Safety issues in assisted reproduction technology

Should men undergoing ICSI be screened for chromosome abnormalities in their sperm?

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The incidence of aneuploidy in gametes of men undergoing ICSI has raised the prospect of there being risks associated with ICSI and the question of whether or not to screen men for sperm aneuploidy before treatment. We report results of a questionnaire undertaken to address how IVF staff perceive this problem, whether ICSI men are already being screened for sperm aneuploidy and the extent to which IVF specialists feel that there is merit in such a test. The results suggest that this is seen as a problem but most feel the risks outweigh the benefits. Most claimed their clinics do not screen sperm for aneuploidy but feel that there is merit in doing so. There are considerable benefits to screening i.e. couples would get additional information about the genetic repercussions of ICSI and could make informed decisions before treatment; screening would also facilitate the design of a large research study to give clearer answers on the safety of ICSI. However, we acknowledge counter arguments i.e. families would not necessarily benefit as most would have the ICSI procedure regardless of screen results; sex chromosome trisomies clinically are not severe enough to worry about in this context and there are other potential risks of ICSI that screening would not address.

Key words: aneuploidy/ICSI/OAT/opinions/sperm

Introduction

The proportion of aneuploid sperm (i.e. with extra or missing chromosomes) in males with severe defects in the conventional parameters of semen quality, has been the topic of numerous studies in recent years (Lahdetie et al., 1997; Calogero et al., 2001; Hansen et al., 2002; Healy and Saunders., 2002). Severe oligozoospermia has been associated with aneuploidy levels of up to 70% (Pang et al., 1999; Pfeffer et al., 1999; Ohashi et al., 2001), i.e. extrapolations from sperm fluorescent in-situ hybridization (FISH) studies involving a few chromosomes at a time have indicated that the most severely affected males may have up to 70% of sperm that have at least one extra or one missing chromosome (Pang et al., 1999; Pfeffer et al., 1999). The vast majority of studies have provided evidence for a highly significant relationship between decreased semen quality parameters and increased sperm aneuploidy (Bernardini., 1997; Lahdetie et al., 1997; Li and Hoshiai, 1998; Martin, 1998; McInnes et al., 1998; Aran et al., 1999; Colombero et al., 1999; Nishikawa et al., 2000; Shi and Martin, 2000; Ushijimal et al., 2000; Vegetti et al., 2000). In other words, we are aware of ~50 studies that address this issue, and the vast majority suggest that men with severe reductions in the usual criteria used to measure sperm have significantly elevated levels of sperm disomy. In our own experience, we have found up to a 15-fold increase in sperm aneuploidy for the chromosomes thought to be most prone to non-disjunction i.e. chromosomes X, Y and 21 (H.G. Tempest, unpublished data) in men with sub-optimal semen parameters. However, the magnitude of the increase varies from laboratory to laboratory and from patient to patient, indeed we are aware of about four studies, including Guttenbach et al., that show no relationship at all (Guttenbach et al., 1997). The apparent discrepancy between reports may be explained by technical reasons (e.g. laboratory specific differences in stringency of scoring criteria) or there may be genuine differences depending on the population of males studied. Specifically, intrinsic (e.g. DNA polymorphisms) or extrinsic (e.g. environmental pollutants) factors may influence sperm aneuploidy depending on the patient cohort studied. Differences in aneuploidy among populations are not widely reported, however both intrinsic and extrinsic factors have been linked to errors in chromosome segregation. For example, cigarette smoke, alcohol and chemotherapy regimes can all cause increased sperm aneuploidy (Robbins et al., 1997; Rubes et al., 1998; Shi et al., 2001) while factors such as age have been clearly associated with increased aneuploidy in both males and females (Griffin et al., 1995; Hassold et al., 1996). Moreover, a recent report has identified a genetic polymorphism as a significant risk factor for Down’s syndrome (Hobbs et al., 2000).
Men with severe oligozoospermia are usually treated by ICSI. Therefore this raises the question of whether, in cases where men have significantly elevated levels of sperm aneuploidy, there is an increased risk of producing aneuploid offspring. This is of especial concern for trisomies of the sex chromosomes that arise 50% of the time in the sperm. Studies that have been performed examining the chromosomal constitution of ICSI conceptions suggest that there is some cause for concern. Bonduelle et al. reported that 9/1084 ICSI conceptions respectively had sex chromosome abnormalities (Bonduelle et al., 1999a); this is 5–10 times the published population frequency (Hassold et al., 1996). More recently Bonduelle et al. compared outcomes of ICSI versus neonate pregnancies and found that 6/1000 had sex chromosome abnormalities in the ICSI group compared with 2/1000 in the control group—a small yet statistically significant increase (Bonduelle et al., 2002).

