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A proposal for reproductive counselling in carriers of Robertsonian translocations: 10 years of experience with preimplantation genetic diagnosis

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BACKGROUND: Carriers of Robertsonian translocations are at increased risk for infertility, repeated miscarriage and aneuploid offspring. In the present study, 10 years of experience with preimplantation genetic diagnosis (PGD) for Robertsonian translocations is reviewed and these data are used to improve the reproductive counselling in the carriers.

METHODS: A retrospective analysis was performed of all requests and cycles for PGD for Robertsonian translocations at our centre between January 1997 and December 2006. Data on the characteristics of the couples and on the PGD cycles were retrieved from the medical records. These data were recorded for the whole group and according to the sex of the carrier.

RESULTS: A total of 111 couples made a request for PGD in our centre, of which 76 had at least one PGD cycle. In the PGD cycles embryo transfer could take place in 66.1% of the cycles with oocyte pick-up and positive hCG was found in 42.7% of the cycles with embryo transfer. The live born delivery rate was 20.2% per cycle with oocyte retrieval and 30.5% per cycle with embryo transfer.

CONCLUSIONS: With a live birth delivery rate of 32.9% per couple, PGD is considered a good option for these couples, especially when there is a coexisting fertility problem. PGD reduces the risk of miscarriage and allows couples to have a healthy child within a relatively short time span compared with spontaneous pregnancies. However, for young, fertile couples, the chances of having a healthy child after a number of spontaneous pregnancies, should not be ignored.

Key words: preimplantation genetic diagnosis / Robertsonian translocations / reproductive counselling / translocation carriers

Introduction

Robertsonian translocations are structural chromosomal aberrations resulting from centromeric fusion of acrocentric chromosomes. They can occur between homologous as well as between non-homologous chromosomes. Their frequency is 0.1% in the general population, 1.1% in couples with recurrent fetal loss and 2–3% in infertile men (Therman *et al.*, 1989; Fryns and Van Buggenhout, 1998). The most frequent Robertsonian translocation is the one involving chromosomes 13 and 14 (der (13;14) (q10;q10)) which accounts for about 75% of all Robertsonian translocations (Nussbaum *et al.*, 2007).

Carriers of a balanced Robertsonian translocations are phenotypically normal, but they are at risk for infertility, repeated miscarriages and offspring with unbalanced karyotypes (Fryns and Van Buggenhout, 1998). For the most common Robertsonian translocations (der (13;14) and der (14;21)) empirical risk data were summarized by Scriven *et al.* (2001) with a risk of $<0.4\%$ for an unbalanced result at second trimester prenatal diagnosis and an overall risk of miscarriage around 15% in case of der (13;14). For female carriers of der (14;21), the estimated risk of trisomy 21 at second trimester prenatal diagnosis is 15%, whereas for male carriers this risk remains $<0.5\%$. Carriers who are confronted with infertility, recurrent abortions

(spontaneous or induced after prenatal diagnosis) may therefore opt for preimplantation genetic diagnosis (PGD) to fulfil their child wish.

In PGD, genetic diagnosis of the preimplantation embryo is made *in vitro* and only unaffected embryos for the tested condition are transferred into the woman's uterus. In the case of Robertsonian translocations, PGD by blastomere biopsy cannot differentiate between chromosomally normal and balanced embryos (Conn *et al*., 1998).

Here we report the results of PGD for Robertsonian translocations in our centre. This present study aims to improve the reproductive counselling of carriers of Robertsonian translocations by reviewing the single-centre experience of 10 years of PGD for this indication.

Materials and Methods

A retrospective analysis was performed of all requests and cycles for PGD for Robertsonian translocations at our centre between January 1997 and December 2006.

Data on parental age and country of residence, reproductive history, ascertainment of the diagnosis of the translocation, age at diagnosis, familial history, karyotype of the non-carrier partner and reason for opting for PGD were recorded for the total group and according to the sex of the carrier.

For each PGD cycle the following data were recorded: the number of cumulus oocyte complexes (COC) at oocyte pick-up (OPU), MII oocytes, 2 pro-nucleate (2PN) zygotes, biopsied and successfully biopsied embryos, results of fluorescent *in situ* hybridization (FISH) analysis of the biopsied embryos, percentage of normal embryos, number of transferred and cryopreserved embryos, positive hCG, ongoing pregnancy, delivery rates and outcome of the children. The data were pooled for the total group and also described separately for male and female carriers.

