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Birth Defects: Clinical Management and Beyond

Birth defects include structural or functional anomalies with measurable effects on physical, intellectual, and social well-being.¹ While it is intuitive in present view that they represent inborn errors of development, birth defects have been perceived historically as omens, portents, or punishments of supernatural origin.² 'Malformed animal or human, creature afflicted with a birth defect' had been referred to as *monster*, the word that came into English use in the fourteenth century. This word comes from the Latin *mōstrum* that harbours the meanings of omen, portent, an abnormal shape, and unnatural growth. It was not until the seventeenth century that William Harvey appreciated monstrosities from the perspective of abnormalities in embryonic development and disorders of conception as described in *Exercitationes de generatione animalium*. It was not until then that Harvey described the possible embryological perturbation that results in cleft lip in humans and animals, the oral aperture without lips and cheeks is seen stretching from ear to ear, and this is the reason, unless I make much mistake, why so many are born with the upper lips divided as it is in the hare and camel..... In the development of the human foetus, the upper lip only coalesces in the middle line at a very late period,³ The scientific appreciation of what had been regarded as monstrosities has evolved into the study of embryological development and its arrest and other perturbations.

In this issue of the *Journal*, several articles reported on the diagnosis, surgical management, and outcomes of congenital anomalies. Tovani-Palone et al shared their experience on centralisation of surgeries for the treatment of cleft lip and/or the palate and decentralisation of outpatient services in Brazil.⁴ Chee et al described the associated anatomic and genetic anomalies commonly encountered in newborns with omphalocele, their postnatal workup and prognosis over a 10-year period.⁵ Of importance to note is the high prevalence of associated congenital anomalies, in particular congenital heart defect. Interestingly, the authors also found that two of the 19 patients had the uncommon condition of alveolar capillary dysplasia.⁶ Xie et al reported on the diagnosis and the surgical management of infants with double aortic arch. As one reads through these articles, one could very much appreciate the excellent outcomes of surgical management of congenital anomalies in this era.

Notwithstanding, birth defects still constitute a significant clinical and public health challenge. Available data suggest that the occurrence of birth defects has not decreased over decades, and may in fact show a slight increase worldwide.⁷ The emerging Zika epidemic represents a new threat to further increasing their occurrence.⁸ The success to primary prevention of congenital anomalies depends on identification of the root causes. Disappointingly, hospital-based^{9,10} and public health surveillance⁷ studies have similarly concluded that a specific cause cannot

yet be determined for the majority of birth defects, identified important current gaps in the knowledge, and cautioned on the challenges of primary prevention. In a population-based cohort study, Feldkam et al could only assigned definite causes of birth defects in about 20% of their cases, 94% of these being related to chromosomal and genetic conditions, 4% attributable to teratogens mostly poorly controlled diabetes, and about 1% related to twinning.⁷

There is no doubt that further studies are required to define the unknown aetiology, which probably involves complex interaction between genetic and environmental factors during the period of conception and early gestation. Congenital heart defects provide an example of how understanding of genetic components of birth defects may impact on clinical outcomes. The major categories of genetic determinants of congenital heart disease including chromosomal abnormalities, copy number variation, and single gene disorders have been related not only to the cardiac phenotypes, but also to survival, neurodevelopmental outcome, and ventricular function.¹¹ At a more mechanistic level, Wang et al have identified two negative autophagy regulators, protein kinase C- α and micro RNA-129-2, which mediate the teratogenicity of hyperglycaemia leading to neural tube defects and that deletion of the *Prkca* gene, which encodes protein kinase C- α , reverses diabetes-induced autophagy impairment, cellular organelle stress and apoptosis, and leads to reduction of neural tube defect in a rodent model.¹² This first demonstration of a gene that plays a role in this birth defect may pave way for new preventive strategies.

We are what we are, we are what we were. The outcome of a newborn is the legacy of what happens to the fetus. The prenatal journey of a fetus is a sequel and destiny of the genetic regulatory pathways, the developmental biology of pluripotent stem cells, and other unknown factors, environmental or otherwise, since the very first moment of life. It is evident from this perspective than the distinction between scientific studies of the gene pathway, developmental biology, and clinical studies of children with birth defects become blurred. Only with the blurring of these boundaries that one could appreciate in the most comprehensive manner how the genetic, developmental, and clinical aspects intertwine and that one can capitalise on the bench discoveries for human use. It is with the blurring of the boundaries

between research laboratories and institutions that one can further foster collaborations and enhance synergisms between developmental biologists, geneticists, toxicologists, epidemiologists, infectious disease experts, paediatric surgeons, and paediatricians to tackle the important clinical and public health challenges of birth defects.

YF Cheung
Chief Editor

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