biopsy of individual blastomeres from cleavage stage embryos (pre-
implantation diagnosis, PID) enable the diagnosis of genetic disorders in the embryo inherited from the father or acquired by postmeiotic errors (Handyside et al., 1989). In some countries like Germany, only PBD is legal but blastomere PID is not permitted.

We present a case of a 39-year-old 11g0p following the seventh cycle of ICSI. In the present cycle, 10 oocytes were retrieved and the first polar bodies were biopsied [analysis by FISH applying probes for the chromosomes 13, 15, 16, 18, 21 and 22 (Abbott, Wiesbaden, Germany)]. Three oocytes were fertilized and showed regular meiotic segregation of the chromosomes investigated, therefore these oocytes had been further cultivated and three embryos were transferred. First trimester screening was done at 12½ weeks of gestation. The nuchal translucency was 1.5 mm, the morphological parameters of the face, the soft markers of chromosomal abnormalities and the hemodynamical parameters of the fetal blood were normal. In first trimester serum biochemistry (Kryptor/Brahms, Hennigsdorf), free beta hCG was 109.7 IU/l (2.73 MoM), PAPP-A was 0.81 IU/l (0.24 MoM). The background risk for Down’s syndrome, based on maternal age, was 1:81, the adjusted risk based on maternal age and ultrasound was only 1:1617, but the adjusted risk based on the above parameters was 1:9 (Fetal Medicine Foundation London, UK). The patient requested an invasive test and a chorionic villus sampling (CVS) test was done at 13½ weeks gestation. Direct preparation and long-term culture showed a female karyotype with a free trisomy 21 in all cells (47,XX,+21). An additional aminocentesis revealed the identical karyotype. DNA then was extracted from cultured CVS cells as well as peripheral blood of both parents using standard methods. PCR-amplification of the informative microsatellite marker D21S1414 mapping to chromosome 21q21 was performed and PCR products were separated (Fig. 1). The results of the microsatellite analysis are in line with the cytogenetic diagnosis of trisomy 21 and indicate paternal origin of the supernumerary chromosome 21 due to paternal isodisomy.

In summary, the false-negative rate of polar body biopsy for Down’s syndrome is thought to be in the region of 10% if the extra chromosome 21 is paternally inherited (Hultén et al., 2008; Hunt and Hassold, 2008; Jones, 2008; Oliver et al., 2008), but original data on this are scarce. By using PID on embryo blastomeres, the clinical error rate of PID are approximately between 1.2 and 6% including telomeric probes (Munne et al., 2000, 2006).

This case highlights the fact that only fetal aneuploidies due to meiotic errors of maternal origin can be diagnosed through PBD, but both paternal derived meiotic and postmeiotic non-disjunction cannot be detected. The significance of PID is in the range of a screening test and cannot replace either a high quality first trimester examination or, in selected cases, an invasive procedure.

**References**


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A complicated IVF twin pregnancy

Sir,

To illuminate the current debates about multiple embryo transfer, we report a case of a woman who survived massive second-trimester haemorrhage but whose pregnancy was further complicated by intrauterine growth restriction, Caesarean section, premature delivery and resultant cerebral palsy of one twin.

A 29-year-old white hairdresser with twin pregnancy following double embryo transfer had massive bleeding at 20 weeks gestation. First Hb was 5.7 g/dl and she was resuscitated with fluids, blood, fresh frozen plasma and cryoprecipitate. She accepted that pre-viability hysterotomy and emergency termination might be required but
wanted to continue the pregnancy. She continued to have intermittent painless bleeding (250–1200 mls/episode) until 24 weeks and was transfused repeatedly. The total estimated blood loss was 181 and 27 units blood were given. At 28 weeks, twin 2 had growth restriction, oligohydramnios and reverse end-diastolic flow in the umbilical artery. In view of the risks of death and long-term handicap, conservative management (anticipating intrauterine death of twin 2) and delivery (worsening prematurity outcomes for twin 1) were discussed. After steroids, the babies were delivered by Caesarean section weighing 1240 g and 740 g. Histology confirmed dichorionic diamniotic placenta with no retroplacental clot or infarcts. The babies were discharged after 2 months in hospital. Twin 1 has confirmed cerebral palsy.

