Oocyte donation in Turner’s syndrome: an analysis of the factors affecting the outcome

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A total of 29 women with Turner’s syndrome (19 monosomy and 10 mosaic) had 68 cycles of oocyte donation that included 29 cycles of initial attempt and 39 cycles of subsequent attempts. Oral oestradiol valerate was used either in a variable dose (42 cycles) or in a constant dose (26 cycles) regimen for the endometrial preparation which was monitored by pelvic ultrasonography. The embryos/zygotes were transferred either fresh (50 cycles) or after cryopreservation (18 cycles) into the Fallopian tube (41 cycles) and uterine cavity (27 cycles) as appropriate. There were 28 clinical pregnancies including two sets of triplets resulting in a pregnancy rate of 41.2% per treatment cycle and an implantation rate of 17.1% per embryo transferred. The recipient’s age, chromosomal constitution or associated uterine or tubal anomaly had no influence on the treatment outcome. The implantation and pregnancy rates were higher in the subsequent than initial cycles (22.6 versus 9.99%, \(P < 0.05\)); 51.3 versus 27.6%, \(P < 0.05\)). An endometrial thickness of \(\geq 6.5\) mm was an important predictor of pregnancy but the endometrial echo pattern failed to predict the outcome. Although the total dose of oestradiol before embryo transfer was higher in the previous cycles than the non-pregnant ones and its gradation (<50 mg, 50–100 mg, <100 mg) influenced the implantation (3.4, 17.5, 26.3% respectively, \(P < 0.05\)) and pregnancy rates (10, 42.2, 61.5% respectively, \(P < 0.05\)), the effect was indirect by altering the endometrial thickness. The number of oocytes fertilized affected the pregnancy rate irrespective of the number of embryos transferred. The implantation and pregnancy rates were higher when fresh rather than frozen–thawed embryos were transferred (20.3 versus 8.2%, \(P < 0.05\); 48 versus 22.2%, \(P < 0.05\)) but the route of transfer was of no statistical importance. The overall miscarriage rate was higher (50%), and was related to the presence of hypertlastic or bicornuate uterus and to a low oocyte fertilization rate.

Key words: donor oocyte/outcome/Turner’s syndrome

Introduction

Turner’s syndrome is characterized by the complete or partial absence of one X chromosome that results in multiple somatic abnormalities and ovarian dysgenesis (Turner, 1938; Ford et al., 1958; Hook and Warburton, 1983). The majority of women with this condition have streak ovaries with the absence of any follicular structure. However, occasionally there may be a few follicles in the ovaries that are able to induce menstrual periods for some time before the onset of a premature menopause (Groll and Cooper, 1976; Rosenfield and Grumbach, 1990; Lippe, 1991). Thus, chances of spontaneous pregnancy are extremely rare in Turner’s syndrome, irrespective of the karyotype. Since the first publication by Bahner et al. (1960), only sporadic pregnancies have been reported from patients with either homogeneous 45XO or mosaic 45XO/46XX chromosomal constitutions. The outcome of these pregnancies was poor with an increased incidence of miscarriage and stillbirths (Dewhurst, 1978; King et al., 1978; Nielson et al., 1979; Wray et al., 1981; Kaneko et al., 1990).

Oocyte donation treatment for women with Turner’s syndrome is expected to offer a better chance of conceiving with less pregnancy wastage. A few cases of Turner’s syndrome have been mentioned in many reports of oocyte donation but their outcomes were not analysed separately (Devroey et al., 1988; Salat-Baroux et al., 1988; Abdalla et al., 1989; Pados et al., 1992). According to other reports, where the outcome of oocyte donation in Turner’s syndrome was assessed, the findings were contradictory with one reporting lower pregnancy rates (Heinze, 1994) while another suggested better results in comparison with other indications (Abdalla et al., 1990). When the outcome of oocyte donation in Turner’s syndrome was compared with that in women with premature menopause the results from the two groups were similar (Press et al., 1995).

