Major congenital anomalies in a Danish region

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ABSTRACT

INTRODUCTION: This study describes the prevalence of congenital anomalies and changes over time in birth outcome, mortality and chronic maternal diseases.

MATERIAL AND METHODS: This study was based on population data from the EUROCAT registry covering the Funen County, Denmark, 1995-2008. The registry covers live births, foetal deaths with a gestational age (GA) of 20 weeks or more, and terminations of pregnancy due to congenital anomalies (TOPFA).

RESULTS: The overall prevalence of congenital anomalies was 2.70% (95% confidence interval: 2.58-2.80). The majority of cases had an isolated congenital anomaly, 13.9% had a chromosomal anomaly and 7.7% were multiple congenital anomalies. The combined foetal and infant mortality in the study area was 11.6 per 1,000 births. 19% (2.2 per 1,000) of these deaths were foetuses and infants with major congenital anomalies. Combined foetal and infant mortality decreased significantly over time for cases with major congenital anomalies ($p < 0.001$), whereas the number and proportion of TOPFA increased. Median GA at TOPFA decreased from 18 to 15 weeks. Among the congenital anomaly cases, 8% had a registration of one of these chronic maternal diseases: diabetes, epilepsy, mental disorder, thyroid disease, asthma, or inflammatory bowel disease. Medication for these conditions accounted for 46% of maternal drug use.

CONCLUSION: Maternal morbidity and use of potentially teratogenic medication have increased among congenital anomaly cases. Foetal and infant mortality for congenital anomaly cases have decreased significantly, probably owing to an increase in early prenatal diagnosis and TOPFA.

FUNDING: The study was funded by Region of South Denmark.

TRIAL REGISTRATION: not relevant.

The surveillance of congenital anomalies serves several purposes, the most important being the identification of teratogenic exposures leading to congenital anomalies and assessment of the impact of primary prevention and prenatal screening policies at population level.

In 2004, the National Board of Health in Denmark recommended a new screening policy for congenital anomalies including a first trimester screening for Down syndrome and a second trimester screening for congenital anomalies (EG) [1]. Before 2004 (EG) an invasive test for Down syndrome was offered to pregnant women aged 35 years or more.

In most cases, women with a chronic disease have to continue their medication during pregnancy for their own safety and the safety of their newborn. A number of chronic diseases which in themselves or via the medication prescribed for these diseases are suspected to act teratogenically. Some of these chronic diseases (EG) have increased in prevalence in young adults over the past decades, e.g. asthma, diabetes and inflammatory bowel disease [2-4]. Furthermore, the use of SSRIs in women of childbearing age has increased rapidly [5].

The surveillance of congenital anomalies based on data from the Danish National Patient Register may be inadequate, since these only include liveborn infants. A substantial proportion of stillborn infants have important congenital anomalies. Furthermore, many serious anomalies are detected in prenatal screening and diagnostics and lead to termination of the pregnancy.

This study reports the prevalence as well as the spectrum of major congenital anomalies in the former Funen County, covering approximately 9% of the Danish population. Furthermore, the study describes and compares foetal and infant mortality before and after the change in the Danish prenatal screening programme; finally, it describes foetal exposures to potentially teratogenic medications for chronic maternal diseases among congenital anomaly cases.

MATERIAL AND METHODS

Data on congenital anomalies are collected routinely in the EUROCAT Registry of the Funen County. The EUROCAT registries are population-based and use (EG) standardised methods of case ascertainment. The registries are based on multiple sources of information including hospital records, birth and death certificates, annual reports from the cytogenetic laboratory and post-mortem examinations, and they include information about live births (LB), foetal deaths (FD) with a gestational age (GA) of 20 weeks or more, and termination of pregnancy (TOPFA) at any GA after prenatal diagnosis of foetal anomaly. All structural malformations, syndromes and chromosome anomalies are included in the database except minor and poorly specified malformations found on a list of exclusion.

The study population includes all foetuses/children with a diagnosis of congenital anomaly, born in the 1995-2008 period by women residing in the Funen County at the time of birth or abortion. The dataset in-

ORIGINAL ARTICLE

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Dan Med J 2014;61(6):A4825

TABLE 1

Number of births and number of congenital anomaly cases, Funen County, Denmark, 1995-2008.

