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a systematic review

Slot, Anna; Eriksen, Nina Bonne; Ringholm, Lene; Damm, Peter; Mathiesen, Elisabeth R

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Congenital heart defects in offspring of women with Type 2 diabetes – a systematic review

Anna Slot[1, 2], Nina Bonne Eriksen[1, 2], Lene Ringholm[1, 3, 4], Peter Damm[1, 2, 5] & Elisabeth R. Mathiesen[1, 2, 3]

ABSTRACT

INTRODUCTION: The risk of congenital heart defects in the offspring of women with Type 2 diabetes is only sparsely described. The aim of this review was to estimate the prevalence of congenital heart defects in offspring of women with Type 2 diabetes in comparison to offspring of women with Type 1 diabetes and to offspring of the background population.

METHODS: This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A literature search was performed in the PubMed, Embase and Cochrane databases. Studies were included if they were published from 2007 to 2018, comprised a minimum of 200 offspring of women with Type 2 diabetes and examined the prevalence of congenital heart defects.

RESULTS: Five cohort studies with a total of 23,845 offspring of women with Type 2 diabetes were included. The studies were heterogeneous with respect to method of diagnosis and whether terminated pregnancies were included, and a meta-analysis could not be performed. The mean prevalence of congenital heart defects was 44 (range: 26-65) per 1,000 offspring. The mean relative risk was 0.82 (range: 0.53-1.01) compared with offspring of women with Type 1 diabetes, and 3.83 (range: 2.53-5.49) compared with the background population. A positive association was described between the prevalence of congenital heart defects and the maternal glycated haemoglobin level, but not with medical treatment.

CONCLUSIONS: The risk of congenital heart defects among offspring of women with Type 2 diabetes was comparable to that of offspring of women with Type 1 diabetes and almost four times higher than in the background population

The number of pregnant women with Type 2 diabetes has increased substantially in recent decades and, in some countries, it now exceeds the number of pregnant women with Type 1 diabetes [1].

While it is well described that the risk of congenital malformations is increased by at least two-fold in offspring of women with Type 1 diabetes [2], data on offspring of women with Type 2 diabetes are scarcer. The most common congenital malformations are heart defects, both in offspring of women with diabetes and in the background population [3]. Congenital heart defects (CHD) often have significant clinical implications for the offspring and thus a major impact on the whole family. Whether the risk of CHD in offspring of women with Type 2 diabetes is comparable to the risk in offspring of women with Type 1 diabetes has only been sparsely investigated [1, 4], and reviews exploring this topic could not be identified in the literature. A strong positive correlation between glycaemic control and the prevalence of congenital malformations, specifically CHD, has been described among offspring of women with Type 1 diabetes [5]. The association between congenital malformations and hyperglycaemia is poorly understood, but hyperglycaemia may induce oxidative stress and cell-membrane damage, causing apoptosis and thereby disturbing organogenesis [5, 6]. Animal studies have indicated that the developing heart is particularly sensitive to hyperglycaemia [7, 8].

The aim of this review was to estimate the prevalence of CHD in offspring of women with Type 2 diabetes compared with offspring of women with Type 1 diabetes and offspring of the background population.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. However, several items were not applicable for this review, i.e. the study

KEY POINTS

- The risk of congenital heart defects among offspring of women with Type 2 diabetes was comparable to that of offspring of women with Type 1 diabetes and almost four times higher than the risk in the background population.
- The mean prevalence of congenital heart defects in the offspring of women with Type 2 diabetes was 44 per 1,000 offspring.
- These findings emphasise the importance of pregnancy planning in women with Type 2 diabetes.
- More research into the pathophysiology and predicting factors of congenital heart defects in offspring of women with Type 2 diabetes is warranted.

SYSTEMATIC REVIEW

1) Center for Pregnant Women with Diabetes, Rigshospitalet
2) Faculty of Health and Medical Sciences, University of Copenhagen
3) Department of Endocrinology, Rigshospitalet
4) Steno Diabetes Center
5) Department of Obstetrics, Rigshospitalet, Denmark

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was not based on a review protocol and statistical analysis was not conducted.