With such inconsistencies in previous reports, there is a need for further assessment of results and the factors influencing outcome of oocyte donation in a larger population of patients with Turner’s syndrome. This is particularly important because the endometrial response to hormone replacement has been reported to be suboptimum in this special category compared with the other causes of premature ovarian failure (Davies et al., 1990; Li et al., 1991). There may also be difficulties in embryo transfer due to associated hypoplasia and malformation of the genital tract. In terms of pregnancy outcome it would be interesting to know whether the increased incidence of miscarriage continues with the use of donor oocytes. This would determine whether an abnormal uterine factor or oocyte chromosomal aberration is the cause of increased pregnancy wastage.

We report on what is, to date, the largest series of oocyte donation treatment in women with Turner’s syndrome. The purpose of the study was to assess the reproductive potential of these women in terms of their endometrial response to

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hormone replacement and the suitability of the mode of embryo transfer. The factors affecting the outcome of oocyte donation were analysed to determine the need for any modification in the treatment of women with Turner’s syndrome.

Materials and methods

Oocyte recipients
A total of 29 women with Turner’s syndrome whose mean (±SD) age was 30.24 ± 4.35 years (range 23–40), had 68 cycles of oocyte donation treatment between January 1988 and December 1995. The chromosomal constitutions were 45X (monosomy) in 19 and 45X/46XX (mosaic) in the remaining 10 women. The two groups of women had 52 and 16 cycles of oocyte donation respectively. Only four of these women had spontaneous menstruation in the past and none had any prior spontaneous conceptions. At the time of treatment all women had gonadotrophin concentrations of >20 IU/l and were experiencing artificial menstrual cycles from administration of oestradiol valerate 2 mg daily for 11 days together with norgestrel 0.5 mg daily for a further 10 days every month (Cycloprogynova 2 mg; Schering, Burgess Hill, West Sussex, UK) while on the waiting list for oocyte donation.

A pre-treatment assessment of these women by hysterosalpingography and/or laparoscopy revealed abnormalities including hypoplastic uterus and tubes (n = 7), bicornuate uterus (n = 4) and blocked tubes (n = 4). Women with hypoplastic and bicornuate uteri had 14 and 5 treatment cycles respectively. Associated infertility causes were present in six couples: a tubal factor was present in four women who had 13 cycles and a male factor was noted in two couples who had four cycles of oocyte donation. Some patients had more than one pelvic anomaly. In the remaining 23 couples, ovarian failure was the only cause of infertility and they received 51 cycles of treatment. All women experienced at least one attempt which comprised the group of 29 initial treatment cycles (42.6%). The remaining 39 subsequent cycles (57.4%) were the second (n = 9), third (n = 8), fourth (n = 6) and fifth (n = 2) attempts, and one patient continued till the ninth attempt before she had a successful outcome.

Hormone replacement
The endometrial preparation for implantation was induced by either variable (Lutjen et al., 1984; Abdalla et al., 1990) or constant (Sethal and Craft, 1987) doses of oral oestradiol valerate (Progynova; Schering). With the variable dose regimen (42 cycles) the recipients received 2 mg oestradiol valerate daily from the beginning of their menstrual cycles and after the onset of the donor’s periods the dose was increased to 4 mg daily. When the donor was at the appropriate stage to receive human chorionic gonadotrophin (HCG; 10 000 IU) and were receiving artificial menstrual cycles from administration of oestradiol valerate 2 mg daily for 11 days together with norgestrel 0.5 mg daily for a further 10 days every month (Cycloprogynova 2 mg; Schering, Burgess Hill, West Sussex, UK) while on the waiting list for oocyte donation.

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Ultrasound monitoring
All recipients were monitored during hormone replacement by serial pelvic ultrasonography (Sonoline 2000; Siemens UK) using a 7.5 Hz transvaginal probe to measure the endometrial thickness and echo pattern in the sagittal plane. Endometrial thickness was measured at its maximum as a double layer from the echogenic interfaces of one endometrial–myometrial junction to the other. Endometrial echo patterns were expressed as their density relative to that of the anterior wall of the myometrium and were accordingly categorized as hypoechoic, isoechoic and hyperechoic. All ultrasonographies were performed by a single observer using one machine to minimize the subjective variation. The endometrial echo pattern on the day before progesterone administration (day of donor’s HCG injection) and endometrial thickness on the day of embryo transfer were compared between different groups and their outcomes.