Mother’s description

I really cannot remember most of the things we talked to the doctors about before the treatment. I just wanted to go ahead and try and have a baby. If they had warned us of what was going to happen I would not have believed them. I was happy to have two embryos back. The night we called the ambulance I thought my babies were going to die. The bleeding was very heavy and wouldn’t stop. . . . The doctors told me that I had bled so much that in order to save my life they may have to take the babies out of my womb to stop the bleeding, I desperately wanted to keep my babies. I received bags and bags of blood. I was so scared, I thought I might die. The nightmare continued for days and days. I kept thinking I had finally stopped bleeding and then I would bleed heavily again . . . When the scan showed that one of the babies was not growing, I remember being told that if the babies were not born, then the small baby would die inside me. If the doctors delivered the babies now the bigger one may suffer. I couldn’t bear the thought of the smaller baby dying inside me and so it was agreed that the doctors would do a Caesarean. The babies were on the unit for a long time but eventually they were discharged. The little one is well, the bigger one is stiff and makes jerky movements all the time. This experience has made me feel guilty and sad. If someone had tried to sit me down before we started the process, I would never have believed it was all possible. I am sure I will never have any children ever again.

Discussion

We have not found a report of such massive second trimester haemorrhage resulting in two live births. Both placenta praevia and placental abruption are increased in multiple pregnancy (MP). Abruption of twin 2’s placenta cannot be excluded though bleeding was presumed to come from twin 1’s placenta. Thus the developmental delay may have been antenatal rather than postnatal.

In IVF, the challenge is to achieve a high pregnancy rate with minimal adverse outcomes (El-Toukhy et al., 2006). Despite the publications demonstrating that MP can be reduced by limiting multiple embryo transfer (Gerris et al., 2002; Hamberger et al., 2005; Khalaf et al., 2008), little has been done to impose restrictions in the UK. In Belgium single embryo transfer is mandatory in first cycles in young patients. In Sweden MP has been reduced <5% with single embryo transfer (Karlstrom and Bergh, 2007). Women <30 years with more than four good morphology embryos on day 3 have a good prognosis in their first cycle, but are also at high risk of MP. Here, selective single embryo transfer could have provided a good chance of pregnancy with reduced likelihood of MP, but was not offered. Cryopreservation of any additional embryos could significantly raise the cumulative odds of a live birth (Martikainen et al., 2001). Failure to implement the UK National Institute of Clinical Excellence (NICE, 2004) guideline recommending local provider funding for three IVF cycles in women <39 years has meant that clinicians and patients are reluctant to offer and accept single embryo transfer, respectively. The vast majority of patients fund their own treatment or have only one cycle funded by the National Health Service (NHS). In Australia, where access to IVF is unlimited, or Belgium, where up to six cycles are state funded, a single embryo transfer policy has been easier to implement. The HFEA consulted (HFEA, 2007) and has established a National Strategy Multiple Births Stakeholder Group to advise on its stated aim to reduce the MP rate <10% within 3 years. It may be a false economy for the NHS to only offer one treatment cycle.

Freestanding assisted conception units may lack a full appreciation of the impact of their practices. Some even argue that MP is not a serious complication (van Wely et al., 2006). Some patients regard twins as a positive outcome (Scotland et al., 2007) and will tolerate any risk, but consent is only legally valid if patients are competent, have relevant information and are not acting under duress. It is arguable how freely decisions can be made if an infertile couple is desperate. Limited funding (personal or NHS) inevitably impacts decision-making.

