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Original paper

Prevalence of chromosomal abnormalities and timing of karyo - type analysis in patients with recurrent implantation failure (RIF) following assisted reproduction

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Abstract

Aims: **To analyze the prevalence and type of karyotype abnormalities in RIF patients and to evaluate the adequate timing for analysis and the presence of possible risk factors.**
Methods: **615 patients (317 women and 298 men) with RIF, having undergone at least 3 sequential failed IVF/ICSI cycles prior to karyotype analysis, were included in this study. Anomaly rates found were compared with published series.**
Results: **Chromosomal abnormalities were diagnosed in 2.1% of patients (13/615): 8 females (2.5%) and 5 males (1.7%) which is significantly higher for the females than in unselected newborns (0.8%) and normo-ovulatory women (0.6%) but lower than in women with high-order implantation failure (10.8%). No significant differences were found with couples at the start of IVF/ICSI (2.0%). Karyotyping all patients prior to IVF/ICSI results in a higher cost than selecting RIF patients. Two subgroups showed an increased prevalence of abnormalities: secondary infertile women with a history of only miscarriages (9.1%) and women with female infertility (6.0%).**
Conclusion: **A karyotype analysis is indicated in all women with RIF. Nulliparous women with a history of miscarriage and women with documented infertility are at greater risk of CA and are to be advised to undergo karyotyping.**

Key words: **assisted reproduction, ART, infertility, IVF/ICSI, karyotype, miscarriage, recurrent implantation failure.**

Introduction

Despite the good results of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), an important group of patients still fails to obtain pregnancy after 3 or more treatment cycles. This situation is defined as "recurrent implantation failure" (RIF) (Raziel et al., 2002; Urman et al., 2005a; Urman et al., 2005b; De Sutter, 2006; Margalioth et al., 2006), although there is no strict definition in the literature of what RIF exactly is. In RIF patients it is customary to rule out underlying pathologies, such as autoimmune problems, thrombophilia, thyroid dysfunction, uterine and genetic anomalies. However, this approach still remains controversial (Urman et al., 2005a; Urman et al., 2005b).

Chromosomal abnormalities in embryos are one of the possible causes of implantation failure (Laverge et al., 1997; Montag et al., 1997; Margalioth et al., 2006). Unlike unbalanced translocations, balanced translocations cause no noticeable phenotypic effect, as there is no loss or gain of genetic material (Nussbaum et al., 2004). However, carriers of a balanced translocation can produce unbalanced gametes, which can cause fertilization failure, implantation failure or embryo loss (Mau-Holzmann, 2005). An increased prevalence of chromosomal structural abnormalities has been documented in RIF patients (Stern et al., 1999; Raziel et al., 2002). This suggests the involvement of karyotype abnormalities in the pathogenesis of implantation failure.

Severe male infertility has been correlated with an increase in chromosomal anomalies (Tuerlings et al., 1998). Karyotyping these patients is therefore good clinical practice. Moreover, different studies have shown a significantly increased prevalence of chromosomal abnormalities in the total group of subfertile couples, candidate for IVF/ICSI (also females), in comparison to a general population (van der Ven et al., 1998; Schreurs et al., 2000; Gekas et al., 2001; Riccaboni et al., 2002; Morel et al., 2004; Nussbaum et al., 2004; Clementini et al., 2005; Kayed et al., 2006; Marchina et al., 2007; Martinez-Garza et al., 2008; Akgul et al., 2009). Consequently, these authors suggest to perform a karyotype analysis in all patients at the start of treatment. This, however, leads to a very high cost for health care providers.

A karyotype analysis is an expensive and labor-intensive investigation and should only be performed in case of a relevant indication. By comparing the prevalence of karyotype abnormalities in a study group of RIF patients with non-male or moderate male infertility, with the prevalence in a general population and in published series, we wanted to evaluate our current practice of karyotyping couples with non-male or moderate male infertility after three subsequent IVF/ICSI cycles which did not lead to pregnancy. The aim of the present study was to evaluate the most adequate timing of karyotype analysis in our hospital. In addition, we tried to identify subgroups of patients with increased chromosomal anomaly rates, in order to possibly justify an earlier performance of a karyotype analysis in these subgroups.

