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ORIGINAL RESEARCH

Long-Term Cardiovascular Health After Pregnancy in Danish Women With Congenital Heart Disease. A Register-Based Cohort Study Between 1993 and 2016

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BACKGROUND: Little is known about the impact of pregnancy on long-term cardiovascular health in individuals with congenital heart disease (CHD). We aimed to determine if giving birth in patients with CHD is associated with higher risk of long-term cardiovascular morbidity.

METHODS AND RESULTS: We studied a cohort of 1262 individuals with CHD giving birth (live or still) from 1993 to 2015 using Danish nationwide registers. We randomly sampled a comparison cohort matched on age of women with CHD who had not given birth at the time. We balanced the 2 cohorts on baseline demographic (eg, education) and clinical variables (eg, CHD severity) using inverse probability of treatment weighting. Individuals were followed for critical (eg, heart failure), other cardiovascular morbidity (eg, arrhythmia), and cardiac surgery/interventions after pregnancy. Individuals were followed for median 6.0 years (interquartile range 3.2–9.2). Among individuals giving birth the incidence rate per 1000 person-years was 1.6, 10.0, and 6.0 for critical and other cardiovascular morbidity and cardiac surgery, respectively. There was no overall difference in risk of neither critical and other cardiovascular morbidity nor cardiac surgery among individuals who gave birth and individuals who did not; adjusted hazard ratios (aHR) were 0.74 (95% CI, 0.37–1.48), 0.88 (95% CI, 0.65–1.19), and 0.78 (95% C,I 0.54–1.12), respectively. However, individuals with obstetric complications had a higher long-term risk of other cardiovascular morbidity (aHR, 1.85; 95% CI, 1.07–3.20).

CONCLUSIONS: Giving birth seemed not to be associated with a higher risk of long-term cardiovascular morbidity among women with CHD. However, individuals having obstetric complications had a higher risk of other cardiovascular morbidity in the long term.

Key Words: congenital heart disease ■ long-term cardiovascular health ■ obstetric complications ■ pregnancy

An increasing proportion of individuals with congenital heart disease (CHD) complete a pregnancy.[1–3] Some of these individuals will experience cardiac and obstetric[4–6] complications related to pregnancy and childbirth and some of the offspring will be at higher risk of neonatal complications.[7–9] However, pregnancy is well tolerated in the short term among most individuals with CHD. Different risk calculators are available for the prediction of the risk related to pregnancy[10–13] but do not assess potential risk after pregnancy. Nevertheless, the burden on the cardiovascular system both during pregnancy and delivery might have long-term implications for the heart and cardiovascular system.[14]

Only a few studies have assessed the association between pregnancy and long-term cardiovascular outcomes among individuals with CHD.[15–24] The knowledge is primarily based on small[15,17,18,20–23]

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CLINICAL PERSPECTIVE

What Is New?

- We show that completing a pregnancy did not seem to be associated with a higher risk of long-term cardiovascular morbidity among women with congenital heart disease.
- However, the subgroup of individuals having obstetric complications during pregnancy had a higher long-term risk of other cardiovascular morbidity.

What Are the Clinical Implications?

- Identification of individuals with congenital heart disease at risk of obstetric complications during pregnancy might also identify individuals at higher risk of long-term cardiovascular morbidity after pregnancy.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
IPTW	inverse probability of treatment weighting

and lesion-specific[17,20,23] studies with short follow-up[15,16,19,21,22] and/or lack of a nonpregnant comparison group,[15,16,18,19,22] making it difficult to assess if changes are due to pregnancy per se or a natural consequence of the CHD.

Among the few studies with a nonpregnant comparison group some lesion-specific studies have reported an association between pregnancy and short-term but not long-term deterioration in right ventricle function,[17] adverse effect of long-term cardiac outcomes,[23] and an increased need for cardiac interventions.[20] Among studies with individuals with a broader group of women with CHD 1 study found no association between pregnancy and cardiac events or heart function 1.5 years after delivery.[21] However, a recent study found an increased risk of adverse cardiovascular health 4.7 years after pregnancy.