Where available, follow-up data of the couples after 31st December 2006 were also recorded.

Before starting a PGD cycle, the couples were informed about the procedure by a clinical geneticist, a reproductive medicine specialist and a reproductive medicine counsellor. The couples signed an informed consent in which the general principles of PGD were summarized and in which the estimated pregnancy rate per cycle (20–25%) and the risk of misdiagnosis (1–5% for FISH procedures) were explained. Couples were also asked to donate their affected embryos and embryos not suitable for transfer or freezing for research.

In order to prepare the clinical PGD cycle, the appropriate FISH probes for the translocations (LSI 13q14 green, Tel 14q orange, 14q32 green, 18q21 orange, Tel 15q red, LSI 21 orange, 21q22-13 orange, 22q11.2 green, cen 15 green, PGT kit) were first tested on the couples' fixed lymphocytes.

All PGD couples underwent *in vitro* fertilization (IVF) treatment. After controlled ovarian stimulation combining GnRH agonist or antagonists, urinary or recombinant gonadotrophins and hCG, ultrasound-guided transvaginal oocyte retrieval was carried out (Vandervorst *et al*., 1998). ICSI was performed as described by Devroey and Van Steirteghem (2004). After ICSI, fertilization and embryo development were assessed daily. Embryos that had reached the 5- to 8-cell stage on day 3 were biopsied. One or two blastomeres were aspirated through a hole in the zona pellucida (De Vos and Van Steirteghem, 2001). The blastomeres of each biopsied embryo were fixed on a slide according to the HCl/Tween 20 method (Staessen *et al*., 1996). From 2004 on, PGD cycles for Robertsonian translocations had additional testing for the most common aneuploidies (chromosomes 13, 16, 18, 21, 22, X, Y) in a second round. The FISH procedure was performed as described by Staessen *et al*. (2003). When two blastomeres were analysed only embryos with concordant normal results in both analysed blastomeres were transferred on day 5 (Staessen *et al*., 2003). From 2006 on only one blastomere was biopsied for PGD for Robertsonian translocations.

After transfer, blood sampling for hCG (at 12 days post-transfer) and ultrasound examinations (at 7 weeks) were performed to document a pregnancy (Vandervorst *et al*., 2000). Prenatal diagnosis was offered because of the small but existing risk of misdiagnosis.

Questionnaires enquiring about the course of the pregnancy and the delivery were sent to the future parents and their obstetricians. In the results different ways to express the success of the PGD cycle will be used (ongoing pregnancy rate, live born delivery rate, take-home-baby-rate) to allow comparison with data from the literature.

After birth, parents and children were invited to the outpatient clinic of the Centre for Medical Genetics to review the child's medical history and for a detailed physical examination. The presence of major malformations (defined as an anomaly that causes functional impairment or requires surgical correction) was recorded. When it was not possible for the family to go to the hospital, questionnaires were sent to be filled in by the parents or the child's paediatrician. A follow-up was scheduled at 2 months, at 1 year and at 2 years as described by Bonduelle *et al*. (2002).

Statistical analyses

Categorical data are represented as number of events/cases and percentages for each group of interest. Comparisons of percentages among female carrier and male carrier groups are presented as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for each comparison made. Continuous data on maternal age, paternal age, birthweight, birth length, birth head circumference and gestational age are represented as mean and standard deviation (SD).

Results

Patients

A total of 111 couples contacted the Centre for Medical Genetics with a request for PGD for a Robertsonian translocation. Forty-one (36.9%) of these couples were Belgian residents at the time of the treatment whereas 70 (63.1%) were living abroad. Overall, the most frequent Robertsonian translocation was der (13;14) (q10;q10) in 67.6% of the carriers, followed by der (14;21) (q10;q10) in 12.6%. Of all the couples, 76 had at least one PGD cycle and the remaining 35 did not proceed to PGD. The characteristics of all couples were summarized in Table I. The group opting for PGD did not differ from the group not opting for PGD, either in terms of residential status, or concerning the Robertsonian translocations most frequently involved. They were also comparable regarding the mean female and male age and the age at which the carriers were diagnosed with a Robertsonian translocation. The majority of the couples were karyotyped primarily for infertility problems, especially in the male carrier group, and the second most common reason was recurrent miscarriages. Only few carriers were diagnosed through karyotyping carried out because of the presence of the translocation in a family member, because of aneuploid offspring or because of fortuitous preconceptional screening. The karyotypes of all carriers' partners were normal.

