BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

Why are discrepant malformations in twins so challenging?

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Linked article: This is a mini commentary on YM Jung et al., pp. 857–864 in this issue. To view this article visit https://doi.org/10.1111/1471-0528.16463

Published Online 1 September 2020.

The paper by Jung et al. in this issue of *BJOG* represents a large cohort of monozygotic (MZ) and dizygotic (DZ) twins with concordant and discordant malformations (*BJOG* 2021; 128:857–864). In same-sexed dichorionic (DC) twins, zygosity was postnatally detected by DNA analysis. Two fascinating aspects are worth describing in detail.

First, the analysis reminds us of the traditional dispute about hereditary and environmental influences already thematised by Sir Francis Galton in 1876: *The History of Twins as a Criterion of the Relative Powers of Nature and Nurture*. Why and how early can identical genomes within the same uterine environment yield different phenotypes? Why have DZ twins similar malformations? It was shown that MZ twins may even differ by gender phenotype (Lu et al. *AJOG* 2018;219:242–54), which is explained by postzygotic nondisjunction, postzygotic rescue of gender chromosomes (X0/XY), mosaicism (XX/XY or X0/XYY), monogenic disturbance (SOX9) or postzygotic mutation of autosomal dominant genes like SRY or testicular feminisation. Discrepant anomalies in monochorionic (MC) twins can also be caused by vascular insults through placental anastomoses associated with microcephaly, periventricular leukomalacia, porencephaly, hydrocephaly, intestinal atresia, renal dysplasia or limb reduction defects. This indicates that in MZ twins the time of splitting determines absolute malformation rates, which are 1/25 in MZ twins with a DC placenta, 1/15 in MC diamniotic twins and 1/6 in MC monoamniotic twins (Gembruch, Ultrasound in Twins in German language, de Gruyter Publisher, Berlin).

It is less known that 5–10% of MC twins are DZ, 80% after artificial reproduction techniques and a melting process of the outer cell mass characterised by blood chimerism and potentially different sex (Li et al. *UOG* 2020;55:502–9). These were not evaluated in the Korean cohort. In some MZ twins with a genetic aberration of both twins the disease may only be expressed in one twin (as described for Beckwith–Wiedemann syndrome or infantile fibromyomatosis leading to death of one MZ monoamniotic twin) (Arabin et al. *UOG* 2009;33:487–91), but we do not know why.

Second, obstetricians are already in a favourable position to diagnose fetal membranes, early malformation or early risks for malformations which are later diagnosed in detail within the first trimester. This is important for parents of twins given the increased risks of a genetic or non-genetic disease of at least one child. MZ twins carry a higher risk of cerebral, gastrointestinal and frequently discrepant cardiac malformations. Early detection of the ultrasound markers for these anomalies is essential to allow for fetal karyotyping and DNA analyses and management, including feticide, if required. When analysing 6366 twin pregnancies, an enlarged nuchal translucency >95th centile predicted malformations in 16.5% and 19% of DC and MC twins, respectively; discrepant crown–rump lengths >10% similarly predicted increased malformations of 20.2% and 33.8%, respectively (Syngelaki et al. *UOG* 2020;55:474–81).

In conclusion, obstetricians must be aware that caring for twin pregnancies implies responsibility for three patients at increased risk of complex diseases and the need to adapt therapy options as early as possible, balancing beneficence for all individuals. The Korean cohort challenges us to reflect on how little we know about the origin of malformations and to improve professional prenatal care in terms of prediction, management and prognosis.

Disclosure of interests

A completed disclosure of interests form is available to view online as supporting information.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL. ■