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expert commentary on important new evidence

Risk factors for congenital abnormalities

A prospective study of a UK multi-ethnic birth cohort suggests that consanguinity is a major risk factor for congenital abnormalities, in particular in children of parents of Pakistani origin.

Overview: In 2011, the rate of congenital abnormalities recorded by 6 regional congenital anomaly registers in England and Wales (covering a third of births) was 219 per 10,000 births (95% CI 214 to 225, Congenital Anomaly Statistics 2011: England and Wales). Congenital abnormalities – structural, chromosomal, genetic and biochemical defects and malformations present at delivery – accounted for 27.7% of all infant deaths in 2011 (Office for National Statistics October 2013). The rate was higher in Asian infants (39.3%) and lower in white infants (25.6%). Babies born to mothers of Pakistani origin have around a four-fold higher risk of death in infancy from congenital abnormalities than babies from other ethnic groups, including those of Indian and Bangladeshi origin (National Perinatal Epidemiology Unit 2010).

A consanguineous marriage is defined as a union between two individuals who are related as second cousins or closer (Hamamy 2012). Consanguineous marriage is traditional and respected in many communities in north Africa, the middle East and west Asia – where intra-familial unions collectively account for 20–50% of all marriages – as well as among migrants from these communities. Evidence suggests that consanguineous unions may be partially responsible for the high numbers of congenital abnormalities in babies of Pakistani origin (Bundey and Alam 1993).

New evidence: Sheridan et al. (2013) analysed data from a large UK multi-ethnic birth cohort to investigate the incidence and causes of congenital abnormalities, in particular in infants of Pakistani origin. The Born in Bradford study is an ongoing cohort study of more than 12,400 women and 13,500 babies recruited between 2007 and 2011. Women attending the antenatal service in Bradford at 26–28 weeks' gestation were recruited and completed an interviewer-administered questionnaire. Babies with congenital anomalies were identified prospectively by clinicians in the local hospital trust.

Congenital anomalies were identified in 386 (3%) of the 11,396 infants for whom maternal questionnaire data were available. The rate of anomalies that were not chromosomal or metabolic disorders in this cohort was 305.74 per 10,000 infants, compared with 165.90 per 10,000 live births across England and Wales in 2010. Congenital abnormalities were more common in babies born to mothers of Pakistani origin (5%) than in those born to white British mothers (2%) or mothers of other ethnicities (3%).

Consanguinity was the largest risk factor for congenital abnormalities. Mothers who were related to the baby's father were more than twice as likely to have infants with congenital abnormalities than were mothers who were not related to the father (first cousins: multivariate risk ratio [RR]=2.19, 95% CI 1.57 to 3.02; other blood: RR=1.99, 95% CI 1.45 to 2.72; p<0.0001 for both). Socioeconomic status did not influence the effect of consanguinity on congenital abnormality.

More than one-third (37%) of babies of Pakistani origin were the offspring of first-cousin unions, compared with less than 1% of babies of white British origin and 5% of those of other ethnicity. Consanguinity was estimated to be a factor in 31% of birth abnormalities among infants of women of Pakistani origin. Education to diploma, degree or higher degree level was associated with reduced

risk of congenital abnormalities in all ethnicities (RR=0.53, 95% CI 0.38 to 0.75, p=0.0002). Smoking, alcohol and obesity were not associated with congenital anomalies.

Commentary: "In their analysis of the Born in Bradford study, Sheridan et al. (2013) identify consanguinity as a major risk factor for congenital anomalies. Although the results provide much needed information on consanguinity and genetic risk of abnormalities, the assertion that a 3.6% absolute increase in congenital anomalies at first cousin level among infants of mothers of Pakistani origin, after adjustment for deprivation, qualifies as major risk is problematic. Despite the fact that socioeconomic status did not influence the effect of consanguinity on congenital abnormality in Sheridan et al. (2013), health inequalities do appear to have a role in the elevated risk of congenital anomalies within people of Pakistani origin. The existing evidence base has identified ethnicity and language (Ali et al. 2006), access to healthcare (Marmot 2010) and deprivation (Vrijheid et al. 2000) as significant contributory factors to inequalities in health in this ethnic group.

"The lack of information in Sheridan et al. (2013) on biraderi – brotherhood groups made up of traditional male lineages – is surprising. This extra-familial network affects the risk of first cousin or other blood marriages in groups of Pakistani origin through its influence on marriage arrangements and population stratification along familial lines. In addition, groups that originate from different regions of Pakistani display differing preference for marriage within the extended family or biraderi. More detail on the origin(s) of the people from Pakistan in the sample in Sheridan et al. (2013) would help to contextualise the results. There is also a need for research on other ethnic groups living in the UK that practise consanguinity, to ensure that the genetic risk associated with consanguineous marriage, rather than the ethnic group of people of Pakistani origin, is the focus of enquiry.

"The findings from this study highlight the importance of continuing to raise awareness and understanding of the genetic risk of congenital abnormalities in communities practising consanguinity. The results also raise the importance of ensuring current prenatal, antenatal and genetic services promote informed reproductive choices that are culturally appropriate." ***– Dr Nasreen Ali, Senior Research Fellow, Mubasshir Ajaz, Doctoral Researcher, and Professor Gurch Randhawa, Professor of Diversity in Public Health and Director, Institute for Health Research, University of Bedfordshire***

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