Oocyte donation, fertilization and embryo transfer
The oocytes were donated anonymously by 57 healthy women whose mean (±SD) age was 29.67 ± 4.14 years (range 23–38); 49 (86%) of them were parous. The mean (±SD) number of oocytes obtained per donation was 10.93 ± 4.99 (range 2–21) which were usually divided between two recipients in the oocyte donation programme so that the mean (±SD) number of oocytes per recipient was 5.5 ± 1.8 (range 2–11). The mean (±SD) number of oocytes fertilized was 3.93 ± 2.05 (range 1–11) from which the mean (±SD) number of embryos/zygotes transferred was 2.75 ± 0.76 (range 1–5; maximum of three after August 1991). The embryos/zygotes were either transferred fresh in 50 cycles (73.5%) or after cryopreservation in 18 cycles (26.5%). The route of transfer was tubal in 41 cycles (60.3%), which comprised zygote intra-Fallopian transfer (ZIFT) in the fresh cycles but tubal embryo transfer (TET) in the frozen cycles, and uterine in the remaining 27 cycles (39.7%). The choice of route was preferentially tubal unless restricted by an unsuitable tubal status (n = 13), fewer numbers of embryos available (n = 3), unfavourable experiences from a previous tubal transfer (n = 6) or patient’s choice regarding anaesthesia (n = 5). The uterine embryo transfers were not difficult even in patients with hypoplastic uterus and none required general anaesthesia. Following embryo/zygote transfer all recipients continued to receive oestradiol and progesterone replacement for another 2 weeks. Pregnancy tests were then performed and, if positive, the hormone replacement was extended until 12 weeks of gestation. The diagnosis of a positive pregnancy was confirmed by a pelvic ultrasound scan at 5 weeks to locate the gestational sac.

Statistical analysis
The influence of different patient characteristics and treatment variables on the outcome of oocyte donation were estimated. The patients were therefore grouped according to their age (in 5 year intervals), chromosomal constitution, uterine and tubal status, the sequence of treatment cycle, the hormone replacement therapy (HRT) regimen, total dose and duration of oestrogen replacement, endometrial thickness and echo pattern, number and type of embryos, and their mode of transfer. The implantation and pregnancy rates were compared between these subgroups to assess the influence of these factors on the outcome. The statistical analysis was carried out by the χ2 test with Yates’ correction or Fisher’s exact test as appropriate for the comparison of incidence and by the Mann–Whitney U-test for comparing the medians between two groups of patients. Since multiple variables may influence the outcome of oocyte donation it is important to establish the effect of an individual factor without it being confounded by others. Many of these variables are also interrelated, for example, the total dose of oestrogen is dependent upon the hormone replacement regimen and the duration of replacement. The
Outcomes of oocyte donation are binomial (either pregnant or non-pregnant) and, subsequently, either miscarried or not. A logistic regression analysis was, therefore, performed to assess the effects of individual factors in a stepwise fashion so that their relative contributions to the outcome could be determined.

Results
When the overall outcome was analysed, 17 out of the 29 women with Turner’s syndrome undergoing oocyte donation treatment had clinical pregnancies confirmed by the presence of a gestational sac on ultrasonography. The treatment was successful on one occasion in 10 women, twice in four women, three times in two women and one woman had success on four occasions. Only one of these women who became pregnant more than once had two viable pregnancies. A total of 28 pregnancies resulted out of 68 treatment cycles giving a pregnancy rate of 41.2% per cycle. A single gestational sac was present in all cases, except for two pregnant women who had triplets. Thus 32 gestational sacs developed following transfer of 187 embryos giving an implantation rate of 17.1% per embryo. Out of 28 pregnancies, eight were aborted prior to 8 weeks, six had spontaneous miscarriages after the detection of a fetal heart beat at 8 weeks, one was tubal ectopic and the remaining 13 pregnancies progressed till delivery. With the incidence of miscarriage of 50% and of ectopic pregnancy of 3.5%, the take-home baby rate was 19.1% per treatment cycle.