Given the level of interest in the literature it seems reasonable to suggest that the increase in sperm aneuploidy associated with male infertility is of significant concern for infertility clinics and families embarking upon ICSI treatment. The question then arises ‘should the male partner be screened for sperm aneuploidy prior to ICSI?’—at least for the sex chromosomes. In our opinion, before this question can be discussed fully, a number of questions remain that, to the best of our knowledge, have hitherto been poorly investigated; these include the extent to which: (i) sperm aneuploidy for ICSI males is perceived as a problem in infertility clinics; (ii) men are already screened for sperm aneuploidy in IVF clinics; and (iii) specialists in infertility clinics feel that there is merit in screening ICSI males for sperm aneuploidy by molecular cytogenetic techniques.

In the first part of this debate we report and discuss the results of a questionnaire-based study in which specialists in infertility clinics were surveyed with these questions in mind. They suggest that there is sufficient interest in this issue to warrant investment in molecular cytogenetic technology in infertility clinics to screen males for levels of aneuploidy as an adjunct to conventional semen analysis. In the second part we place these results in the wider context of a debate on the pros and cons of implementing a sperm aneuploidy screening service for ICSI couples.

Materials and methods
A one-page questionnaire was sent to scientists, clinicians, nurses and counsellors to all infertility clinics operating in the UK (Figure 1). In total 590 questionnaires were sent; the questionnaire was made deliberately short (consisting of only 5 questions) in order to maximize the return. For this reason, a self-addressed envelope was also included. In order to avoid leading questions, participants were asked about a number of genetic factors associated with male infertility e.g. constitutional chromosome abnormalities and Y-chromosome deletions. The brief covering letter accompanying the questionnaire explained the purpose of the study. The questionnaire was anonymous.

Statistical analysis
In order to establish whether the responses were statistically significant, standard $\chi^2$-analysis was used.

Results
Of the 590 questionnaires sent, 190 (32.2%) were completed and returned; 78 (13.2%) were returned as ‘no longer known at this address’. In order to maximize return, the respondents were not asked to give their name. It was therefore difficult to determine accurately what proportion of UK clinics were represented; however analysis of the postmark on the return envelopes suggested that 55–70% of all UK clinics were represented by at least one respondent. Figure 1 also shows the number of answers obtained for each question in this study.

All individuals questioned were invited to state their position in the infertility clinic; however the majority declined to do so; thus the analysis is based on the cohort in general rather than opinions among individual career groups within IVF clinics. However, of the 49 that did state their occupation, 21 gave their job description as ‘consultant’ suggesting that the ‘decision makers’ of the IVF clinics were represented significantly in the study.

Approximately 82% (156) of respondents worked at clinics where ICSI was routinely performed. Of these, 126 (80.7%) indicated that their clinics routinely performed karyotype analysis on patients undergoing ICSI, 65 (41.7%) performed Y-chromosome deletion analysis and 18 (11.5%) of the participants worked in clinics where chromosome analysis of sperm before treatment was performed.

Approximately half (49.5%) of the respondents felt there was an increased risk of a child being born with congenital abnormalities when conceived by ICSI versus standard IVF treatment. This was significantly more than the 54 (28.4%) ($P < 0.005$ by $\chi^2$-test) who felt there was no increased risk of congenital abnormalities in babies conceived by ICSI versus standard IVF treatment [42 respondents (22.1%) were unsure].

Of the participants who felt that there was an increased risk of congenital abnormalities associated with ICSI, 61, by far the largest majority (64.9%), felt this risk was due to chromosomal abnormalities in the sperm used for the procedure. Of the remainder, 11 (11.7%) felt it was due to the actual ICSI procedure itself and 14 (14.9%) were unsure of the cause. Around 8 (8.5%) respondents felt other factors were responsible for the increase and, when invited to comment on what they thought they were, responses included “chromosomal abnormalities in the egg used for the procedure”, “artificial selection of sperm” and “individual circumstances” Thus a significant majority ($P < 0.0005$) cited chromosome abnormalities in the sperm as the major risk factor (in their opinion) for ICSI treatment.