	Total live- and stillbirths	Total congenital anomaly cases	Live births	Foetal deaths from 20 weeks	Termination of pregnancy	Prevalence per 10,000 births
1995-1999	29,026	697	603	28	66	240.1
2000-2004	26,775	715	610	17	88	267.0
2005-2008	21,719	677	534	14	129	311.7
All years	77,520	2,089	1,747	59	283	269.5

TABLE 2

Congenital anomaly cases within subtypes, Funen County, Denmark, 1995-2008.

	n	% of total	Prevalence per 10,000 births
Chromosomal anomaly	291	3.9	37.5
Syndrome	88	4.2	11.4
Isolated neural tube defects	64	3.1	8.2
Isolated CHD	552	26.4	71.3
Isolated renal anomalies	149	7.1	19.2
Other isolated congenital anomalies	785	37.6	101.3
Multiple congenital anomalies	160	7.7	20.6
All	2,089	100	269.5

CHD = congenital heart defects.

cludes the following variables: type of birth (LB; FD; TOPFA), the International Classification of Diseases 10th edition (ICD10) code and written text for all malformations, birth weight, GA (EG), maternal age, maternal diseases before pregnancy and medications taken during the first trimester of pregnancy. Cases were classified according to EUROCAT subgroups and the computer algorithm for classification into isolated and multiple congenital anomalies [6].

Data on the number of births or foetal deaths after 20 weeks of gestation (with or without congenital anomalies) to women resident in the county of Funen in the 1995-2008 period were obtained from the Danish Medical Birth Registry. Information on foetal deaths was obtained from the Danish National Patient Register. Data on number of deaths in the first year of life were found in the Register of Causes of Death. The total number of births (live and stillbirths) in the Funen County during the study period was 77,402.

The new screening recommendations from the National Board of Health were implemented in the Funen County in 2005.

The tests performed for effect of period on infant and total mortality were likelihood ratio χ^2-tests performed with SAS software (version 9.2).

Trial registration: not relevant.

RESULTS

During the 14 years from 1995 through 2008, a total of 2,089 cases with major congenital anomalies were recorded by the EUROCAT Registry displaying a 2.70% (95% confidence interval: 2.58-2.80) overall prevalence of congenital anomalies. The prevalence increased over the years from 2.41% in 1995-1999 to 3.12% in 2005-2008. The increase was mainly explained by increasing prevalence of chromosomal and renal anomalies. The prevalence of chromosomal anomalies increased from 33 per 10,000 births in 1995-1999 and 2000-2004 to 49 per 10,000 births in 2005-2008. The prevalence of isolated renal anomalies was 13 per 10,000 births in 1995-1999, 19 per 10,000 births in 2000-2004, and it increased to 29 per 10,000 births in 2005-2008. The distribution of birth outcome (live births, foetal deaths and TOPFA) are presented in **Table 1**. The number of foetal deaths decreased over time and the number of TOPFA increased. The median GA for live births was 39 weeks for all three time periods, and the median GA for foetal deaths was 32 or 33 weeks for the three periods. The median GA for TOPFA decreased from 18 weeks in 1995-1999 to 15 weeks in 2005-2008.

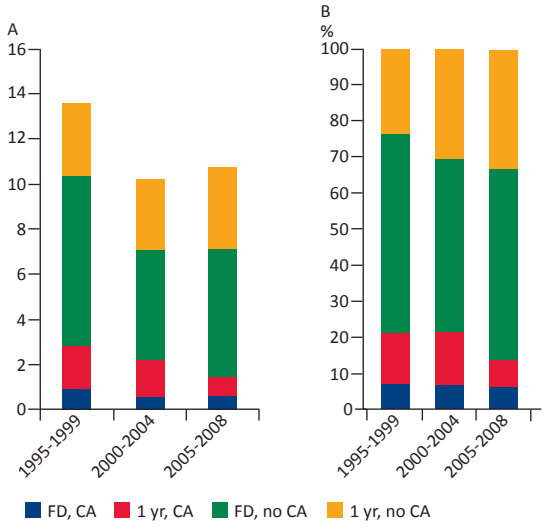
The distribution of type of congenital anomaly is presented in **Table 2**. The majority of cases (74.2%) had an isolated congenital anomaly (one organ system affected). Chromosomal cases accounted for 13.9%, syndromes for 4.2% of all cases and 7.7% had multiple congenital anomalies (major congenital anomaly in two or more organ systems).

Mortality

During the study period, there were 533 foetal deaths from GA 20 weeks, and 369 infants died before the age of one year in the study area. This gives a combined foetal and infant mortality of 11.6 per 1,000 births ranging from 13.5 in 1995-1999 to 10.2 in 2000-2004 (**Figure 1**). A total of 59 of the 533 foetal deaths (11.1%) had a major congenital anomaly, and 115 of 369 infant deaths (31.2%) had a major congenital anomaly. This gives a foetal and infant mortality with congenital anomalies in the population of 2.2 per 1,000 births with a significant decline from 1995-1999 to 2005-2008 (from 2.8 per 1,000 births to 1.5 per 1,000 births, p = 0.0055) (Figure 1). Mortality with congenital anomalies within the first week after birth declined from 1.14 per 1,000 births in 1995-1999 to 0.32 per 1,000 births in 2005-2008 (p = 0.0101). There was no change in total mortality within the first week after birth in these two periods (3.20 and 3.18 per 1,000 births, respectively), which means that 35% of all first-week deaths in 1995-1999 were associated with a major congenital anomaly, whereas only 10% of all first-week deaths in 2005-2008 were associated with a major congenital anomaly.