The recipients’ and donors’ characteristics were compared between pregnant and non-pregnant cycles (Table I). The median age of the recipients, proportion of chromosomal subtypes, presence of associated tubal and male infertility, and hypoplastic and bicornuate uterus were similar irrespective of the treatment outcome. In the pregnant group there was a trend towards a greater number of subsequent treatment cycles compared with the non-pregnant group but this failed to reach statistical significance (71.4 versus 47.5%). The number of cycles using a constant oestrrogen regimen was higher in the pregnant group than in the non-pregnant one (53.6 versus 30%; $P < 0.05$). The number of constant oestrrogen regimen cycles was also higher in the subsequent cycles of the pregnant group than in the initial cycles (48.7 versus 24.1%; $P < 0.05$).

The total dose of oestrrogen used before embryo transfer was higher in the constant regimen than in the variable regimens [median (range): 96 (72–136) mg versus 59 (40–178) mg; $P < 0.05$] and also in the pregnancy cycles than non-pregnancy cycles [median (range): 78 (48–120) mg versus 65 (40–178) mg; $P < 0.05$] but the duration of oestrrogen replacement was similar irrespective of the outcome of treatment. The endometrial thickness and echo pattern before embryo transfer were not different between pregnant and non-pregnant cycles. The donor age and parity, number of oocytes donated and number of oocytes received were similar in the pregnant and non-pregnant groups but the number of oocytes fertilized and embryos transferred were higher in the successful cycles ($P < 0.003$; $P < 0.05$). Between pregnant and non-pregnant cycles there were no statistically significant differences either in the proportion of cycles using fresh (85.7 versus 65%) or frozen embryos (14.3 versus 35%) or in the route of embryo transfer (50.8 versus 49.2%; $P < 0.05$).

When the implantation and pregnancy rates were assessed individually in different age groups, according to the chromosomal constitutions and with varied pelvic anomalies there were no statistically significant differences between the groups (Table II). The male factor patients did not have any effect on overall fertilization rate and were therefore included in the study. The outcomes were better in the subsequent treatment cycles in comparison with the initial treatment cycles with both the implantation (22.6 versus 9.99%; $\chi^2 = 4.41$, $P < 0.05$) and pregnancy rates (51.3 versus 27.6%; $P < 0.05$). Similarly the constant oestrrogen regimen was superior to the variable one in rates of implantation (27.1 versus 11.1%; $\chi^2 = 6.84$, $P < 0.01$) and pregnancy (55.5 versus 31.7%; $P < 0.05$). However, the trend of improved outcome with the constant oestrrogen regimen over the variable one did not reach statistical significance when assessed separately in the initial (implantation rate 21 versus 6.5%; pregnancy rate: 50 versus 19%) and subsequent treatment cycles (implantation rate 31.25 versus 15.5%; pregnancy rate: 57.9 versus 45%).

The average dose and duration of oestrogen before embryo transfer in the variable regimen is usually <50 mg and <15 days respectively. Thus the cycles using a higher dose of oestrogen (>50 mg) were the ones with constant regimen or a prolonged variable regimen. In order to assess whether the difference in outcomes with two oestrrogen regimens was due to the higher daily dose rather than to the sequential increase over a prolonged period, the cycles were categorized either according to the dose (<50 mg, 50–100 mg and >100 mg) or according to the duration (<15 days and ≥15 days). Analysis of the former indicated that there was a dose–response difference between the three groups with a greater success with higher dose in terms of both the implantation (3.4, 17.5, 26.3%; $\chi^2 = 6.09$, $P < 0.05$) and pregnancy rates (10, 42.2, 61.5%; $\chi^2 = 6.25$, $P < 0.05$). However, the treatment outcomes were not influenced by the duration of oestrrogen.