Thus, it still remains unclear to what extent completing a pregnancy has an impact on long-term cardiovascular health among individuals with CHD. Consequently, clinicians are challenged when advising individuals with CHD, who are considering pregnancy. A better understanding of how completing a pregnancy influences long-term cardiovascular health among individuals with CHD is therefore essential.

We examined cardiovascular morbidity after delivery in a nationwide cohort of individuals with CHD. Because of the increased cardiac-vascular volume overload during pregnancy, childbirth, and the postpartum period we hypothesized that individuals with CHD who give birth will have a higher risk of long-term cardiovascular morbidity as compared with women with CHD who do not give birth.

METHODS

Setting and Design

In Denmark, all citizens have free access to health care and are assigned a unique identification number, which enables individual-level linkage across national registries.[25,26] We conducted a nationwide registry-based cohort study with data from the Danish National Patient Register[27,28] and the Danish Medical Birth Register.[29,30] We included individuals with CHD giving birth (ie, delivery cohort) and a 1:1 age-matched cohort of women with CHD who had not given birth at date of matching (ie, comparison cohort). Data will not be made available to other researchers for the purpose of reproducing the results because this would be a violation of the Danish General Data Protection Regulation and Data Privacy Regulation by Statistics Denmark.

Participants

The source population for the study was all women born between 1977 and 2000 diagnosed with a CHD between 1977 and 2015. Information about CHD was obtained from the Danish National Patient Register, which is a population-based administrative register holding information on all hospital admissions since 1977 with diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*) before January 1, 1994 and *Tenth Revision* (*ICD-10*) thereafter.[27,28] All women with a diagnosis of CHD (*ICD-10*, Q20-Q26; *ICD-8*, 746–747) between 1977 and 2015 were included except *ICD-10* Q26.5–Q26.6 and *ICD-8* 746.7 and 747.5–747.9, which are not specific for CHD. To increase the positive predictive value of the diagnosis of CHD, we excluded individuals with unspecific diagnoses using an algorithm previously described.[31] Hence, a diagnosis of atrial septal defect was excluded if given at ages <2 months without an associated operation code, a diagnosis of congenital stenosis of aortic valve was excluded if given at ages >40 years etc (for more details see Appendix in[31]). Based on the available information CHD was categorized into simple, moderate, and complex based on the modified World Health Organization criteria.[13] Individuals with more than 1 diagnosis were categorized according to the more severe diagnosis. Diagnoses included in each category are displayed in Table S1.

Delivery Cohort

The cohort of individuals giving birth was identified by linkage to the Danish Medical Birth Register[29,30]

and the Danish National Patient Register[27,28] where all both live and stillbirths are registered. Information about miscarriages and abortions was not available and the delivery cohort therefore constituted women giving birth only. Deliveries until 2014 were identified in the Danish Medical Birth Register and deliveries (live and stillbirths) in 2015 were identified in the Danish National Patient Register as a primary *ICD-10* diagnosis of O80–84. Individuals were included in the delivery cohort at the date of their first delivery (index date). The cohort of individuals giving birth was further categorized into women with and without obstetric complications during pregnancy, defined as gestational hypertension, preeclampsia, and/or gestational diabetes.

Comparison Cohort

From the source population of women with CHD we sampled a comparison cohort. Individuals in the comparison cohort were assigned an index date corresponding to the date of delivery. For each individual who gave birth we randomly sampled 1 age-matched (±1 year) woman who, at the index date, had not given birth and was alive. The comparison cohort was sampled using replacement.

Cardiovascular Morbidity

Information regarding cardiovascular morbidity after delivery was obtained from the Danish National Patient Register.[27,28] We divided the cardiovascular outcomes into 3 groups in order to distinguish between severe and less severe long-term morbidity: (1) critical cardiovascular morbidity (heart failure, aortic dissection, and cardiac arrest); (2) other cardiovascular morbidity (atrial arrhythmia, valvular heart disease, and ischemic heart disease) and (3) cardiac surgical or transcatheter interventions. We included all hospital contacts with a primary or secondary diagnosis of these diseases/procedures (see Table S2 for ICD codes) registered after the index date.