Materials and Methods

Research design and study group

By use of a retrospective design, 615 patients (317 women and 298 men) with RIF, referred for karyotype analysis between January 2000 and June 2008, were included in the present study. They were referred after ≥ 3 sequential failed IVF/ICSI cycles. These cycles were not interrupted by a clinical miscarriage or ectopic pregnancy. Few patients (n = 8) previously had a successful pregnancy. Failed cycles were defined as: cycles where embryo transfer did not lead to pregnancy visible on ultrasound. Only cycles with fresh embryos were taken into account. Exclusion criteria contained: presence of an earlier indication to karyotype analysis (i.e. abnormal phenotype, primary amenorrhea, recurrent (two or more) miscarriage, non-obstructive azoospermia or severe oligoasthenoteratozoospermia) and cycles with frozen embryos or sperm or oocyte donation. The study was approved by the ethics committee of the University Hospital of Ghent.

Karyotype analysis

All patients consented to having their karyotype analysis done and the karyotype analyses were performed at the Centre for Medical Genetics of our hospital. Screening for karyotype changes was performed by Giemsa banding studying more than 20 metaphases of peripheral lymphocytes. When presuming mosaicism, additional metaphases were examined. Chromosome polymorphisms such as hyperchromatic chromosomes, pericentric inversions of chromosome 9, satellite chromosomes and low grade mosaicisms (< 5-10%) were not considered (Sonntag et al., 2001). In case of an aberrant result, additional fluorescent in-situ hybridization was performed. The nomenclature was converted to the most recent ISCN 2009 guidelines. Since some of the aberrations were determined with older methods than currently available, they could not be further specified.

Control group

The prevalence of karyotype aberrations in our patient population was compared to a general population. As there are no data available regarding the general prevalence of karyotype aberrations in adults, published data of a Danish population of 34910 unselected newborns were used (Nielsen and Wohlert, 1991). This control group was similarly used in several other studies (Stern et al., 1999; Nussbaum et al., 2004; Clementini et al., 2005; Papanikolaou et al., 2005) .

Furthermore, we compared our prevalences with data published in varying studies, in which a karyotype analysis was performed at different points in time during the infertility treatment. The following groups of subfertile patients were used: A. populations with routine karyotype analysis at the start of fertility treatment (2078 couples candidates for IVF/ICSI (Clementini et al., 2005) and 1206 normoovulatory women, candidates for IVF/ICSI (Papanikolaou et al., 2005)); B. a population with RIF, who received a karyotype analysis after 10 embryo transfers without achieving clinical pregnancy (Stern et al., 1999); and C. a population with high-order implantation failure (≥ 6 failed IVF trials or 15 embryo transfers (Raziel et al., 2002)).

Statistical tests

The Fisher's Exact test (setting P at 0.05) was used to assess differences between proportions.

Results

Properties of the study group

In total, 615 patients (317 women and 298 men) were included. Most patients (94.5%) were Caucasian. The mean female age at the moment of karyotype analysis was 33.1 ± 3.8 years. Mean span of infertility at that time was 5.0 ± 2.4 years (range 1-17). The couples had undergone 5.0 ± 1.9 failed cycles (range 3-15). An average of 10.2 ± 5.5 embryos had been transferred unsuccessfully (range 3-50).

In total 83.2% of all women reported with primary infertility. From the remaining 52 secondary infertile women, only 8 were multiparous at the start of IVF/ICSI treatment, and 44 nulliparous (i.e. only having experienced miscarriages). Indications for infertility treatment were as follows: 44.5% male (mild or moderate, i.e. with a semen sample containing at least 5 million motile spermatozoa), 21.8% female (endometriosis, tubal obstruction, and/or ovulatory disorders), 19.6% combined (male and female) and 14.2% unexplained.