The review was based on a search for all population- or region-based cohort studies including offspring of women with Type 2 diabetes published from January 2007 to February 2018. The PubMed, Embase and Cochrane databases were searched using basically the following Medical Subject Heading (MESH) terms (PubMed), Subject Heading terms (Embase) and text words: congenital abnormalities/congenital abnormality/congenital anomalies/congenital anomaly/congenital malformations/congenital malformation/cardiac anomalies/cardiac anomaly/congenital heart defect/congenital heart disease AND diabetes mellitus Type 2/pregnancy in diabetics/diabetes Type 2/T2DM/Type 2 diabetes/pre-gestational diabetes/pregestational diabetes/pre-pregnancy diabetes/non-insulin dependent diabetes/maternal diabetes AND pregnancies/pregnancy/pregnant/gestation.

The search was conducted on 1 February 2018. In total, 521 titles were identified in PubMed, 1,032 titles in Embase and 429 titles in the Cochrane database. Based on the titles, 120, 144 and 12 abstracts, respectively, were read by the first author.

The inclusion criteria were studies each including data on CHD in a minimum of 200 offspring of women with Type 2 diabetes from independent cohorts. The cohort size was a pragmatic choice made to minimise the uncertainty when evaluating the prevalence of rare events such as CHD in a relatively small sample size.

A total of seven studies with cohorts counting more than 200 offspring were identified. Hereof, three were Canadian cohort studies [9-11]. The national Canadian cohort study [9] with the longest observation period and the largest cohort size included the observation periods used in the two other Canadian studies [10, 11], indicating that these three cohorts were not independent. Thus, only five studies [9, 12-15] were included in this review.

The mean prevalence and mean relative risk of CHD for the included studies were calculated without weighting in relation to the size of the included populations.

RESULTS

The five studies in this review [9, 12-15] included an estimated total number of 23,845 offspring of women with Type 2 diabetes, ranging from 371 to 11,019 (**Table 1**).

The studies were mainly nation-wide cohort studies from Canada, Taiwan, Denmark and Norway [9, 13-15] that used the International Classification of Diseases, ninth version (ICD-9) or ICD-10 diagnosis codes, to identify the cases, but in one retrospective cohort study from the US, ultrasound heart examinations of all offspring born by women with diabetes was performed [12] (Table 1). Two studies [12, 13] included pregnancies that were terminated due to antenatally diagnosed foetal CHD, whereas the remaining three studies [9, 14, 15] did not report on this issue. Three studies [12-14] excluded CHD existing together with chromosomal anomalies, whereas the two remaining studies [9, 15] did not report on chromosomal anomalies. Three studies [12-14] included only singleton pregnancies, and two studies [9, 15] included all pregnancies, but data were given per offspring. Due to the heterogeneity of the studies, it was not possible to perform a formal meta-analysis and sub-analysis. Apart from excluding studies with less than 200 offspring, formal risk of bias within or between studies was not evaluated.

When the relative risk of CHD was not presented in the individual studies, it was calculated as the risk of CHD in offspring of women with diabetes divided with the risk of CHD in offspring of the background population [9, 14, 15]. When the prevalence was not given, it was estimated as the relative risk in offspring of women with Type 2 diabetes (2.53) times the prevalence in the backgrounds population (0.0102), corresponding to a prevalence of 25.8 per 1,000 offspring of women with Type 2 diabetes (Table 1) [13].

In three studies [9, 13, 15], the exact number of offspring of women with Type 2 diabetes was not given and therefore it was estimated in the following manner:

In the Canadian study [9], the prevalence of offspring of women with Type 2 diabetes increased from 0.0019 to 0.0047, and we estimated the average prevalence of offspring of women with Type 2 diabetes to 0.0033. With a total number of 2,839,680 offspring and a prevalence of offspring of women with diabetes of 0.0033, this equals 9,371 offspring of women with Type 2 diabetes.