This extreme case demonstrates the full panoply of severely morbid, and potentially fatal, consequences of MP to both mother and babies (Braude, 2006; Kilby et al., 2006). The first reported IVF-related death was associated with twins (Bewley and Wright, 1991), and IVF technologies are now cited in the UK Confidential Enquiry into Maternal Deaths (CEMACH, 2007). As doctors’ professional responsibility is to ‘first of all, do no harm’, they cannot be indifferent to MP and must consider singletons the ideal outcome of treatment. If pregnancy rates were equal, it would surely become unethical, in most cases, to perform multiple rather than single embryo transfer.

Authors’ Role

All authors contributed to writing up the case.

Acknowledgment

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References


Further grounds for abandoning the concept of testicular dysgenesis syndrome: a response to the paper of Akre and Richardi (2009)

Introduction

The concept of testicular dysgenesis syndrome (TDS) was originally propounded by authors who noted that the components of the syndrome [hypospadias, impaired sperm quality, cryptorchidism and testicular cancer (TC)] all seem to be risk factors for one another. So they hypothesized that there is a common cause viz high intrauterine estrogen levels (Sharpe and Skakkebæk, 1993; Skakkebæk et al., 2001). However, evidence seems sparse that intrauterine estrogen levels are implicated in one of the components of the syndrome—

TC (Cook et al., 2009; Wohlfahrt et al., 2009). Moreover, doubt has been expressed by critics that the components actually do share causes (Storgaard et al., 2006; Akre and Richardi, 2009). Indeed this doubt prompted the latter authors to suggest that the concept of TDS should be abandoned. Here I offer support for this suggestion. Without denying that some cases of TC may have prenatal causes, I adduce three forms of evidence to suggest that another factor—low post-natal testosterone (T)/gonadotrophin (G) ratios (T/G ratio)—also predisposes to (at least some cases of) this cancer. Moreover, since T levels are also markers of sperm quality (another component of TDS; Zalata et al., 1995), the whole notion of the syndrome seems in disarray. This is so because I take a syndrome (of this sort) to require by definition a. a cause (or causes) common to all its components, and b. no other major cause.

The evidence relating TC to T is discussed below.

Secular trends in men’s testosterone concentrations

It is well established that men’s T concentrations decline slowly with age. However, longitudinal studies of men’s T levels have yielded sharper estimates of age-related T decline than their cross-sectional counterparts (Andersson et al., 2007; Travison et al., 2009). In other words, even when age is controlled, men’s T levels have shown a widespread secular decline (perhaps of the order of 1% per year). Such a decline is further suggested by the worldwide increase in diabetes and metabolic syndrome, both of which are associated with low T levels in men (Haring et al., 2009; Yeap et al., 2009). Potential causes of this secular decline in T are (i) endocrine disruptors and (ii) increasing obesity. However, regardless of these cause(s), I suggest that a consequence of the declining T levels is the reported concomitant secular increase in incidence rates of TC.

The association of TC with occupational exposure to heat

If diminished post-natal T levels were a cause of TC, then any agent which lowers T would be a risk factor for TC. Such a risk factor is heat. For instance, poor sperm quality and low T/G ratios have been reported in welders (Bonde, 1990, 1992). Similar effects have been reported following the exposure of male mice to scrotal heat stress (Perez-Crespo et al., 2008).

There have been several reports of occupational exposure to heat as a risk factor for TC (Haughney et al., 1989; Zhang et al., 1995; Anderssen et al., 2003; Hobbesland et al., 1999). Moreover reported associations of TC with welding and metal-working (Pollan et al., 2001; Romberg et al., 2003; Walschaerts et al., 2007) may, at least partially, be explained by heat exposures. So may the reported excess of TC among U.S. Gulf War veterans (Levine et al., 2005).

Lastly, Guidotti (2007) (without specifically noting the potential risk of heat itself) meta-analyzed eight studies and claimed that the associations reported in them between the occupation of firefighting and risk for TC meet medicolegal evidential criteria (‘balance of probabilities’), but may fall short of the more exacting standards of science and the criminal law (‘excluding reasonable doubt’).