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Published in:
Obstetrical and Gynecological Survey

DOI:
[10.1097/OGX.0000000000000543](https://doi.org/10.1097/OGX.0000000000000543)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Groen, H., Bouman, K., Pierini, A., Rankin, J., Rissmann, A., Haeusler, M., Yevtushok, L., Loane, M., Erwich, J. J. H. M., & De Walle, H. E. K. (2018). Stillbirth and Neonatal Mortality in Pregnancies Complicated by Major Congenital Anomalies: Findings from a Large European Cohort. *Obstetrical and Gynecological Survey*, 73(3), 131-132. <https://doi.org/10.1097/OGX.0000000000000543>

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Stillbirth and Neonatal Mortality in Pregnancies Complicated by Major Congenital Anomalies: Findings From a Large European Cohort

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Prenat Diagn 2017;37:1100–1111

ABSTRACT

Modern ultrasound technology has revolutionized prenatal screening and provided women with a means of obtaining clinical information that can help inform their decision making about their pregnancy through detection of congenital anomalies (CAs). Not all CAs are detectable in the gestational window where abortion is legally allowed. In these instances, clinical geneticists and obstetricians play a key role in providing accurate information to patients regarding prognosis. Studies have found that CAs exist in up to 20% of stillbirths and that 4.7% of stillbirths in normally formed fetuses are attributed to CAs. Evidence on the associations between specific CAs and stillbirth risk is less clear, to the extent that comparative evaluation of fetal survival in pregnancies complicated by CAs is often difficult.

This large-scale analysis draws data from national and regional registries participating in the European Surveillance of Congenital Anomalies (EUROCAT) network to assess pregnancies complicated by CA. The aim of this study was to generate prognostic information that may be used by parents to reach an informed decision about continuation or termination of a pregnancy. Specifically, this study sought to determine the prevalence of stillbirth and early (death within 7 days of live birth) or late neonatal mortality (death between 7 and 27 days after live birth) for common chromosomal anomalies such as trisomies 13, 18, and 21; syndromes such as monogenic anomalies and skeletal dysplasias; and other isolated anomalies according to EUROCAT guidelines. Data were collected for cases between 1998 and 2011, and instances where termination of the pregnancy occurred were excluded. Cases were identified prenatally or after birth.

The analysis group consisted of 73,337 cases of pregnancies complicated by CAs with known mortality outcomes. The most common times of discovery for CAs were “at birth” (34.8%), “prenatal” (20.2%), within 1 week (11.4%), and between 1 and 12 months (11.5%). Perinatal mortality associated with CA was found to be 0.127% (95% confidence interval, 0.123–0.131). Stillbirth was most commonly found in chromosomal anomalies, whereas early and late neonatal mortalities were most prevalent in chromosomal anomalies and syndromes. The highest rates of stillbirth among isolated CAs were among central nervous system and respiratory anomalies, diaphragmatic hernias, and abdominal wall defects. Stillbirth predominantly occurred at extreme preterm gestational age (37.9%) compared with 28 to 32 weeks of gestation (16.1%) and term (21.5%). Mortality occurred in the majority of cases for trisomy 18 (77.3%), trisomy 13 (75.5%), and anencephaly (99.6%).

This study used a large database consisting of cases with a wide range of anomalies to find that prognosis of pregnancy differs greatly according to CA. This study provides a robust reference for decision making to be used by parents and health care providers in the case of CA presentation.

EDITORIAL COMMENT

(Approximately 3% to 4% of live births are associated with a CA, including structural abnormalities, as well as chromosomal and genetic disorders. It is generally acknowledged, and parents are counseled, that there is an increased risk of stillbirth or perinatal death associated with

prenatally detected fetal abnormalities. However, the magnitude of risk with different categories of disorders is not well documented, nor are the mechanisms of stillbirth always well understood.

In this abstracted article, the authors collected data from 13 registries of EUROCAT and measured perinatal mortality, stillbirths, and early and late neonatal mortality rates for different categories of CA, including chromosomal abnormalities, syndromes, and isolated anomalies. Among 73,337 cases, the perinatal mortality rate associated with CA was 1.27 per 1000 births (95% confidence interval, 1.23–1.31). The average stillbirth rate was 2.68% (range, 0%–51.2%), and the early and late neonatal mortality rates were 2.75% (range, 0%–46.7%) and 0.97% (range, 0%–17.9%), respectively. There were significant differences in the timing of fetal demise in fetuses with chromosomal anomalies and syndromes, and with most isolated anomalies, compared with the general population. The highest term stillbirth rates were seen in fetuses with chromosomal and central nervous system anomalies.

The highest stillbirth rate was seen in chromosomal abnormalities, most specifically trisomies 13 and 18, whereas the stillbirth rate in Down syndrome was only less than 5%. Central nervous system anomalies also had high stillbirth rates, especially anencephaly, hydrocephaly, encephalocele, and holoprosencephaly, although some of these rates were not as high as we often consider them to be. Ventral wall defects also had a relatively high stillbirth rate (approximately 5%), and single ventricle/hypoplastic left or right heart had a 5% to 8% loss rate.

Although it was not evaluated in this article, the mechanism of stillbirth in different fetal anomalies likely differs substantially and may include arrhythmia or heart failure/hydrops in cases of congenital heart disease and umbilical cord compression with renal disorders leading to anhydramnios. The mechanism

of stillbirth in cases of neural tube defects or other central nervous system abnormalities, or even with many chromosomal abnormalities, is unknown.

Despite the likelihood that the mechanisms of stillbirth vary substantially, we have a bit of a “one-size-fits-all” approach to antenatal surveillance of pregnancies affected by fetal anomalies. In many practices, all fetuses with an anomaly undergo serial (every 3–4 weeks) ultrasound evaluation for fetal growth, regardless of whether the particular anomaly is associated with an increased risk of growth restriction or likely to progress such that intervention could change the prognosis or outcome. In addition, many such patients undergo antenatal surveillance, with nonstress tests and often biophysical profiles, every week or twice weekly, regardless of whether there is an increased risk of stillbirth. Nonstress test can detect fetal heart rate changes associated with uteroplacental insufficiency, but there are limited data on effectiveness in preventing stillbirth in an anomalous fetus, a circumstance in which the pathogenesis is likely very different with uncertain timing and type of fetal heart rate abnormalities.

While this article is a bit of data-dense and somewhat dry report, there are some additional interesting findings. For example, the loss rate of some common aneuploidies is lower than generally quoted, perhaps because more severely affected fetuses are more likely to undergo termination. The stillbirth rate of spina bifida is higher than that of Down syndrome (6% vs 5%), albeit not by much, and that of gastroschisis and omphalocele are nearly identical. In addition, they found that countries in which pregnancy termination is not available (Ireland) have substantially higher rates of perinatal mortality. I often counsel patients making the difficult decision to terminate in the setting of a likely lethal disorder that they are not changing the ultimate outcome; they are only changing the timing of that outcome; these data support that approach.—MEN)