Prevalence and type of karyotype abnormalities in the study population

Chromosomal abnormalities were diagnosed in 13 out of 615 patients (2.11%): 8 females (2.52%) and 5 males (1.68%). In the female subgroup, 6 autosomal abnormalities (1.89%) were found: 5 reciprocal translocations and 1 inversion of chromosome 3. Two sex chromosome aberrations (0.63%) were reported: 1 deletion of the long arm of the X chromosome and 1 gonosomal mosaicism. The male karyotype aberrations contained 4 autosomal abnormalities (1.34%: 2 reciprocal translocations, 1 inversion of chromosome 16 and 1 marker chromosome) and one gonosomal abnormality, a XYY mosaicism. Not more than 1 karyotype aberration was present in each couple (Tables I and II).

Prevalence of karyotype abnormalities compared with a general population and other published series of infertile populations

Significant differences were found between the prevalences of karyotype abnormalities in our total and female study group and a population of unselected newborns (with an prevalence of 0.85% in the general and 0.78% in the female group of newborns (Nielsen and Wohlert, 1991)). An increased, though insignificant, prevalence was noted in comparison with the male newborns (0.91%) (Table III).

A significantly increased prevalence of karyotype abnormalities was found in the women of present study in comparison with a population of normoovulatory women at the start of IVF/ICSI treatment (0.58% (Papanikolaou et al., 2005)). A significantly lower prevalence was noted compared to women with high-order implantation failure (10.77% (Raziel et al., 2002)). Compared to a group of couples at the start of IVF/ICSI (1.97% in total, 1.92% in women and 2.02% in men (Clementini et al., 2005)), our general and female RIF population showed an insignificantly increased prevalence of karyotype abnormalities. The prevalence of karyotype abnormalities in the male subgroup was lower than in couples at the start of the IVF/ICSI (Table IV).

Analysis of risk factors

One group of patients in our study at high risk of carrying a karyotype abnormality were nulliparous women with secondary infertility, who experienced

Table I. — Chromosomal abnormalities observed in women.

		amount	*percentage*
Normal		309	97.48%
Abnormal		8	2.52%
autosomal aberrations		6	1.89%
reciprocal translocations (5)	46,XX t(2;4)(q11;q25)	1	0.32%
	46,XX,t(3;4)(q13.2;q21)	1	0.32%
	46,XX,t(17;19)(q25;q13.1)	1	0.32%
	46,XX,t(1;17)(q21.2;p11)	1	0.32%
	46,XX,t(6;11)(q21.1;q22)	1	0.32%
inversion (1)	46,XX,inv(3)(p13q25)	1	0.32%
sex chromosome aberrations		2	0.63%
	46,X,del(X)(q27)	1	0.32%
	45,X[10]/47,XXX[6]/46,XX [84]	1	0.32%
	Total	317	100.00%

Table II. — Chromosomal abnormalities observed in men.

		amount	*percentage*
Normal		293	98.32%
Abnormal		5	1.68%
autosomal aberrations		4	1.34%
reciprocal translocations (2)	46,XY,t(3;4)(q29;q23)	1	0.34%
	46,XY,t(8;19)(q23;q13.3)	1	0.34%
inversion (1)	46,XY, inv(16)(p13q11)	1	0.34%
Marker chromosome (1)	47,XY,+mar[4]/46,XY[54]	1	0.34%
sex chromosome aberrations			
	47, XYY[5]/46,XY[25]	1	0.34%
	Total	298	100.00%

one or more miscarriages (4/44 or 9.09% compared to 4/258 or 1.55% in women with primary infertility and 0/8 in multiparous patients with secondary infertility). Additionally, women with female infertility showed a higher prevalence of aberrations (4/67 or 5.97% in reference to 2/60 or 3.33% with combined infertility, 1/45 or 2.22% with unexplained infertility and 0/136 with male infertility). No correlation was found between sperm quality and the presence of chromosomal abnormalities in the male partner. However, as stated above, no males with severe sperm dysfunction were included. No correlation between the morphological quality of the transferred embryos and parental karyotype abnormalities could be found.

Discussion

For both men and women, structural chromosome rearrangements represent the largest group of karyotype abnormalities. The type of abnormality most frequently noted is the autosomal reciprocal translocation. This is not different from abnormalities found in the general population.