The indications for IVF with PGD were therefore (mainly male) infertility and recurrent miscarriages of mainly female origin.

For the 35 couples who did not go through with PGD, they did so because of the occurrence of a spontaneous pregnancy in three,

Table I Characteristics of the 111 couples

	Female carrier	Male carrier	Total group
Only request			
Number of couples	16	19	35
Mean maternal age (years ± SD)	32.8 ± 2	34.9 ± 3.5	33.9 ± 5
Median maternal age	34.0	35.0	34.5
Range	24–45	29–42	24–45
Mean paternal age (years ± SD)	38.0 ± 5	36.0 ± 2.5	36.9 ± 4.8
Median paternal age	38.0	37.0	37.5
Range	30–46	28–43	28–46
Age at diagnosis of translocation (years)	29.1	33.5	31.3
Karyotyping for infertility	4	14	18
Karyotyping for miscarriages	5	0	5
Karyotyping for familial history	3	1	4
Karyotyping for aneuploid offspring	1	2	3
Karyotyping for preconceptional screening	1	1	2
Unknown reason for karyotyping	2	1	3
PGD for infertility	8	17	25
PGD for miscarriages	5	2	7
PGD for history of affected offspring	0	0	0
Unknown reason for PGD	3	0	3
With PGD			
Number of couples	28	48	76
Mean maternal age (years ± SD)	33.0 ± 3.5	32.0 ± 1.5	32.5 ± 4.5
Median maternal age	34.0	31.0	33.0
Range	24–39	24–41	24–41
Mean paternal age (years ± SD)	34.5 ± 3.5	36.5 ± 2.5	35.5 ± 5.6
Median paternal age	34.0	37.0	37.0
Range	26–42	25–51	25–51
Age at diagnosis of translocation (years)	30.3	33.6	31.9
Karyotyping for infertility	6	35	41
Karyotyping for miscarriages	14	0	14
Karyotyping for familial history	3	3	6
Karyotyping for aneuploid offspring	3	1	4
Karyotyping for preconceptional screening	1	1	2
Unknown reason for karyotyping	1	8	9
PGD for infertility	10	40	50
PGD for miscarriages	16	1	17
PGD for history of affected offspring	2	0	2
Unknown reason for PGD	0	7	7
Number of cycles	40	85	

because of the financial burden in six and because of psychological reasons in one. In 10 couples PGD could not be offered at the time of the request (for five FISH was not available, in one there was a combined risk translocation/monogenic disorder and in four maternal factors considerably lowered the pregnancy chance). For 15 couples no follow-up information was available.

The 76 couples that underwent PGD had 143 pregnancies in their personal history (123 spontaneous and 20 after assisted reproduction without PGD) resulting in 122 miscarriages and the birth of 21 children. Only few of the conceptuses were karyotyped meaning that other factors contributing to the miscarriages could not be excluded.

Follow-up after the study period was available for 18 couples, of which six continued PGD (one couple for a second child), four turned to using donor gametes, in three spontaneous pregnancy occured, three continued assisted reproduction but without PGD

and two decided not to have children. In nine of these 18 couples a pregnancy was achieved (five after PGD).

PDG treatment cycles

The characteristics and outcome of the PGD cycles are shown in Tables II, III and IV, respectively. Since the gender of the translocation carrier might influence the results of the PGD treatment, results are given for the male and female carriers separately as well as for the whole group together.

In total 124 PGD cycles with OPU were performed and a mean of 14.5 COC were retrieved per cycle. The number of the oocytes retrieved did not differ between the male and the female carrier group. Of the COCs, 58.8% were fertilized and 39.7% of the COCs gave rise to a successfully biopsied embryo. In 4% of the analysed blastomeres no FISH result was obtained. Normal FISH results (normal and balanced embryos) were obtained in 43.7% of the embryos with diagnosis and this was true for both male and female carriers.