### Table I. Comparison of the recipient and donor characteristics in the pregnant and non-pregnant cycles. Values are medians with the ranges in parentheses

<table>
<thead>
<tr>
<th></th>
<th>Pregnant cycles (n = 28)</th>
<th>Non-pregnant cycles (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients’ age (years)</td>
<td>29.5 (23–39)</td>
<td>29.5 (23–40)</td>
</tr>
<tr>
<td>Total dose of oestrigen (mg)</td>
<td>78 (48–120)</td>
<td>65 (40–178)</td>
</tr>
<tr>
<td>Duration of oestrigen (day)</td>
<td>16 (10–22)</td>
<td>15 (9–32)</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>9.4 (6.5–13)</td>
<td>9 (4.5–11.8)</td>
</tr>
<tr>
<td>Donors’ age (years)</td>
<td>31 (23–36)</td>
<td>29 (23–38)</td>
</tr>
<tr>
<td>Donors’ parity (% parous)</td>
<td>19 (86.4)</td>
<td>30 (85.7)</td>
</tr>
<tr>
<td>Number of oocytes donated</td>
<td>13 (2–21)</td>
<td>11 (4–18)</td>
</tr>
<tr>
<td>Number of donor oocytes received</td>
<td>7 (2–11)</td>
<td>6 (3–11)</td>
</tr>
<tr>
<td>Number of oocytes fertilized</td>
<td>5 (1–11)</td>
<td>4 (1–10)</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>3 (1–5)</td>
<td>3 (1–4)</td>
</tr>
</tbody>
</table>

$^aP < 0.05$ (Mann–Whitney U-test).

$^bP < 0.003$ (Mann–Whitney U-test).
replacement before embryo transfer, whether <15 days or ≥15 days (Table II).

If a cut-off point of 6.5 mm of endometrial thickness on the day of endometrial transfer was taken to be the outcome predictor there was no implantation or pregnancy below this range, which influenced the results significantly (P < 0.05; P < 0.05). However, when the cut-off was raised to 7.5 mm the outcome was unaffected. Endometrial echo patterns, whether hypoechoic, isoechoic or hyperechoic, also failed to predict the treatment outcome since implantation (14.3, 18.9, 16.6%) and pregnancy rates (38.5, 46.1, 37.9%) were similar. The implantation rates were similar irrespective of the number of embryos transferred; the pregnancy rate appeared to increase with an increase in the number of embryos transferred but this failed to reach statistical significance due to small numbers in some groups. Transfer of fresh embryos resulted in better outcomes than transfer of frozen ones in terms of both implantation (20.3 versus 8.2%; P < 0.05) and pregnancy rates (48 versus 22.2%; P < 0.05). Comparison of the route of embryo transfer did not reveal any significant effect on the treatment outcome (Table II).

The effect of treatment variables on the outcome in the absence of any influence of the type and number of embryos transferred was analysed. If those cycles where three fresh embryos were transferred (38 cycles; 56%) were considered separately, the factors which still influenced the results were the total dose of oestrogen and the endometrial thickness before embryo transfer. If the patients were grouped according to the total amount of oestrogen replaced (<50 mg, 50–100 mg and >100 mg), the dose response was maintained with both implantation (4.7, 21.9, 30.3%; χ² = 5.05, P < 0.05) and pregnancy rates (14.3, 60, 72.7%; χ² = 6.29, P < 0.05). In these selected cycles there was no implantation and therefore no pregnancy when the endometrium thickness was <6.5 mm (P < 0.05; P < 0.05).