The prevalence of karyotype abnormalities in our female population (2.52%) is comparable to the results presented in the literature for women with RIF (2.73% (Stern et al., 1999)). In the male population, a lower prevalence (1.68%) of aberrations is found compared to populations of RIF men (2.26% (Stern et al., 1999)). It is well known that especially men with aberrant sperm quality (e.g. azoospermia or extreme oligospermia) show a higher prevalence of chromosomal abnormalities (Mau-Holzmann, 2005). Since they are karyotyped prior to ART treatment, these latter men are not included in our study. This "selection bias" explains the present low prevalence of karyotype abnormalities in the male subgroup. It allows us, however, to estimate the prevalence of karyotype abnormalities in males with 'pure' RIF, having normal or only moderately subnormal sperm.

Compared to a newborn population, a significantly increased amount of karyotype abnormalities was found in our female RIF population. For men, no significant increase could be noted. It is clear that karyotype analyses should be part of the investigations in RIF patients. Indeed, further IVF/ICSI cycles are not recommended in case an aberration is found, and specific treatment opportunities are available (e.g. preimplantation genetic diagnosis or gamete donation, see below). As to male RIF patients, the insignificant results could mean that routine karyotype analysis in this subgroup is not indicated. Of course again, men with severe male infertility were excluded from present study and should be karyotyped at the start of treatment.

Table III. — Prevalence of chromosomal abnormalities in the studied population with RIF, compared to a general population of unselected newborns (according to Nielsen and Wohlert, 1991).

Studied males + females	studied males	studied females	General population of unselected newborns	Unselected boys	Unselected girls
2.11% (13/615) [a]	1. 68% (5/298)	2.52 % (8/317) [b]	0.85% (295/34910) [a]	0.91% (162/17872)	0.78% (133/17038) [b]

Table IV. — Incidences of chromosomal abnormalities in different studies with a variable timing of karyotype analysis in the course of the infertility treatment.

	couples candidate for IVF/ICSI treatment	minimal 3 failed IVF/ICSI cycles	minimal 3 embryo transfers not leading to pregnancy	minimal 6 failed IVF cycles
Clementini et al., 2005	1.92% (40/2078 women) 2.02% (42/2078 men) 1.97% (82/4156 persons)			
Papanikolaou et al., 2005	0.58% (7/1206 normo-ovulatory women)			
Present study		2.52% (8/317 women)		
1.68% (5/298 men) 2.11% (13/615 persons)				
Stern et al., 1999			2.53% (13/514 persons)	
Raziel et al., 2002				10.77% (7/56 women)

The question arises whether RIF patients represent a subgroup with an increased prevalence of karyotype abnormalities compared to IVF "starters". A significantly increased number of chromosomal aberrations was reported in a female population with high-order implantation failure (Raziel et al., 2002) compared to our study group. This supports the suspicion of a risk of karyotype abnormalities increasing in parallel with the number of failed IVF/ICSI treatments. A female RIF population with ≥ 10 embryo transfers (Stern et al., 1999) is comparable to the present study group and shows similar prevalences. Comparison with the population of IVF "starters" (Clementini et al., 2005), showed a lower prevalence of abnormalities in our male subgroup. This result must be interpreted in the context of the "selection bias" described above. In the female subpopulation, a similar prevalence of chromosome abnormalities was found. We did observe a significantly increased rate of aberrations in our study compared to a group of only normo-ovulatory women (Papanicolaou et al., 2005). This could be attributed to the timing of analysis, the presence of ovulatory problems or a combination of both. Furthermore, limited numbers of patients and differences in inclusion criteria, methods of performing karyotype analyses and ethnic differences, make statistical comparison difficult. Unfortunately, we could not include a regression analysis, which could have empowered the implications of the present study.