It is beyond the scope of the present study to furnish detailed data on the abnormal FISH results, since these are the object of an ongoing study to document the relative importance of the different segregation patterns as well as the value of additive testing of aneuploidy for chromosomes not involved in the translocation. However, we can state that in approximately 13% of the biopsied embryos a discordant result between the two analysed blastomeres was obtained, leading to the exclusion of these embryos for transfer.

Table II Results of PGD cycles in female and male carriers of Robertsonian translocations

	Female carriers	Male carriers	Total group
Cycles with OPU	40	84	124
COC	575	1226	1801
Oocytes/cycle with OPU	14.4	14.6	14.5
MII oocytes	487	985	1472
2PN zygotes	381	678	1059
Embryo biopsy	261	456	717
Succesful biopsy	261	454	715
FISH on blastomere(s)	246	437	683
FISH result	241	414	655
Normal result	105	181	286
Cycles with embryo transfer	28	54	82
Cryopreserved embryos	25	37	62
Positive hCG	9	26	35
Biochemical pregnancies	1	6	7
Ongoing pregnancies	8	20	28
Singleton	4	13	17
Twin	4	6	10
Triplet	0	1	1
Prenatal diagnosis	0	5	5
Deliveries of live born children	7	18	25
Live born children	10	25	35

FISH, fluorescent *in situ* hybridization; PGD, preimplantation genetic diagnosis.

Table III Outcome of the PGD cycles for female and male carriers of a Robertsonian translocation stratified according to gender

	Female carriers	Male carriers	OR (95%CI)
Ongoing pregnancies			
Per couple	8/28 (28.6%)	19/48 (39.6%)	0.56 (0.22–1.67)
Per cycle with OPU	8/40 (20.0%)	20/84 (23.8%)	0.80 (0.32–2.01)
Per embryo transfer	8/28 (28.6%)	20/54 (37.0%)	0.68 (0.25–1.83)
Live born deliveries			
Per couple	7/28 (25.0%)	17 /48 (35.4%)	0.61 (0.22–1.72)
Per cycle with OPU	7/40 (17.5%)	18/84 (21.4%)	0.78 (0.29–2.05)
Per embryo transfer	7/28 (25.0%)	18/54 (33.3%)	0.67 (0.24–1.86)

OPU, oocyte pick-up; PGD, preimplantation genetic diagnosis.

In 42 cycles there was no embryo transfer and this was due to the absence of chromosomally normal embryos in 57.1% of these cycles. In 28.6% of the cycles without embryo transfer only one chromosomally normal embryo was available and in 14.3% of these cycles no embryo biopsy could be performed.

Embryo transfer took place in 66.1% of the cycles with OPU, and positive hCG was found in 42.7% of the cycles with embryo transfer. The live born delivery rate is 20.2% per cycle with oocyte retrieval and 30.5% per cycle with embryo transfer. Couples with a positive hCG had a take-home-baby-rate of 71.4%.

Children

A total of 40 children were born of which 17 were singletons and 23 were multiples. The mean birth parameters and gestational ages of the live born children are summarized in Table V. The children were on average born 12.9 months after the finishing of the PGD work-up of their parents. Five of the children were stillborn, leaving 16 live born singletons and 19 live born multiples. The risk of having (a) stillborn child(ren) was thus 1/17 (5.9%) in the singleton and 2/10 (20%) in the twin pregnancies.

No major external malformations were observed in the stillborns but no autopsy was performed. On the contrary, 3 (8.6%) live born children presented a major malformation (oesophageal atresia, congenital hip luxation, urethral anomaly). Two of these children were singletons and one had a healthy twin brother.