FIGURE 1

Foetal and infant mortality, Funen County, Denmark 1995-2008. **A.** Prevalence per 1,000 births of foetal and infant death with and without congenital anomalies. **B.** Proportion of foetal and infant deaths with and without congenital anomalies.



1 yr = first year of life; CA = congenital anomaly; FD = foetal death.

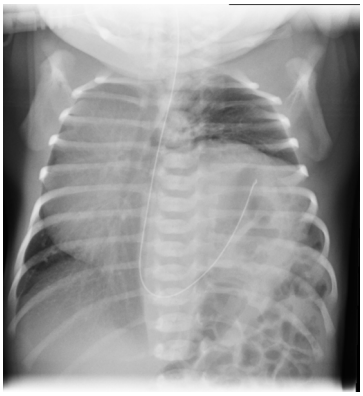
Chronic maternal disease before pregnancy

For 1,827 cases (87.5 %), no maternal disease before pregnancy was reported. A total of 258 cases were reported with a disease before pregnancy, and for four cases this information was not stated. Among those with reported disease before pregnancy, 25 women had a congenital anomaly. The most common chronic maternal diseases requiring medication are presented in **Table 3**. For maternal asthma and maternal mental disorders, there was a significant increase in the number of cases during the three periods ($p < 0.01$ for mental disorders and $p < 0.001$ for asthma). Overall, 8.0% (168/2,089) of cases with major congenital anomaly had a mother suffering from one or more of the six chronic diseases: diabetes, epilepsy, thyroid diseases, asthma, inflammatory bowel disease or a mental disorder. In the 1995-1999 period, 4.4% (31 of 697) of the mothers were reported to have at least one of these six diseases compared with 11.4% (77 of 677) in 2005-2008 ($p < 0.001$). Drug use in the first trimester of pregnancy was reported for 260 cases (12.5% of all cases) of which 127 cases (6.1% of all cases) were exposed to drugs used for treatment of the six chronic diseases mentioned above.

DISCUSSION

The prevalence of major congenital anomalies in the Funen County, Denmark, during the 1995-2008 period was 2.70%, and it followed an increasing trend over time. The increase was mainly explained by more cases being diagnosed with a chromosomal anomaly or a renal malformation than in the preceding years. The new screening recommendation with first trimester screening for Down syndrome and an ultrasound screening for major congenital anomalies around week 19 was implemented in 2005, and this may explain the changes over time. Foetuses with Down syndrome are likely to be miscarriages in the first trimester, so first trimester screening will result in an increase of the diagnosis compared with diagnosis at birth [7]. The Down syndrome data from the Funen County for the 1990-2009 period were analysed in a EUROCAT multicentre study [8]. The study showed an increase in the prevalence of Down syndrome throughout Europe, which was mainly explained by an increase in maternal age at birth. Overall, the European live birth prevalence remained stable, but with wide differences between countries due to differences in prenatal screening and termination policies. The prevalence of congenital hydronephrosis is related to the presence of a prenatal ultrasound screening programme in the region [9]. The pan-European data from EUROCAT have also showed an increasing prevalence of both chromosomal and non-chromosomal major congenital anomalies over the past decade [10]. The increase in the proportion of TOPFA in this study started before 2005. During the 1995-2004 period, there was a steady increase in the number of cases with severe congenital anomalies diagnosed prenatally followed by TOPFA, although the only national screening recommendation in these years was the maternal age screening for Down syndrome by invasive tests. It is a positive effect of the national screening programme that the median GA for TOPFA has decreased from 18 weeks in 1995-1999 to 15 weeks in 2005-2008.

The observed distribution of types of congenital anomalies is comparable to the overall EUROCAT findings [6] with 7.0% multiple congenital anomalies compared with 7.1% in this study. The main difference relative to our Funen population is the high number of cases diagnosed with a genetic syndrome: 4.2% compared



Newborn with severe congenital anomaly.

TABLE 3

Proportion of mothers reported to have a pre-pregnant chronic medical condition and to have medication for this disease during the first trimester of pregnancy. Data for all congenital anomaly cases, Funen County, Denmark, 1995-2008.