When asked to choose a statement that best described their current opinion about ICSI, 122, the significant majority (64.2%) ($P < 0.0005$), felt there were minimal risks with ICSI but that the risks were outweighed by the benefits. Of the remainder, 35 (18.4%) required further information before forming an opinion; 17 (8.9%) felt there were no additional risks with ICSI over standard IVF treatment; 10 (5.3%) felt that there were considerable risks with ICSI but that it was still a worthwhile treatment overall. Significantly, none of the respondents felt the risks of ICSI outweighed the benefits and they would therefore recommend it to patients. Of the 6 (3.2%)
that held opinions described as ‘other’ responses included “safety depends on indication for ICSI” and “individual circumstances must be taken into account”.

Our results demonstrate that counselling about the risks of ICSI is widespread in IVF clinics as 184 (96.8%) indicated their patients were counselled and just 6 (3.2%) suggested they were not.

Finally, we were interested to note that 97, a significant majority (51.1%), felt that there was merit in pre-screening the sperm for chromosomal abnormalities prior to ICSI. This compared with 43 (22.6%) who felt there was no merit in so doing and 50 (26.3%) who were unsure. In other words over twice as many IVF specialists are supportive of our hypothesis that such a screen should be implemented in addition to

Figure 1. Questionnaire sent to clinics and number of responses for each question.
assessing regular semen parameters, compared with those who were not. This is highly significant ($P < 0.0005$) by $\chi^2$-analysis.

Discussion

Questionnaire results

The non-Mendelian transmission of aneuploidy to the offspring of couples undergoing ICSI is a serious medical issue and one of considerable debate among the scientific community (Lahdetie et al., 1997; Calogero et al., 2001; Hansen et al., 2002; Healy and Saunders, 2002). The results of the questionnaire part of this study seem to suggest that there is enough concern about sperm aneuploidy in infertility clinics to warrant inclusion of a screen for sperm aneuploidy prior to ICSI. It seems that, for the most part, these opinions are made on the basis that the majority of IVF specialists questioned believe that there is an increased risk associated with ICSI (most likely to do with increased sperm aneuploidy) compared with standard IVF, but that the risks outweigh the benefits. They also indicate that screening for sperm aneuploidy is not a practice that is widespread with only 18 (11.4%) of the respondents suggesting that this occurs in their clinics compared with 126 (80.7%) who said that constitutional karyotyping was commonplace. Of these 18, nine were almost certainly from the same clinic as they were returned in the same envelope with a 'with compliments' slip attached. Further questioning of a senior member of that particular laboratory (results not shown) revealed that information gleaned from screening sperm for aneuploidy beforehand was used for research purposes only and information was not yet passed on to patients. Informal discussions with colleagues suggest that this is also the case in other clinics that examine sperm for aneuploidy. Thus, although 18 respondents said that their clinic counselled and arranged for patients to have sperm chromosome analysis, it seems certain that some (if not most) are counselled about the risks of ICSI and then given the opportunity to take part in an anonymous research programme. A further possibility is that some respondents did not understand the term chromosome analysis of sperm in this context. At this time therefore we are not aware of any clinic in the UK which screens for sperm aneuploidy and then uses that information as a means for genetic counselling of patients. It is clear that about twice as many respondents of this questionnaire think it is a good idea compared with those who do not. Clearly however, while very important, the opinions of IVF specialists are only one part of the decision-making process on this issue and the hard scientific facts should be considered in context.