With a stepwise logistic regression analysis, in a model where all the treatment cycles were considered, the variables that independently influenced the pregnancy rate were: the endometrial thickness cut-off of 6.5 mm, the number of oocytes fertilized and whether or not fresh embryo were transferred. If the order of treatment cycles was included in the model, the subsequent treatment cycles had better outcomes than the first treatment cycle, irrespective of other factors. The influence of the type of embryo transferred (fresh or frozen) was lost in this model probably due to the smaller number of frozen embryo cycles in the subsequent attempts (Table III). The same statistical test was performed to identify the factors that influenced the development of the prognostically important endometrial cut-off of 6.5 mm. The total dose and duration of oestrogen replacement affected the endometrium independently without any influence of other factors such as age, chromosomal constitution, type of uterus, hormone replacement regimen or the sequence of treatment cycle (Table IV). Thus the role of total dose of oestrogen on the pregnancy rate was indirect by affecting the endometrial thickness. The higher pregnancy rate with the constant dose rather than the variable dose of oestradiol replacement was due to the difference in the total dose in the two regimens indirectly influenced the endometrial thickness. Logistic regression analysis showed that the high miscarriage rate was influenced by the presence of hypoplastic or bicornuate uterus and a lower number of oocytes fertilized (Table V).

Discussion

With oocyte donation the chances of conception and delivery of a healthy baby have become a reality for women with Turner’s syndrome. The first pregnancy using a donated oocyte in a hormone replacement cycle was reported in a patient with primary ovarian failure due to ovarian dysgenesis (Lutjen

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### Table III. Logistic regression analysis determining the factors that independently influenced pregnancy following oocyte donation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Logistic regression coefficient (SE)</th>
<th>Reduction in the log likelihood</th>
<th>Degrees of freedom</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cycles*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>4.1739 (12.0646)</td>
<td>8.232</td>
<td>1</td>
<td>0.0041</td>
</tr>
<tr>
<td>(≤6.5 mm or ≥6.5 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of oocytes fertilized</td>
<td>0.3498 (0.1583)</td>
<td>5.962</td>
<td>1</td>
<td>0.0146</td>
</tr>
<tr>
<td>Fresh embryos</td>
<td>0.6579 (0.3335)</td>
<td>4.318</td>
<td>1</td>
<td>0.0377</td>
</tr>
<tr>
<td>Considering the order of treatment cycles (initial or subsequent)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>3.9011 (11.6704)</td>
<td>5.804</td>
<td>1</td>
<td>0.0160</td>
</tr>
<tr>
<td>(≤6.5 mm or ≥6.5 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of oocytes fertilized</td>
<td>0.4243 (0.1682)</td>
<td>8.317</td>
<td>1</td>
<td>0.0039</td>
</tr>
<tr>
<td>Subsequent treatment cycles</td>
<td>0.5746 (0.2985)</td>
<td>3.982</td>
<td>1</td>
<td>0.0460</td>
</tr>
</tbody>
</table>

The log likelihood for the models = 92.139 (degrees of freedom = 15* and 16**).

### Table IV. Logistic regression analysis determining the factors that independently influenced the development of cut-off endometrial thickness (<6.5 mm or ≥6.5 mm) before zygote/embryo transfer

<table>
<thead>
<tr>
<th>Factors</th>
<th>Logistic regression coefficient (SE)</th>
<th>Reduction in the log likelihood</th>
<th>Degrees of freedom</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of oestrogen</td>
<td>0.1395 (0.0658)</td>
<td>10.754</td>
<td>1</td>
<td>0.0010</td>
</tr>
<tr>
<td>Duration of oestrogen</td>
<td>0.5100 (0.1968)</td>
<td>13.018</td>
<td>1</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

The log likelihood for the model = 40.587 (degrees of freedom = 9).

### Table V. Logistic regression analysis determining the factors that independently influenced miscarriage in pregnancies following oocyte donation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Logistic regression coefficient (SE)</th>
<th>Reduction in the log likelihood</th>
<th>Degrees of freedom</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oocytes fertilized</td>
<td>0.8500 (0.3837)</td>
<td>7.500</td>
<td>1</td>
<td>0.0062</td>
</tr>
<tr>
<td>Uterine anomalies</td>
<td>1.4961 (0.7918)</td>
<td>5.408</td>
<td>1</td>
<td>0.0200</td>
</tr>
</tbody>
</table>

The log likelihood for the model = 38.816 (degrees of freedom = 16).