				1995-2008, %		
	1995-1999, % (n[a] = 697)	2000-2004, % (n[a] = 715)	2005-2008, % (n[a] = 677)	total (n[a] = 2,089)	cases in EUROCAT database	ATC-codes
Maternal disease before pregnancy						
No maternal disease reported	90.1	87.6	84.6	87.5	–	–
Maternal congenital anomaly	1.9	0.7	1.0	1.2	–	–
Asthma/allergy	1.3	3.6	5.8	3.%	–	–
Diabetes	0.4	1.3	0.6	0.8	–	–
Epilepsy	1.0	0.4	1.3	0.9	–	–
Mental disease	0.7	1.0	3.0	1.5	–	–
Inflammatory bowel disease	0.4	1.5	0.7	0.9	–	–
Thyroid diseases	0.6	0.6	1.0	0.7	–	–
Other diseases	3.0	3.1	2.8	3.0	–	–
Unknown	0.3	0.1	0.1	0.2	–	–
Maternal drug use in the first trimester of pregnancy						
Insulin	–	–	–	–	0.9	A10
Antiepileptics	–	–	–	–	0.8	N03A
Asthma medication	–	–	–	–	2.6	R03
SSRI	–	–	–	–	1.1	N06A
Thyroid and antithyroid	–	–	–	–	0.8	H03
Inflammatory bowel disease	–	–	–	–	0.2	H02
Total cases who took at least one of the six drug groups	–	–	–	–	6.1	–
Total pregnancies with drug use in first trimester	–	–	–	–	12.5	–

CA = congenital anomaly; SSRI = selective serotonin reuptake inhibitor.
a) Total number of cases with CA.

with the 2% EUROCAT average, and a prevalence of genetic syndromes of 12.7 per 10,000 births on Funen compared with 4.8 per 10,000 in EUROCAT. This difference may partly be explained by the longer follow-up through childhood of the Funen EUROCAT Registry (five years), whereas many EUROCAT registries only include cases diagnosed before one year of age. However, we also believe that the high rate of syndromes is explained by an awareness of rare genetic diseases among the clinicians seeing patients in our region.

Infant mortality for all births in the region did not change significantly over time (5.06, 4.71 and 4.42 per 1,000 births), but mortality with congenital anomalies decreased significantly. The most striking result is the decrease in mortality with congenital anomalies within the first week after birth: 1.14 per 1,000 births in 1995-1999 and 0.32 in 2005-2008. The main difference between the two time periods is the number of TOPFA which increased from 13 annual cases in the late nineties to an average of 32 annual cases in 2005-2008. Most TOPFAs were performed for either lethal or severe congenital anomalies with high mortality in infancy. Therefore, we are able to conclude that the new screening programme from 2005 has had major impact on the foetal and infant mortality with congenital anomalies; especially on the mortality within the first week after birth. However, the new screening programme may not be the only factor contributing to the reduced mortality with congenital anomalies. A higher prenatal detection rate and planning of the place of birth for pregnancies with specific anomalies such as severe congenital heart defects (CHD) (EG) and diaphragmatic hernia may also have reduced the mortality [11, 12]. However, due to the limited number of cases with these specific anomalies, we are unable to substantiate this with evidence from our data.

Our data have shown an increase in the number of mothers with chronic diseases. The highest increase was observed in mothers with asthma and/or allergy and mothers with mental disorders. The increase may be explained in two ways: either an increase in general of these diseases (EG) among women at child-bearing age or a more relaxed attitude towards becoming (EG) pregnant among women who have a chronic disease associated with an increased risk for pregnancy complications. From the literature we have found documentation of an increase in several of these chronic diseases, e.g. asthma, diabetes and inflammatory bowel disease in Denmark over the past decades [2-4].

A total of 76% (EG) of the pregnant women with six

chronic diseases took medication for their disease (127/168). There are concerns for the use of SSRI during pregnancy, both due to increased risk of congenital anomalies [13] and due to possible risks of other developmental problems during childhood [14]. It is well-known that antiepileptic medications in general and valproate [15] in particular increases the risk of congenital anomalies. For maternal diabetes, the increased risk of congenital anomalies seems to be related to the diabetic control and not the insulin used [16]. Deciding on medication use during pregnancy may be difficult, since both the disease and the medication may place the foetus at risk. When drugs are licensed for marketing, information with respect to reproductive toxicity is only available from pre-marketing animal studies. However, these studies in animals are seriously limited in their ability to predict human teratogenesis because of wide variations in species-specific effects, even among mammalian species [17]. Moreover, pregnant women are excluded from pre-marketing clinical trials in humans, and safety in pregnancy has therefore not been established at the time of licensing. This means that the safety of the medications used in pregnancy can only be studied through post-marketing surveillance. The ongoing EUROmediCAT study [18] will develop an efficient system for safety evaluation of medication used during pregnancy in relation to congenital anomalies.

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ACCEPTED: 11 February 2014

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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