BJOG DEBATE

Zygosity testing should be encouraged for all same-sex twins

BJOG PERSPECTIVES

FOR: A genetic test is essential to determine zygosity

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Twin pairs are either monozygotic (MZ) or dizygotic (DZ). Diagnosis of zygosity has traditionally been based on sex, genetics and/or chorionicity (Derom et al. *Twin Res*, 2001;4:134–6). A monochorionic placenta, determined using first-trimester ultrasound scans and confirmed by placental examination at birth, means the twin pair is MZ, with rare exceptions. Different-sex, dichorionic pairs are usually DZ. However, as approximately one-third of MZ pairs and nearly all DZ pairs have separate chorions and placentae, it is impossible to determine zygosity by placentation alone. For these pairs, a genetic test is essential.

The above rules of zygosity determination are frequently misunderstood, mainly because of the false assumptions that all dichorionic twin pairs are DZ and that MZ pairs must be physically identical. Up to one-third of families could be misinformed about twin zygosity, resulting in difficulties with medical decision-making, confusion and/or distress (Cutler et al. *Twin Res Hum Genet* 2015;18:298–305; van Jaarsveld et al. *BJOG* 2012;119:517–18).

There are many documented reasons why zygosity knowledge is medically important (Derom et al. *Twin Res* 2001;4:134–6; Keith et al. *J Reprod Med* 1997;42:699–707). Identification of monochorionicity allows referral for clinical monitoring to detect twin-to-twin transfusion, which, if not managed correctly, poses a high risk of fetal death and neurological injury. Postnatally, MZ pairs are perfectly compatible donors for one another. The diagnosis of a disease in one twin typically means that the co-twin is at increased risk, more so for MZ pairs. Furthermore, due to placental blood sharing between MZ pairs, genetic tests should be performed on tissues other than blood.

Twins and parents attest that zygosity knowledge is important for understanding the phenotypic differences between twins, defining their social relationships, defining themselves as individuals, determining the likelihood of further twins in the family and for avoiding embarrassment when questioned (Derom et al. *Twin Res* 2001;4:134–6; Cutler et al. *Twin Res Hum Genet* 2015;18:298–305; van Jaarsveld et al. *BJOG* 2012;119:517–18). Zygosity knowledge can also invoke a positive emotional response (Cutler et al. *Twin Res Hum Genet* 2015;18:298–305). Zygosity is valuable for twin research, in which free zygosity testing is often offered (Derom et al. *Twin Res* 2001;4:134–6). For all the above reasons, knowledge of chorionicity and zygosity has been called a 'birthright' (Keith et al. *J Reprod Med* 1997;42:699–707).

We would like to encourage the standard practice that same-sex twins and their families be advised that if they wish to know the pair's zygosity, the only way to be certain is to have a zygosity test. In many countries the current cost is €100 to €300 (US$100 to US$300). We understand that some may not wish to know and that, in some families, there may be ethical implications if only one of a pair of twins seeks such information, but counselling options are available in such instances. We also support raising awareness of the methods for determining chorionicity and zygosity. We believe that this will benefit both twins and researchers.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

AGAINST: Benefit of this knowledge should be weighed against the potential pitfalls

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Genetic testing has become commonplace in medicine and also increasingly accessible to patients. Genetic testing falls broadly into two categories—diagnostic and predictive testing (e.g. disease susceptibility testing). How zygosity testing (ZT) dovetails with genetic testing will be considered below. Twins' websites, targeting parents, list several reasons for the importance of ZT including 'for parental interest', 'avoiding embarrassment about twins being identical', 'helping to decide whether to treat twins as individuals or as identical' and 'determining the risk of having more twins'. Only the latter really carries any medical worth, though with poor predictability.

The pregnancy care required by multiple gestations is dictated by their chorionicity and amnionicity, which are determined by ultrasound. These findings may provide an inference of zygosity, but ZT alone during pregnancy carries unjustified risk and furthermore is rarely performed even when a diagnostic test is indicated, as this knowledge rarely contributes to pregnancy management.

Various medical benefits have been proposed as justifying ZT after birth.

Organ transplantation: knowing that your sibling is a potential ideal organ donor. There are numerous personal, psychosocial and medical factors that influence whether a family member considers being a donor or not. Zygosity alone cannot override these, but knowledge of this information in advance may put undue stress and pressure on individuals regarding a circumstance that, for the majority, will never arise. The assessment of zygosity or compatibility of relatives for organ transplantation is best addressed where the actual need for transplantation exists.

Disease prediction: diagnosis of a disease (genetic or other) in one twin often increases the risk in the co-twin. Genetic disease prediction is far-reaching with broad medical, psychological and social implications. This is supported by data from genetic testing for Huntington's disease (Kromberg et al. S Afr Med J 2013;103 (12):1023–6) or *BRCA* mutations. Predictive certainty for an incurable disease weighs unfathomably on an individual; predictive knowledge of a disease that carries significant risk and requires significant intervention to mitigate (e.g. mastectomy), no less so. Not everyone with a suggestive family history chooses to be screened for genetic susceptibility, nor does everyone screening positive choose to have preventive interventions. Knowledge of genetic predisposition to disease may affect someone's mental and physical health, their desire to marry, to have a family and other aspects of their work and personal life. Appropriate counselling and support should accompany predictive testing (Robson et al. J Clin Oncol 2010;28:893–901). Knowledge of zygosity before the onset of disease in either twin removes an individual's ability (perhaps moot in evidently identical twins) as to whether they wish to know the certainty of such genetic susceptibility or not upon the discovery of a co-twin's diagnosis.

The benefits of ZT for research cannot be underestimated. However, such testing should conform to local research ethics standards, including informed consent and clear processes to determine whether this information is disclosed to the participants or not. Disclosure should be accompanied by appropriate genetic counselling.

Zygosity testing for personal reasons cannot be prohibited. However, for the reasons outlined above the benefit of this knowledge should be weighed against the potential pitfalls. Parents choosing to undertake ZT purely for reasons of curiosity should be counselled about the implications of the results for their children's futures, before such testing is performed. The cost of such personal ZT should not be borne by public healthcare.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.