicate an eventual pregnancy. One patient had pre-existing hypertension which was treated and well controlled. No uterine malformation was identified in our study population; in one case, a hypoplastic uterine cavity was identified.

Twelve patients had 29 previous OD cycles abroad, all using frozen–thawed embryos. Two live births resulted by Caesarean section from uneventful singleton pregnancies (birth weights of 2100 and 2850g.).

Figure 1 depicts the flow of events in the studied patients. The clinical pregnancy rate per embryo transfer was 40% (12 out of 30). The triplet pregnancy was successfully reduced to a singleton pregnancy, and was uneventful later on. One fetal demise occurred at 33 weeks in a patient who presented PE and delivered vaginally. The delivery rate per embryo transfer was 27% (eight out of 30). Five out of eight patients presented pregnancy-associated hypertensive disorders; two patients developed PIH and three developed PE including one case of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. No other maternal complications were observed in our patients.

Seven patients gave birth to eight healthy infants. All patients delivered by Caesarean section, and the indications were severe PE in two cases and feto-pelvic disproportion in the others. The median gestational age (range) at the delivery was 37.5 (33–41) weeks. In 50% of the pregnancies (four out of eight), delivery took place before term. The mean birth weight of the singletons and twins was 2789±698 g (1630–3790) and 1990±28 g, respectively. Among the nine delivered newborns (including the fetal demise), five (55.5%) had a birth weight below the 10th centile adjusted by number of fetuses and newborn gender, according to local standards (Santamaria *et al.*, 1998).

Discussion

The first on-going pregnancy using OD in a hormonal replacement cycle was reported in 1984 (Lutjen *et al.*, 1984). Since then, many series of oocyte recipients have been published reporting high pregnancy rates (Abdalla *et al.*, 1990; Sauer *et al.*, 1991; Navot *et al.*, 1994; Pados *et al.*, 1994; Paulson

et al., 1994; Remohi *et al.*, 1997b). However, only a few reports and with a limited number of patients evaluated the pregnancy rate in Turner's syndrome patients. The pregnancy rate was found to be ~25–46% depending on the type of donors, i.e. egg sharing (Pados *et al.*, 1994; Press *et al.*, 1995; Yaron *et al.*, 1996) or exclusively voluntary donors (Khastgir *et al.*, 1997; Foudila *et al.*, 1999). A higher rate of biochemical abortions was present compared with our general recipient population (29 versus 12.8%). However, the rate of first-trimester miscarriages was not as high as in other published series (25 versus 40–60%) (Press *et al.*, 1995; Yaron *et al.*, 1996; Khastgir *et al.*, 1997; Foudila *et al.*, 1999). Yaron *et al.* (1996) suggested a compromised endometrial receptivity in patients with X chromosome abnormalities which could be the reason for the observed high rate of biochemical abortions. The clinical pregnancy rate per embryo transfer found in our series (40%) is in accordance with the pregnancy rate reported in other series where oocytes were obtained from young donors who were not enrolled in an IVF programme themselves, and also with our results in our non-Turner recipient population (44.7%).

Pregnancy-associated hypertensive disorders are frequently described in the general population of oocyte recipients (23–38%) (Sheffer-Mimouni *et al.*, 2002). This has been explained by the advanced maternal age and the high rate of multiple gestations. We also found a high rate of hypertensive disorders in our series, which could not be explained by maternal age or multiple pregnancies. This finding was also previously reported in Turner's syndrome recipients in another series (Foudila *et al.*, 1999). Some authors support the hypothesis that the development of PIH and PE in oocyte recipients may be due to altered or inadequate immunoprotection of the fetoplacental unit, due to short duration of exposure to non-maternal antigens (Salha *et al.*, 1999).

In this series, no cardiac complications were observed; however, our patients were assessed by a cardiologist (including echocardiography) before entering our programme. This finding does not preclude the importance of careful cardiological examination in this particular subgroup of egg recipients.

Furthermore, in order to reduce the risk of hypertensive disorders, it is of utmost importance to reduce the proportion of multiple pregnancies. As demonstrated by Soderstrom-Anttila *et al.* (2003), elective single embryo transfer (eSET) is also feasible in OD cycles, not affecting clinical pregnancy and delivery rates, but diminishing the proportion of twin pregnancies. Currently eSET is always proposed to our Turner's syndrome recipients and the decision is made together with the couple after thorough counselling. Under no circumstance is a transfer with more than two embryos performed in these patients.

In conclusion, similar pregnancy rates can be obtained in Turner's syndrome patients compared with the general population of oocyte recipients. A high rate of hypertensive disorders during pregnancy was observed, stressing the need for adequate counselling and obstetrical follow-up. This high rate of pregnancy-associated hypertensive disorders has led to a high rate of prematurity and intrauterine growth restriction.

Although the number of cases in this study is limited, these results call for further studies and stress the need for the intensive surveillance of such pregnancies.