Discussion

A majority of PGD patients with a Robertsonian translocation were referred to our centre from abroad, especially from Germany

Table IV Outcome of the PGD cycles for female and male carriers of a Robertsonian translocation in relation to the percentage of normal embryos and maternal age at the start of the cycle

	Female carriers	Male carriers	OR (95%CI)
<50% normal embryos			
Ongoing pregnancy per cycle with FISH diagnosis	6/24 (25.0%)	6/38 (15.8%)	1.78 (0.50–6.33)
≥50% normal embryos			
Ongoing pregnancy per cycle with FISH diagnosis	2/15 (13.3%)	14/41 (34.1%)	0.30 (0.60–1.50)
Maternal age ≤35 years			
Ongoing pregnancy per cycle with OPU	6/25 (24.0%)	16/62 (25.8%)	0.91 (0.31–2.67)
Ongoing pregnancy per embryo transfer	6/18 (33.3%)	16/40 (40.0%)	0.75 (0.24–2.41)
Maternal age >35 years			
Ongoing pregnancy per cycle with OPU	2/15 (13.3%)	4/22 (18.2%)	0.69 (0.11–4.37)
Ongoing pregnancy per embryo transfer	2/10 (20.0%)	4/13 (30.0%)	0.56 (0.08–3.94)

FISH, fluorescent *in situ* hybridization; PGD, preimplantation genetic diagnosis; OPU, oocyte pick-up.

Table V Mean birth parameters and gestational age of live born children after PGD for parental Robertsonian translocations

	Birthweight (g ± SD)	Birth length (cm ± SD)	Birth head circumference (cm ± SD)	Gestational age (weeks ± SD)
Singleton boys ($n = 6$)	3154 ± 565	51.0 ± 2.9	34 ± 1.9	37.8 ± 1.5
Twin boys ($n = 5$)	2471 ± 713	46.4 ± 3.7	32.9 ± 2.8	34.3 ± 2.4
Singleton girls ($n = 8$)	3016 ± 582	48.4 ± 3.2	33.9 ± 1.8	38.6 ± 2.0
Twin girls ($n = 5$)	1880 ± 650	42.6 ± 5.0	30.7 ± 2.6	33.6 ± 2.0
Triplet girls ($n = 3$)	1573 ± 272	39.3 ± 1.7	ND	35.1 ± 0

ND, not documented.

and Italy. This can be explained by the Centre for Reproductive Medicine UZ Brussels being a reference centre for ICSI. In addition in some countries PGD was technically and/or legally not feasible at the time of referral (Benagiano and Gianaroli, 2004; Krones *et al*., 2005). For most of the foreign couples, the costs of the PGD treatment were not covered by the health insurance and financial aspects were hence regularly considered as the reason why couples eventually did not opt for PGD. For the couples for whom PGD was technically not available it should be noted that their requests dated from the beginning of the study period and that nowadays PGD is available for all non-homologous Robertsonian translocations.

Not surprisingly the majority of the patients was carrier of the der (13;14) (q10;q10) since this is overall the most common Robertsonian translocation (Nussbaum *et al*., 2007).

The mean age of the women was higher than the maternal age at the first (27.9 years) and second/higher order (31.0 years) delivery in the general Flemish population, but this was expected since the majority of the couples in this study had, a longstanding desire to have a child (http://www.iph.fgov.be/epidemio/morbidat/nl/bases/MAT7.htm).

In the current series there was more primary infertility in the male carrier group and more miscarriages in the female carrier group, and this was in line with what is known from the literature (Nussbaum *et al*., 2007). In the total group 50 of the 76 couples (65.6%) could not conceive without ART and 17 (22.4%) did conceive earlier but presented with recurrent miscarriages. The main reason for the couples to seek help was therefore to conceive. Only few couples opted for PGD to avoid an ongoing pregnancy of an affected (aneuploid) child and this was in contrast with PGD for monogenic disorders where the main reason for PGD was to allow termination of pregnancy in case of an affected fetus (Sermon *et al*., 2007).

For female and male carriers together, the chance of having an ongoing pregnancy after embryo transfer was 34.1%, and the crude delivery rate was 31.6% after an average of 1.6 cycles per couple. One couple had two live born children in subsequent pregnancies. The clinical pregnancy rate was comparable with the figures obtained in ICSI without PGD, so that we could assume that the embryo biopsy did not decrease the pregnancy chance (Andersen *et al*., 2008).

It is noteworthy that after PGD having a positive hCG meant a take-home-baby-rate of 71.4%, whereas in the couples' previous pregnancies (without PGD) their take-home-baby-rate was only 7.9%.