Pros and cons of screening ICSI males for sperm aneuploidy

Screening for sex chromosome aneuploidy in sperm before ICSI might allow genetic counsellors to allay the fears of those families who are at low risk (i.e. those that have low levels of sperm aneuploidy). ‘Normal’ levels of sex chromosome aneuploidy are thought to be around 0.3% i.e. 2–4 sperm with an extra or missing sex chromosome in every 1000 (Griffin et al., 1995). Men about to embark upon ICSI with similar levels should be, theoretically, at no increased risk of producing offspring with sex chromosome aneuploidy. In some men however, sex chromosome aneuploidy in sperm may be 10–30 times that of normal levels (Pang et al., 1999). In this scenario, based on existing data regarding the maternal versus paternal contribution to sex chromosome aneuploidy (Hassold et al., 1996), reasonably accurate estimates of potential risk of transmission can be made by genetic counsellors. Equipped with this information families can then make informed decisions about whether or not to continue with ICSI and, if they do, whether to have prenatal diagnosis of any subsequent pregnancy. The question of where to draw the line between ‘high risk’ and ‘low risk’ is, however likely to be a contentious one. An interesting analogy is that of the triple screen test for pregnant women. On the whole, families who are given a risk of around 1 in 250 as a result of the triple screen are offered amniocentesis (Wellesley et al., 2002). The figure of 1 in 250 has been chosen on the balance of several lines of evidence as the most appropriate threshold point. Perhaps therefore a threshold based on similar levels of risk should be established for ICSI men with elevated levels of sperm aneuploidy.

An additional benefit of providing an assessment of sperm aneuploidy to a large number patients is that it would be the first stage in which a very large number of ICSI males could be screened as part of a research study. Pregnancies could be followed up subsequently in order to establish more accurate estimates of the risk of transmitting trisomy through ICSI. The purpose of this study would be, ultimately, to generate enough data to provide more accurate assessments of the risk of transmitting trisomy for ICSI couples. In particular, the issue of whether ICSI perpetuates the risk of trisomy 21 could be addressed. A further advantage of such a technology being widespread is that the regular screening of sex chromosome aneuploidy might provide a means by which the efficacy of any new chemotherapeutic treatment regimes might be monitored. This would be particularly applicable if any pharmacogenomic approaches that addressed the problems of chromosome segregation directly were developed. Should such approaches prove effective, they might then provide means of treating male infertility that are less labour intensive and do not have the risks associated with producing aneuploid offspring as has been suggested for ICSI.

It is often argued that there is an apparent discrepancy between the high levels of sperm aneuploidy in ICSI males and the relatively reassuring figures for ICSI outcome. However, closer analysis of the data might suggest that this is not necessarily the case. Klinefelter syndrome (47,XXY) arises as a result of XY sperm disomy ~50% of the time whereas a 47,XXY karyotype is 100% paternally derived (Hassold et al., 1996). Thus, a significant increase in sperm aneuploidy should, in theory, lead to an increased risk of these and other disorders in ICSI offspring. Recent work provides significant evidence that there is a several fold increase in sex chromosome abnormalities associated with ICSI treatment (Bonduelle, 1999a,b, 2002) however, to the best of our knowledge these men were not screened for the incidence of sex chromosome abnormalities in their sperm beforehand. Had this been the case, then a more accurate correlation between the incidence of sex chromosome aneuploidy in sperm and the karyotype of the child might have been possible and we suggest that then there would have been a very close correlation. Indeed to the best of our knowledge, there have been no large controlled studies that have screened sperm aneuploidy before ICSI, then monitored pregnancies throughout and then estimated the levels of paternally derived aneuploidy in the subsequent offspring. Clearly such a project would be an extremely difficult undertaking but it would help us resolve more fully the
question of the relationship between sex chromosome sperm aneuploidy and ICSI outcome. In this case, we might expect a very close correlation between the level of YY disomy and XXY children (since all XYY conceptuses are paternally derived). We might expect a slightly lower but nonetheless significant correlation between Klinefelter syndrome and XY sperm disomy since ~50% of these errors ordinarily arise in the sperm. However we would expect only a weak correlation between XX disomy and XXX conceptuses as the majority of these normally arise as a non-disjunction event in the ovary (Hassold et al., 1996). In order to screen for sex chromosome abnormalities in sperm, it is necessary to look at least one autosome to distinguish disomic from diploid sperm: i.e. a sperm with two sex chromosomes and one autosome is assumed to be disomic whereas a sperm with two sex chromosomes and two autosomes is assumed to be diploid (Griffin et al., 1995). In this case it seems reasonable to suggest that the autosome screened should be chromosome 21. While Down’s syndrome (trisomy 21) is predominantly (~90%) maternally derived (Hassold et al., 1996), a tenfold increase in the incidence of disomy 21 in the sperm could potentially double overall risk of trisomy 21 in the offspring. We are not aware of any studies demonstrating an increased risk of Down’s syndrome associated with ICSI. However any increase would be unlikely to have been seen using the methodologies of current studies (Bonduelle et al., 1999a,b, 2002). This is for two reasons: (i) because of the relatively small number of live births studied (around 1000 each, in test and control groups); and (ii) because the parental origin of the aberrant chromosome was not determined. As a comparison, had the same approach been used to address the question of whether Down’s syndrome (incidence 1 in 700 live births) was associated with maternal age, it is questionable whether a statistically significant difference would have been seen between the two groups. Paternally-derived Down’s syndrome accounts for about 1 in 7000–14 000 live births; while this cannot be thought of as common, its incidence is similar to that of myotonic dystrophy and Edward’s Syndrome. It is therefore reasonable to suggest that any significant increase in this disorder associated with the use of ICSI treatment might be of clinical concern. It is questionable however whether clinicians and patients would necessarily distinguish between the maternally- and paternally-derived forms given that the clinical features are identical. Nevertheless given that screening sperm for sex chromosome abnormalities requires the examination of at least one autosome, we propose that this autosome should be chromosome 21. In fact, the majority of aneuploid conceptuses (including presumably those that arise as a result of injection of an aneuploid sperm) are thought not to reach the stage of clinical recognition (Hassold et al., 1996). Of those in which a pregnancy is demonstrably established, the majority result in spontaneous abortions. In fact only cases of sex chromosome aneuploidy or trisomy 21 can usually result in live births (with very rare exceptions e.g. trisomies 18 and 13). While spontaneous abortions can be very stressful for families (particularly if there have already been several pregnancy losses), it is, in our experience, the prospect of having aneuploid offspring (even with mild clinical features) that is of most concern to ICSI families. Thus, we propose that, at the moment, if sperm aneuploidy screening of ICSI men is to go ahead, the sex chromosomes and chromosome 21 should be screened alone. To conclude, the increased risk of transmitting trisomy through ICSI is therefore quite well established for the sex chromo-