In the Norwegian study [13], the prevalence of offspring of women with Type 2 diabetes increased from 0.00106 to 0.00271, and we estimated the average prevalence of offspring of women with Type 2 diabetes to 0.00189. With a total number of 914,427 offspring and a prevalence of offspring of women with Type 2 diabetes of 0.00189, this equals 1,728 offspring of women with Type 2 diabetes.

In the Taiwanese study [15], the total number of offspring of women with Type 2 diabetes was estimated as the total number of offspring with CHD among women with Type 2 diabetes (n = 628) divided by the prevalence of CHD in offspring of women with Type 2 diabetes of 0.9579, equalling 11,019 offspring.

The same calculations were performed for women with Type 1 diabetes (**Table 2**).

The mean prevalence of CHD among the offspring

of women with Type 2 diabetes was 44 (range: 26-65) per 1,000 offspring, corresponding to a relative risk of 3.83 (range: 2.53-5.49) compared with the background population and 0.82 (range: 0.53-1.01) compared with the offspring of women with Type 1 diabetes (Table 2).

There was a positive relation between glycated haemoglobin (HbA_{1c}) level and CHD prevalence in a mixed population from the US, where approximately two thirds of the women had Type 2 diabetes and one third of the women had Type 1 diabetes [12]. The prevalence of CHD was 83 per 1,000 offspring when HbA_{1c} concentration was ≥ 69 mmol/mol (8.5%) and 39 per 1,000 offspring when HbA_{1c} concentration was < 69 mmol/mol (8.5%) [12].

In the Danish study [14], the relative risk of CHD between offspring of women with Type 2 or Type 1 diabetes compared with the background population was approximately four, irrespective of the used treatment modality (diet alone, oral antidiabetic agents or insulin).

DISCUSSION

This review identified five papers including an estimated total of 23,845 offspring of women with Type 2 diabetes and found a mean prevalence of CHD in the offspring of 44 per 1,000 offspring. The risk of CHD among the offspring of women with Type 2 diabetes was at the level of the offspring of women with Type 1 diabetes and almost four times higher than the risk in the background population.

The prevalence of CHD varied from 25.8 to 64.7 per 1,000 offspring in the five included studies. The Danish [14] and the Canadian [9] studies used ICD-10 codes to identify CHD and reported similar results. The Taiwanese study [15] used the less specific ICD-9 codes, which might explain their comparatively higher prevalence of CHD [9, 14]. As expected, the highest

TABLE 1

The prevalence and relative risk of congenital heart defect in 22,746 women with Type 2 diabetes compared with the background population.

Country	Type of study	Offspring, n	Method for diagnosis of defect	Inclusion of terminated pregnancies	Prevalence/1,000 offspring	Risk in relation to background population	Reference
USA	Retrospective	371	Ante- and postnatal echocardiography	Yes	65	–	[12]
Canada	Population-based cohort	9,371[a]	ICD-10 codes	No	41	5.49	[9]
Taiwan	Nationwide Population-based cohort	11,019[b]	ICD-9 codes	No	58	3.49	[15]
Denmark	Nationwide Population-based cohort	1,356	ICD-10 codes	No	31	3.80	[14]
Norway	Nationwide Population-based cohort	1,728[a]	ICD-10 codes	Yes	26[c]	2.53	[13]
Total		23,845			44[d]	3.83	

ICD-X = International Classification of Diseases, Xth revision.

a) Average prevalence of women with diabetes/offspring × the total number of offspring.

b) Total number of offspring with congenital heart defects in the group of women with diabetes/the prevalence of congenital heart defect in offspring of women with diabetes.

c) Relative risk in offspring of women with Type 2 diabetes × the prevalence in the background population: 10.2/1,000.

d) Mean value.

TABLE 2

Relative risk of congenital heart defect in women with Type 2 (T2D)- or Type 1 diabetes (T1D).