Also remarkable is the fact that the PGD children were on average born 12.9 months after the finishing of the PGD work-up of their

parents, whereas these parents had been trying to reproduce for 3.5 years before their intake in the PGD program.

The outcome of a PGD treatment did not differ statistically between female and male carriers, between younger and older women and between couples with less or more than 50% normal embryos.

Reports in the literature often contained only small numbers of patients and the methods for PGD differed from the use of painting probes on first polar bodies to enumeration probes on biopsied blastomeres or even the use of blastomere fusion with bovine oocytes. Moreover, hormonal stimulation protocols, culture conditions for the embryos and attitudes towards the number of embryos to be transferred could importantly vary between different centres. This made comparison between several studies difficult. We looked at three of the larger studies (11–15 couples per study) by Munné *et al*. (2000a, b) and Gianaroli *et al*. (2002) and found that they obtained an ongoing pregnancy rate of 43.8–56.2% per cycle with embryo transfer and that 40–60% of their couples took at least one baby home. The figures reported by the ESHRE PGD Consortium gave clinical pregnancy rates of about 25% which was thus comparable with our results (Sermon *et al*., 2007). In the ESHRE consortium data and in Gianaroli's study, mean maternal age ranged from 32 to 35.5 years, but for Munné's studies no data on maternal age were published.

The birth parameters of the live born children were comparable with those of children born after ICSI without PGD (Bonduelle *et al*., 2005). The stillbirth rate was high, although these figures should be considered with caution because of the small numbers. In Belgium perinatal death, defined as demise of a fetus/neonate of more than 500 g, is seen in 6.4 per thousand births. When only fetuses/neonates with a birthweight of more than 1000 g are considered, this figure is further decreased to 3.9 per thousand. For twin pregnancies, the risk of perinatal death is 26.3 per thousand, compared with 5.6 per thousand in singletons (figures published online by Studiecentrum voor Perinatale Epidemiologie for 2004). In agreement with what is generally known, we found that especially multiple pregnancies were at risk for fetal demise, and further reduction of twin pregnancies should be one of the aims in the future developments of IVF in general and PGD in particular (Dodd and Crowther, 2005).

With respect to the interpretation of the results of PGD for Robertsonian translocations, one should also consider the natural reproductive history of translocation carriers. Sugiura-Ogasawara *et al*. (2004), Carp *et al*. (2004) and Ozawa *et al*. (2008) looked at this natural reproductive outcome and found that 43–63.3% of the carriers took a baby home after the first ongoing pregnancy after the diagnosis of the translocation had been made. Some of the couples however experienced a large number of miscarriages and the first successful pregnancy occurred after an average period of 23 months. In the present study the take-home-baby-rate of the pregnant couples was much higher after PGD (71.9%) than after their previous pregnancies without PGD (7.9%). These results were in line with earlier findings of Verlinsky *et al*. (2005) who observed for pregnant couples with a translocation (reciprocal and Robertsonian) an improvement of the take-home-baby-rate from 11.5% before PGD to 81.4% after PGD.

Moreover in the present series their seemed to be an important time gain with most children being delivered about 13 months after the finishing of the PGD work-up.

When we compared the natural history of Robertsonian translocation carriers with the results we obtained by doing PGD, we concluded that PGD is a valuable reproductive option for these carriers, especially when there is a coexisting fertility problem, when the psychological burden of repeated miscarriages out-weighs the possible burden of an IVF treatment or when the couple is older and cannot afford to wait 2 years before maybe getting pregnant.

In view of the available information we would attempt to propose certain guidelines for the reproductive counselling of carriers of Robertsonian translocations.

Known carriers, who have not been karyotyped as a result of either infertility or repeated miscarriages, should be offered the possibility of a spontaneous pregnancy and should not be immediately directed towards a fertility clinic.

Carriers who have been karyotyped because of repeated miscarriage, should be informed that PGD can increase their take-home-baby-rate and can fulfil their child wish earlier, but that this necessarily involves IVF treatment, and all that that entails.

Carriers who have been karyotyped because of infertility, should be offered PGD in addition to the IVF treatment they already need.

These guidelines should, of course, only be used in a context of open discussion with the concerned couples, and should not be interpreted as *a priori* inclusion or exclusion criteria for carriers.

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