omes but not for chromosome 21. There is, theoretically, an increased risk of transmitting paternally derived trisomy 21 although this has yet to be determined on a large cohort of ICSI outcomes. Moreover, an increase in sperm aneuploidy for the ‘non-21’ autosomes is of less concern in terms of screening in ICSI males but could, theoretically, lead to increased incidence of spontaneous abortion (Hassold et al., 1996) thus further limiting the chances of a live birth.

If a screen for sperm aneuploidy were implemented, appropriately trained individuals could estimate the potential of conceiving aneuploid offspring by performing FISH and counting the proportion of aneuploid sperm in the male partner. The test could be done at the same time as the semen assessment and, probably, could be organized in order not to delay the progress of the ICSI cycle. This procedure is nevertheless costly in that it involves development or procurement of high quality fluorescent probes, staff training, the cost of each individual test, the purchase of a high specification epifluorescence microscope and the costs involved in establishing the technique as routine. A number of clinical laboratories, however, now already have epifluorescence microscopes and the cost of the test, if borne by the patient, would be minor in comparison with the total cost of the ICSI procedure. A second drawback of implementing the procedure is that scoring about 5000 sperm per patient is very time consuming. This problem may ultimately be circumvented by automated approaches for the scoring of sperm aneuploidy that should be less labour intensive; these are under development in a number of laboratories. Thus, before such a service is offered, it needs to be established that these and other drawbacks are outweighed by the benefits.