One could compare different strategies in karyotyping patients undergoing IVF or ICSI. A first strategy supposes a karyotype analysis in all patients at the start of IVF/ICSI treatment, while a second strategy presumes karyotyping only severely infertile men at the start and the rest of RIF patients after 3 sequential failed cycles. It is clear that the second strategy will be cheaper, but patients are at increased risk of spontaneous abortion or having a child with an unbalanced karyotype and will have to deal with the physical and psychological stress of fertility treatments. On the other hand, only a relatively small proportion of patients would "benefit" from routine karyotyping at the start of fertility treatment (1.97%, Clementini et al., 2005). The question arises if a community or patients themselves are willing to pay a substantial extra cost to protect a small group of patients against these risks. Of course, in order to further study this topic, a more in depth cost-effectiveness study is needed, including a quality-adjusted life year (QALY) analysis.

When exploring risk factors which could justify an earlier performance of karyotype analysis, two subgroups were identified. A significant increase of karyotype abnormalities was noticed in nulliparous women with secondary infertility and a history of at least one miscarriage and in women with a female indication for infertility treatment. Different authors have found a similar increase in chromosomal anomaly rates in women with secondary infertility or a history of miscarriage (Clementini et al., 2005; Papanicolaou et al., 2005). This may correlate with an interference of chromosomal abnormalities with early embryo development, implantation or early embryo loss. Possibly, they result from alterations in cell cycle control genes or certain cytoplasmic factors disrupting the normal sequence of chromosome replication and segregation, which could be related

to the infertility (Margalioth et al., 2006). These results suggest a possible benefit of routine karyotyping at the start of infertility treatment in this subgroup of women. The high proportion of women with primary infertility in our study confirms their bad prognosis in terms of treatment outcome in comparison with secondary infertile women. Several studies confirm the increased prevalence of karyotype aberrations in women with female infertility (Gekas et al., 2001), while others fail to demonstrate such a correlation (Stern et al., 1999). Papanikolaou et al. (2005) found a decreased prevalence of chromosomal abnormalities in normo-ovulatory women, compared to a general population. The present study supports the relationship between ovulatory disorders and karyotype abnormalities, which might indicate the need for an earlier karyotype analysis also in these women.

Several studies have described an inverse relationship between karyotype abnormalities in men and sperm concentration (Riccaboni et al., 2002; Clementini et al., 2005). High prevalences of chromosomal abnormalities in men with azoospermia or severe oligospermia lead to the assumption that chromosomal aberrations interfere with the meiotic process and cause a total or partial block in spermatogenesis (Clementini et al., 2005). Conflicting results are found regarding karyotype abnormalities in subfertile men with normal or mildly abnormal sperm quality (Gekas et al., 2001; Riccaboni et al., 2002). Also, the present study could not find any correlation between sperm quality and karyotype abnormalities in our male population .

There was no correlation between the quality of the transferred embryos and male or female chromosomal abnormalities, as shown in other studies (Stern et al., 1999; Raziel et al., 2002). In addition, most transferred embryos were of good or average quality, which means that this parameter offers no additional information in the exploration of risk factors for karyotype abnormalities.

Preimplantation genetic diagnosis (PGD) is the most often used treatment after detection of a chromosomal abnormality. It is supposed to offer important advantages, although its real value is being disputed (Stephenson and Sierra, 2006; Stephenson, 2008). Another alternative is oocyte or sperm donation. In discussing both alternatives, psychological aspects should be taken into account: PGD is in theory the only safe treatment method that allows couples with an abnormal karyotype to obtain a genetic own child.

Although karyotype anomalies seem to be more frequent in RIF patients, the absolute prevalence still is only about 2%. It is therefore obvious that the RIF will have to be explained by other causes in the majority of patients, such as uterine, autoimmune and thrombophilic disorders. Further investigation of these pathologies is similarly indicated, besides karyotyping, in RIF patients.

In conclusion, autosomal aberrations, and in particular reciprocal translocations, represent the largest group of karyotype abnormalities in the present population with RIF. A karyotype analysis can be considered indicated in women with RIF. Men with severe male infertility should be karyotyped before starting IVF or ICSI, but it is not clear whether this should still be done after 3 failed cycles in the men with moderate male infertility. Categories at greater risk were nulliparous women with a history of at least one miscarriage and women with a female indication to IVF or ICSI treatment. These women should undergo a karyotype analysis prior to starting IVF or ICSI.

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