Since then many series of oocyte donation have included a few cases of Turner’s syndrome and reported overall pregnancy rates of ~30% per cycle (Rosenwaks et al., 1986; Devroey et al., 1988; Salat-Baroux et al., 1988; Abdalla et al., 1989; Cornet et al., 1990). When compared with patients with secondary ovarian failure, the pregnancy rate following oocyte donation in Turner’s syndrome has been reported to be either higher (Abdalla et al., 1990) or identical (Press et al., 1995). As the majority of women had more than one treatment cycle in this series, the improved success rate may be attributable to the option of modification of hormone replacement regimen and mode of zygote/embryo transfer in the subsequent cycles from the experiences in the initial treatment cycle.

The uterine response to a standard dose of hormone replacement has been reported to be poor in women with Turner’s syndrome, resulting in smaller uterine thickness, thinner endometrial lining and less advanced endometrial dating compared with women with idiopathic ovarian failure (Li et al., 1991). The suboptimum endometrial response might impair implantation of embryos and account for the poorer outcome of oocyte donation treatment for Turner’s syndrome patients (Hens et al., 1989; Heinze, 1994). Recently Press et al. (1995) have shown that endometrial thickness and echo pattern before embryo transfer were similar in Turner’s syndrome and idiopathic ovarian failure patients. The total dose of oestrogen used for oocyte donation treatment is much higher than the usual dose required in post-menopausal women for inducing regular withdrawal bleeding. Thus the suboptimum endometrial response on low dose oestrogen replacement as reported by Li et al. (1991) can be rectified by a higher dose and longer duration of oestrogen stimulation. This was supported by our findings of higher incidence of constant oestrogen regimen, in which a higher dose of oestrogen is used, in the subsequent cycles when the initial cycles had been less satisfactory. With adequate hormone replacement therapy the development of secretory endometrium confirmed that the uterine receptors are normal and capable of responding to hormone replacement therapy (Cornet et al., 1990). This view has been confirmed by the satisfactory implantation and pregnancy rates in the present study.

The total dose of oestrogen replacement before embryo transfer was higher in the pregnant cycles than non-pregnant...
ones. Since the duration of oestrogen replacement was similar in both the pregnant and non-pregnant groups, it was the higher daily dose of a constant regimen, rather than a prolonged variable regimen, that led to an improved outcome. This finding was in contradiction to a previous report of oocyte donation in women with ovarian dysgenesis where successful outcome was limited to the use of a variable dose oestrogen replacement with additional midcycle supplementation (Cornet et al., 1990). However, the common factor in both the reports was a higher total dose of oestradiol in the most effective hormone replacement regimen, be it constant dose or with midcycle supplementation. A higher pregnancy rate was reported in the subsequent cycles probably due to optimal endometrial development since the response to oestrogen in individual woman was already known from the initial attempt. Thus a dummy cycle for monitoring the hormonal response before oocyte donation would be helpful in these patients. The benefit of the subsequent cycle was over and beyond the higher total dose of oestrogen in the constant regimen that was more frequently used following previously poor endometrial responses. Individualization of the mode of embryo transfer from the experience of a previous cycle also played an important role as the route was changed from tubal to uterine in six cycles. Our finding was in contrast to another report that has shown a better outcome in the initial cycle followed by a decline in subsequent cycles (Press et al., 1995).

In women undergoing oocyte donation for other indications, transvaginal sonographic assessment, both before starting progesterone and on the day of embryo transfer, demonstrated thicker endometrium in the pregnant cycles in comparison with the non-pregnant ones. The cut-off point for the endometrium as a predictor for the outcome varied considerably between reports, from 7.5 to 10 mm (Check et al., 1993a; Abdalla et al., 1994). In women with Turner’s syndrome the uterus is of a relatively smaller size and it is unreasonable to expect a similar endometrial thickness to that of other women. This view was supported by the report that the individual uterine size is the main factor in the development of endometrial thickness in gonadotrophin-stimulated cycles (Strohmer et al., 1994). In the present study, the outcome of oocyte donation was satisfactory, even with a relatively thinner endometrium, and there was no difference in the endometrial thickness between pregnant and non-pregnant cycles. There were pregnancies when the endometrial thickness was <7.5 mm but none was <6.5 mm, which should be the realistic cut-off point for the Turner’s syndrome patients before embryo transfer. Sonographic assessment of endometrial appearance before progesterone replacement was predictive of implantation in donor oocyte recipients in some studies (Shapiro et al., 1993; Coulam et al., 1994). However, no significant difference in the pregnancy rate according to the echo pattern was observed either in the present study or in other reports (Alam et al., 1993; Check et al., 1993a).