What is not clear (and, possibly, is unlikely to be so until such a service is implemented) is how patients would respond given the information that they were at high risk of transmitting aneuploidy to their offspring. Giltay et al. (1999) reported that a significant majority [42 out of 75 (56%) Dutch couples] continued with ICSI even though they were carrying constitutional chromosome abnormalities and were counselled extensively that they were at a significant risk of having an affected child (Giltay et al., 1999). It could be argued however that the patients in that study benefited from the information that they were at risk of an affected child so that they could come to an informed decision, indeed nearly half of these opted for amniocentesis given this information. If this were the case, then it would be a strong argument in favour of screening sperm for aneuploidy levels prior to ICSI. An alternative interpretation however is that the results suggest that, even given information about elevated sperm aneuploidy, families would, on the whole, go ahead with ICSI anyway and thus screening for sperm aneuploidy would be a fruitless exercise. We have difficulty with this second viewpoint for the following reasons: closer analysis of the data by Giltay et al. (1999) reveals that 31% of the patients in the study declined ICSI given the information about their genetic risk. It is, in fact highly unlikely for a sub-fertile man to decline ICSI under normal circumstances (S.T.Homa, personal communication). This leads us to conclude that a significant proportion may take the decision to refrain from ICSI if they were identified as high risk whereas more still would opt for prenatal diagnosis with a view to either terminating or preparing for an affected child. In either case, therefore, the information is highly valuable to the patients and their reproductive planning. 233
A further issue is that factors other than elevated sperm aneuploidy may lead to an increased risk of trisomic offspring as a result of ICSI. These include the disruption of the meiotic spindle during the injection process (e.g. Pang et al., 1999) and inadequate decondensation of the sex chromosomes in the sub-acrosomal region (Sbracia et al., 2002). If either of these hypotheses prove to at least contribute to the observed increase in sex chromosome abnormalities in ICSI children then this might lessen the need to screen ICSI males for aneuploidy. However, given that sex chromosome aneuploidy levels are elevated in ICSI males and elevated levels of sex chromosome abnormalities have been reported in ICSI children it seems unlikely that there would not be at least some relationship between the two findings.

A final consideration is whether sex chromosome abnormalities are clinically severe enough to be of sufficient concern for ICSI clinics and families. The majority of sex chromosome abnormalities are only diagnosed if they are picked up prenatally or when affected individuals are having reproductive problems. Indeed, most are not detected at all and fewer couples are opting for a therapeutic abortion when a sex chromosome abnormality is diagnosed (Abramsky et al., 2001). In the context of this study then it raises the question of whether these relatively mild symptoms during childhood warrant investing in an extensive screening programme for sperm aneuploidy. On one side of the argument, if couples would mostly continue with ICSI anyway and the disorder would be unlikely to be detected unless it was looked for specifically, then there is little point in implementing the screen. On the other, the reproductive and secondary sexual development problems associated with sex chromosome abnormalities vary from individual to individual and can be quite severe. We should therefore inform couples (to the best of the genetic counsellor’s knowledge) of the risk of having an affected child, particularly if they are willing to pay for the test. Moreover, although the risk of paternally-derived trisomy 21 is only theoretical at this stage, it may be argued that it is of sufficient concern to warrant further investigation. This could be achieved by screening a large number of ICSI males for disomy 21 levels in sperm and monitoring obstetric outcome by karyotyping.

In conclusion, screening for sperm aneuploidy is not commonly practised in IVF clinics. There are pros and cons of implementing such a screen, and, in our experience, about twice as many IVF specialists favour the idea compared with those who do not. The benefits of screening at least for chromosomes X, Y and 21 include the added information it gives to families about their reproductive health and the fact that it can be implemented without delaying ICSI. With this knowledge, the patients can then make informed decisions regarding their treatment, and whether they wish to opt for prenatal diagnosis and/or plan for a potentially affected child. There is a further benefit that it would allow a larger research programme that would ultimately give clearer answers on the safety of ICSI e.g. with regard to the risk of transmitting Down’s syndrome. Indeed, it could be argued that, if karyotyping is recommended for these men (in which an abnormality is found in about 12% of ICSI men; Nakamura et al., 2001) then sperm aneuploidy certainly should be implemented as abnormal levels are likely to be found in far more fertile men. On the other hand the following can be argued in response: (i) families would not benefit from such a screen as the majority would go ahead with ICSI regardless of the information given; (ii) sex chromosome abnormalities are clinically not severe enough to worry about in this context and (iii) even if we do screen for sperm aneuploidy it would not take into account other associated risks of the ICSI procedure. In our opinion the first point is questionable given a closer analysis of the data (Giltay et al., 1999). The second point is central to the debate and is likely to be resolved more clearly when the question of the risk of transmitting Down’s syndrome is more clearly established. The third point is theoretical at this stage and it seems likely that there is at least some significant relationship between levels of sperm aneuploidy and incidence of trisomic offspring in ICSI couples. The only certainty is that the debate will continue for some time before the test becomes widespread.

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References