	T2D		T1D			
Country	offspring, n	risk in relation to background population (A)	offspring, n	risk in relation to background population (B)	A/B	Reference
Canada	9,371	5.49	7,800	6.32	0.87	[9]
Taiwan	11,019	3.49	3,975	6.61	0.53	[15]
Denmark	1,356	3.80	2,845	3.75	1.01	[14]
Norway	1,728	2.53	4,092	2.95	0.86	[13]
Total	23,474	3.83[a]	18,721	4.91[a]	0.82[a]	

a) Mean value.

prevalence was reported in the American study [12], where the CHD diagnosis was based on a neonatal echocardiography from live births and included autopsies from miscarriages and terminated pregnancies.

Both the Canadian and the Danish study found that the relative risk of CHD in offspring of women with Type 2 diabetes was increased compared with the background population [9, 14]. This is in line with the assumption that the risk of CHD is increased when the foetus is exposed to elevated maternal glucose levels during organogenesis, as described in previous studies and reviews [16, 17]. Only one study [14] included data on the use of oral antidiabetic agents or insulin in relation to CHD and found no effect of treatment modality on the risk of malformations. Further studies are needed to elucidate the contribution of poor glycaemic control and treatment modality to the risk of CHD in offspring of women with Type 2 diabetes.

In the Danish [14] and Norwegian [13] studies, the different types of CHD were evaluated, and all specific CHD phenotypes were associated with maternal pregestational diabetes mellitus (relative risk ranges 2.74-13.8 and 1.73-6.60, respectively).

A positive association between maternal HbA_{1c} level in early pregnancy and the prevalence of CHD among the offspring of women with Type 2 and Type 1 diabetes was found [12]. This is in line with findings in animal models [7, 8]. Two studies [13, 14] explored the relation between glycaemic control and CHD using surrogate markers of elevated glycaemic levels as episodes with hospitalisation for acute diabetic complications such as ketoacidosis [14] or development of large-for-gestational-age in infants [13]. Both studies [13, 14] found positive associations with a higher prevalence of CHD. Women with Type 2 diabetes often have better glycaemic control than women with Type 1 diabetes [4, 12, 18, 19], but the risk of CHD is largely comparable in the offspring of women with Type 2 and Type 1 diabetes [9, 13, 14]. This could indicate that other risk factors influence the prevalence of CHD in women with Type 2 diabetes, i.e. a higher BMI and maternal age, ethnicity, lack of folic-acid supplementation and a poorer macro- and micronutrient intake, factors that are often associated with a lower socioeconomic status [4, 18-20].

The strength of this study is the large sample size counting more than 23,000 offspring of women with Type 2 diabetes, 18,000 offspring of women with Type 1 diabetes and data from offspring in the background population from various parts of the world. Furthermore, the literature search was conducted systematically in the PubMed, Embase and Cochrane databases and included both MESH terms (PubMed and Cochrane), subject headings (Embase) and text words. To clarify what could have caused the variation in the prevalence and the relative risks, it was described in detail how the studies differed, i.e. terminated pregnancies, chromosomal defects and diagnostic methods.

It is a limitation that only studies published in the past ten years were included. Extending the search period would likely have revealed more studies, although the further back the search dates, the fewer studies differentiate between Type 2 diabetes and Type 1 diabetes. Based on a pragmatic judgement when planning this review, only studies with a minimum of 200 offspring of women with Type 2 diabetes were included. We did this to limit bias on the prevalence of CHD. This possibly excluded some studies, but only one study [12] included 371 women, and the remaining four studies each included more than one thousand offspring of women with Type 2 diabetes, which makes the assessment of the prevalence of CHD more precise. The included studies were heterogeneous with respect to method of diagnosis of CHD and whether terminated pregnancies were included or not. These factors could affect the prevalence estimates. Due to heterogeneity of the studies, it was not possible to perform a formal meta-analysis and sub-analysis.

CONCLUSIONS

The risk of CHD among offspring of women with Type 2 diabetes was comparable to the risk in offspring of women with Type 1 diabetes and it was almost four times higher than the risk in the background population. This calls for an enhanced focus on pregnancy planning in women with Type 2 diabetes and warrants more research into the pathophysiology and predicting factors of CHD.

CORRESPONDENCE: *Elisabeth R. Mathiesen*. E-mail: elisabeth.reinhardt.mathiesen@regionh.dk

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