References

- Abdalla HI, Baber R, Kirkland A, Leonard T, Power M and Studd JW (1990) A report on 100 cycles of oocyte donation; factors affecting the outcome. *Hum Reprod* 5,1018–1022.
- Baudier MM, Chihal HJ and Dickey RP (1985) Pregnancy and reproductive function in a patient with non-mosaic Turner syndrome. *Obstet Gynecol* 65 (3 Suppl),60S–64S.
- Foudila T, Soderstrom-Anttila V and Hovatta O (1999) Turner's syndrome and pregnancies after oocyte donation. *Hum Reprod* 14,532–535.
- Joris H, Nagy Z, Van de Velde H, De Vos A and Van Steirteghem A (1998) Intracytoplasmic sperm injection: laboratory set-up and injection procedure. *Hum Reprod* 13 Suppl 1,76–86.
- Kaneko N, Kawagoe S and Hiroi M (1990) Turner's syndrome—review of the literature with reference to a successful pregnancy outcome. *Gynecol Obstet Invest* 29,81–87.
- Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S and Reindollar RH (2003) Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. *Fertil Steril* 80,498–501.
- Khastgir G, Abdalla H, Thomas A, Korea L, Lataarche L and Studd J (1997) Oocyte donation in Turner's syndrome: an analysis of the factors affecting the outcome. *Hum Reprod* 12,279–285.
- Kohler C, Steinbach C and Muller R (1985) [Fertility and Turner syndrome]. *Zentralbl Gynakol* 107,904–907.
- Lippe B (1991) Turner syndrome. *Endocrinol Metab Clin North Am* 20,121–152.
- Lutjen P, Trounson A, Leeton J, Findlay J, Wood C and Renou P (1984) The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 307,174–175.
- Magge AC, Nevin NC, Armstrong MJ, McGibbon D and Nevin J (1998) Ullrich–Turner syndrome: seven pregnancies in an apparent 45,X woman. *Am J Med Genet* 75,1–3.
- Meyer L, Birkhauser M, Buhler E and Pavic N (1989) [Fertility and Turner mosaicism syndrome]. *Geburtshilfe Frauenheilkd* 49,825–829.
- Navot D, Drews MR, Bergh PA *et al.* (1994) Age-related decline in female fertility is not due to diminished capacity of the uterus to sustain embryo implantation. *Fertil Steril* 61,97–101.
- Pados G, Camus M, Van Steirteghem A, Bonduelle M and Devroey P (1994) The evolution and outcome of pregnancies from oocyte donation. *Hum Reprod* 9,538–542.
- Paulson RJ, Hatch IE, Lobo RA and Sauer MV (1997) Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod* 12,835–839.
- Press F, Shapiro HM, Cowell CA and Oliver GD (1995) Outcome of ovum donation in Turner's syndrome patients. *Fertil Steril* 64,995–998.
- Remohi J, Gerardo A, Garcia-Velasco JA, Gaitan P, Simon C and Pellicer A (1997a) Endometrial thickness and serum oestradiol concentrations as predictors of outcome in oocyte donation. *Hum Reprod* 12,2271–2276.
- Remohi J, Gartner B, Gallardo E, Yalil S, Simon C and Pellicer A (1997b) Pregnancy and birth rates after oocyte donation. *Fertil Steril* 67,717–723.
- Salha O, Sharma V, Dada T *et al.* (1999) The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. *Hum Reprod* 14,2268–2273.
- Santamaria R, Verdú J, Martín C and García G (1998) Tablas Españolas de Pesos Neonatales Según edad Gestacional. Laboratorios Menarini, SA, Barcelona.
- Sauer MV, Paulson RJ, Macaso TM, Francis MM and Lobo RA (1991) Oocyte and pre-embryo donation to women with ovarian failure: an extended clinical trial. *Fertil Steril* 55,39–43.
- Sheffer-Mimouni G, Mashiach S, Dor J, Levran D and Seidman DS (2002) Factors influencing the obstetric and perinatal outcome after oocyte donation. *Hum Reprod* 17,2636–2640.
- Soderstrom-Anttila V, Vilska S, Makinen S, Foudila T and Suikkari AM (2003) Elective single embryo transfer yields good delivery rates in oocyte donation. *Hum Reprod* 18,1858–1863.
- Swapp GH, Johnston AW, Watt JL, Couzin DA and Stephen GS (1989) A fertile woman with non-mosaic Turner's syndrome. Case report and review of the literature. *Br J Obstet Gynaecol* 96,876–880.

- Tarani L, Lampariello S, Raguso G et al. (1998) Pregnancy in patients with Turner's syndrome: six new cases and review of literature. *Gynecol Endocrinol* 12,83–87.
- Van Steirteghem AC, Nagy Z, Joris H et al. (1993) High fertilization and implantation rates after intracytoplasmic sperm injection. *Hum Reprod* 8,1061–1066.
- Walker JJ (2000) Pre-eclampsia. *Lancet* 356,1260–1264.
- Wray HL, Freeman MV and Ming PM. (1981) Pregnancy in the Turner syndrome with only 45,X chromosomal constitution. *Fertil Steril* 35,509–514.

- Yaron Y, Ochshorn Y, Amit A, Yovel I, Kogosowki A and Lessing JB (1996) Patients with Turner's syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation. *Fertil Steril* 65,1249–1252.

Submitted on July 18, 2005; resubmitted on October 17, 2005; accepted on October 21, 2005