There were no differences in the implantation and pregnancy rates between women with Turner’s syndrome of different age groups. This was in accordance with the unchanged uterine receptivity with age that has been reported among oocyte recipients (Navot et al., 1991; Sauer et al., 1992; Abdalla et al., 1993). It confirms that there is no decline in prognosis with the duration of hypo-oestrogenism that directly correlates with age in primary ovarian failure. There were no differences in the outcome between monosomy and mosaic Turner; the latter may have had premature menopause rather than primary amenorrhoea and therefore have a shorter duration of ovarian hormone deficiency. The suboptimum endometrial response in Turner’s syndrome was thought to be dependent on the duration and severity of oestrogen deficiency (Davies et al., 1990). With a uniform treatment outcome irrespective of the age and Turner type in the present study, it seems that a higher total dose of oestrogen replacement can improve the endometrial receptivity.

The pregnancy rate was unaffected irrespective of the presence of hypoplastic or bicornuate uteri and the presence of other associated infertility factors. The improved pregnancy rate reported with tubal rather than uterine transfer in other studies of oocyte donation (Abdalla et al., 1990) has not been demonstrated in the present study. This could be due to the presence of associated hypoplastic tubes that may have restricted transfers both mechanically and functionally. However, there may not be any difference in the outcome with different routes of embryo transfer even in individuals with healthy tubes as shown in a prospective study (Balmaceda et al., 1992). The finding of improved pregnancy rate with fresh rather than frozen–thawed embryo transfer was not unexpected as this has also been reported in other studies of oocyte donation (Abdalla et al., 1990; Leeton et al., 1991). The difference was evident even after correcting for the number of embryos transferred, which are usually fewer in the frozen–thawed cycles. It was, therefore, the quality of embryo that was responsible for the improved pregnancy rate since the higher quality embryos are usually selected for fresh cycles. Another influencing variable for the outcome was the number of oocytes fertilized, independent of the number of embryos transferred although these values are correlated. It indicates that oocyte quality was primarily responsible, as the confounding effects upon fertilizing ability of sperm factor and the number of donor oocytes available, have been eliminated.

The functional aspect of oocytes appeared to influence the miscarriage rate which was higher in the presence of a low oocyte fertilization rate. The higher miscarriage rate even with the use of donor oocytes suggests that a uterine factor may also be responsible for adverse pregnancy outcome. In women with bicornuate uterus the miscarriage rate was higher. The possibility of uterine anomaly contributing to the high rate of fetal wastage has been suggested by others but remains debatable (Check et al., 1993b). The poor pregnancy outcome in this study was also influenced by the presence of a hypoplastic uterus which may have been associated with uterine anomaly. The presence of a hypoplastic uterus along with hypovascularization has been postulated elsewhere (Belercq et al., 1992) as the cause of a higher miscarriage rate. Further studies are therefore required to assess the effect of hormone replacement on uterine blood flow in women with Turner’s syndrome and its effect on the pregnancy outcome following oocyte donation.

In conclusion, the outcome of oocyte donation in women
with Turner’s syndrome was similar to other conditions which have a need for a higher total dose (>50 mg) of oestradiol replacement for optimum endometrial response. A minimum endometrial thickness of 6.5 mm was required for successful outcome which commonly persisted in the subsequent cycles, rather than the first. The individual experience in the initial treatment cycle helped to select the appropriate hormone replacement and the ideal mode of embryo transfer, suggesting the relevance of a dummy cycle. However, the most important predictor of the outcome was the number of oocytes fertilized which influenced both pregnancy and miscarriage rates. The presence of hypoplastic or bicornuate uterus increased the risk of miscarriage.

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