# 2. Invited commentary: Early Neonatal Death in Ireland and Congenital Anomalies

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### Congenital anomalies and mortality

Congenital anomalies can be defined as structural or functional anomalies (metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects. They are responsible for 303,000 deaths worldwide per annum (WHO, 2016). Congenital anomalies can contribute to long-term disability, the most common being severe heart defects, neural tube defects and Down syndrome. In more than half of cases the exact cause is often unclear, although congenital anomalies may be the result of one or more genetic, infectious, nutritional or environmental factors. Prevention is possible in some cases, for example, through vaccination, fortification of foods with folic acid or iodine and adequate antenatal care.

In 2015, the National Perinatal Epidemiology Centre (NPEC) reported a total of 488 perinatal deaths from 65,904 births of at least 500g birthweight or at least 24 weeks gestation across the 19 Irish maternity units. Stillbirths, early neonatal and late neonatal deaths accounted for 294 (60.2%), 166 (34.0%) and 28 (5.7%) respectively (O'Farrell et al, 2017).The perinatal mortality rate (PMR) was 7.0 per 1,000 births and the corrected PMR (corrected for congenital anomaly) was 4.3 per 1,000 births The corrected PMR across the 19 Irish maternity units ranged from 1.1 to 8.1 per 1,000 births in 2015.Major congenital anomaly was the primary cause of death in almost sixty percent (n=98, 59.0%) of the 166 early neonatal deaths that occurred in 2015. Chromosomal disorder accounted for seventeen percent of the 98 neonatal deaths due to congenital anomaly (n=17 of 98, 17.3% %).

Recent regional Irish data showed that congenital abnormalities accounted for 47% of deaths in the neonatal period and prematurity for 41% of deaths (Finn et al., 2014). In another Irish study, the principal causes of death were congenital malformations 34% (n=43), prematurity 49% (n=63) and asphyxia 11% (n=14). This study also showed that the most common diagnoses of the 43 neonatal deaths due to congenital malformations, were Trisomy 18, Trisomy 13, Potters sequence, anencephaly and congenital cardiac malformations (McCoy B et al., 2010).

In contrast, current findings from the UK showed that major congenital anomaly was the primary cause of death in just 27.4% and 27.5% of early neonatal deaths respectively. (Allanson ER et al., 2016, Manktelow et al 2016). The legislation prohibiting termination of pregnancy and the lack of universal pregnancy anomaly scans in Ireland may be the major factors involved in this disparity. Lack of universal early pregnancy scanning in Ireland may also be partially responsible for the postnatal diagnosis of major congenital anomalies, such as Congenital Diaphragmatic Hernia (Chukwu J et al., 2009). Furthermore, several papers have shown that patient and health care professionals support routine antenatal scans and testing but this has yet to be implemented across all Irish maternity units (Lynch CM et al., 2007).

In Europe, the pregnancy outcome for 50-90% of major congenital anomalies, including many that can be classified as rare diseases, is a Termination Of Pregnancy for Fetal Anomaly (TOPFA). The proportion of women in Ireland going abroad for a TOPFA is estimated at 25-30% for lethal anomalies such as anencephaly, and up to 38% for chromosomal trisomies (Mc Donnell et al, 2016). Using Congenital Heart Defects (CHD) as an example there are an estimated 36,000 liveborn children with CHD per annum in Europe and 3000 die as a TOPFA, late fetal death or early neonatal death. There was a large variation in TOPFA due to CHD between European countries, ranging from 0% to 32%. The rate of children liveborn with a CHD associated with Down syndrome was 0.5 per 1,000 births, with more than a fourfold variation between countries (Dolk H et al., 2011).

### Interventions to improve management and outcomes:

Antenatal diagnosis of congenital anomaly has many benefits including informed discussion with families about management and optimal site of delivery whether in a regional centre or locally. In addition, the need for urgent tertiary and quaternary input may dictate the location of birth and the advent of the New Children's Hospital with a maternity hospital attached will allow families to stay close to their baby requiring intensive medical care. Furthermore, there is evidence of improved outcomes with early recognition and antenatal transport to specialist centres (Javid PJ et al., 2004; Phibbs CS et al., 2007; Watson SI et al, 2014). Increased staffing and education in perinatal and paediatric palliative care services are required to allow rapid transfer home if this is the family's preference.

Planning of services and resources are hampered by the lack of a detailed clinical and surveillance registry and in recent years the NPEC has provided invaluable information to rectify this issue. The European Surveillance of Congenital Anomalies and Research (EUROCAT (www.eurocat-network.eu) is a network of population-based registers of congenital anomaly in Europe, with a common protocol and data quality review for all its member registries, covering 1.5 million annual births in 22 countries. In Ireland, there are three HSE regional EUROCAT registries providing congenital anomaly surveillance for the East, Southeast and South, with annual births of 25,742 (38.3%), 7,104 (10.6%) and 9,263 (13.8%) respectively, representing a total of 62.6% of all national births (n= 67,295) in 2014. There is no congenital anomaly surveillance for the remaining 25,186 (37.4%) births occurring in the remaining HSE regions. Due to a tightening of the interpretation of data protection legislation in recent years, some of the registries are experiencing difficulties in ascertaining cases, which can affect the accuracy of data. With appropriate legislation, congenital anomaly surveillance can be readily extended nationally. The forthcoming Health Information & Patient Safety Bill publication and enactment in 2017/2018 is expected to provide for national surveillance.

EUROCAT data includes live births, stillbirths and TOPFA. However, the proportion of mothers in Ireland who choose to go abroad for a TOPFA is generally unknown, although there are estimates, as previously discussed, based on individual studies of specific anomalies. The high proportion of pregnancies affected by major congenital anomalies in Europe ending in a TOPFA impacts on the variation in rates between Ireland and the rest of Europe with Ireland having a higher incidence of major congenital anomalies and higher perinatal and neonatal unadjusted mortality rates.

The EUROCAT-EUROPLAN recommendations for the primary prevention of congenital anomalies, endorsed in 2013 by the European Union Committee of Experts on Rare Diseases, includes feasible and evidence-based measures from which national plans can adopt and implement actions based on country priorities (Taruscio D et al.,2015).

National clinical pathways from the Royal College of Physicians of Ireland are integrating antenatal and postnatal early management of complex congenital anomalies such as congenital diaphragmatic hernia across multiple disciplines

and sites to ensure co-ordinated urgent and long-term care. Partnership with European and international collaborators is ongoing and there is an increased focus on parent and family support group involvement in research planning and implementation.

Many congenital anomalies are rare diseases. The EU Commission (EU Commission, 2017) has mandated more effective co-ordinated management and care of rare diseases in member states through National Rare Disease Plans (Department of Health, 2014), and European Reference Networks (Health Service Executive, 2014). The vital diagnostics and clinical genetics services have enhanced diagnosis of patients with rare disorders to optimize care. Rapid developments in genomics also offer diagnosis and classification of diseases to allow targeted therapeutic options for children with rare disorders, which is promoted by the EU with the European Medicines Agency (EMA). This information is especially valuable for parents and families in planning their child's management with the clinical team and future pregnancy outcomes. New treatments for conditions currently considered life-limiting can be developed in partnership with families and health care providers. A good example is Spinraza (nusinersen), the first drug approved to treat children and adults with spinal muscular atrophy (SMA). The U.S. Food and Drug Administration (FDA) recently approved Spinraza to treat SMA, a rare and often fatal genetic disease affecting muscle strength and movement (Finkel RS et al., 2017). The recognition of the association between Zika virus outbreaks and an increase in microcephaly and other congenital malformations, has resulted in enhanced public health surveillance and vaccination research.

Paediatric pathology services are crucial to diagnose rare conditions including postmortem diagnosis of rare diseases. A study by Brodlie et al found that over a quarter of neonatal autopsies yielded new information, which in 3% of cases was crucial (Brodlie M et al., 2002). However, in 2015 the NPEC reported that an autopsy was undertaken in only 53.3% of all stillbirths and 14.5% of early neonatal deaths in Ireland, resulting in an autopsy uptake rate of 50.4% of all perinatal deaths (O'Farrell I et al, 2017).

The evolution and collaboration of International congenital anomaly and rare disease registers and networks on projects regarding children with rare diseases will be especially valuable to Irish researchers. The International Clearinghouse for Birth Defects Surveillance and Research (www.icbdsr.org) already collaborates in projects with the EUROCAT network. In 2010, the 63rd World Health Assembly passed a resolution calling for Member States to agree to promote primary prevention and improve the health of children with congenital anomalies by: developing and strengthening registration and surveillance systems; developing expertise and building capacity; strengthening research and studies on etiology, diagnosis and prevention and promoting international cooperation.

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