Statistical Analysis

Propensity score weighting was used to statistically balance the delivery cohort with the comparison cohort on all measured background characteristics.[32] A propensity score was estimated using probit regression including demographic and clinical variables listed in Table 1 with exception of age, on which we matched. Assessment of baseline characteristics was made before the estimated date of start of pregnancy (index date-280 days) or corresponding date for comparison women. Balance on baseline characteristics after inverse probability of treatment weighting (IPTW) was assessed using standardized mean differences.

Individuals were followed from the date of index until date of event, death, emigration or December 31, 2016 whichever came first. All analyses were conducted with the delivery cohort as an overall group as well as divided into individuals with and without obstetric complications during pregnancy. The crude cumulative incidence proportion of the 3 outcomes was computed and plotted separately according to delivery. Because of privacy regulation by Statistics Denmark, data were aggregated so each step on the plot contained at least 5 observations. Incidence rates of the 3 outcomes were calculated per 1000 person-years. Cox proportional hazards regression models with IPTW and robust variance estimation[32] were used to estimate the association between completing a pregnancy and long-term cardiovascular health. In all analyses we examined cardiovascular outcomes on an intention-to-treat basis during follow-up.[33] A woman in the comparison cohort could give birth during follow-up. In this case, she was enrolled in the delivery cohort and matched with a comparison woman; however, she was not censored from the comparison cohort. The censoring of these women may share common causes with our outcome of interest through the exposure (delivery) and the censoring would therefore be informative.[33–35] IPTW analyses were restricted to women with propensity scores within common support.[32] The proportional hazard assumption was evaluated visually using log-log plots. The associations between completing a pregnancy and long-term cardiovascular health was reported as crude hazard ratio (HR) and adjusted HR (aHR) with 95% CI.

Sensitivity Analyses

To examine the robustness of our results several sensitivity analyses were carried out. First, all analyses were conducted using Poisson regression of number of cardiovascular events as outcome with logarithm of follow-up time as offset and weighted by IPTW to assess the sensitiveness of proportional hazard assumptions. Also, analyses were conducted after trimming of the most extreme weights (first and 99th percentile) and with the propensity score specified using a missing indicator approach.[36] To examine the influence of not censoring women from the comparison cohort if they subsequently gave birth, we also conducted the analyses with censoring at time of delivery.

Lastly, to examine if completing more pregnancies was more detrimental as compared with completing 1 pregnancy, we designed a cohort study within the delivery cohort. We constructed a cohort of individuals who gave birth more than once. The date of the second delivery was used as index date and a comparison woman who had given birth only once at the given date was sampled with replacement. However, becuase most women gave birth more than once the

Table 1. Characteristics of Delivery and Age-Matched Nondelivery Comparison Cohort With and Without Inverse Probability Weighting

	Without inverse probability weighting				With inverse probability weighting				
	No delivery n=1262		Delivery n=1262		No delivery n=1244		Delivery n=1248		Standardized mean differences
Age (median and IQR)	26.0 (22.5–28.9)		26.0 (22.6–29.0)		26.2 (22.6–29.1)		25.7 (22.3–28.7)		
Income* (median and IQR)	133 649 (80 797–179 750)		144 398 (88 199–197 493)		137 954 (84 705–186 408)		136 720 (82 613–189 385)		0.00
Educational level†, n (%)									
Low	363	(29.0)	317	(25.2)	341	(27.4)	340	(27.2)	0.00
Medium	494	(39.5)	474	(37.7)	483	(38.8)	484	(38.8)	0.00
High	395	(31.5)	467	(37.1)	420	(33.8)	424	(34.0)	0.00
Severity, n (%)									
Simple	761	(60.3)	810	(64.2)	788	(63.3)	785	(62.9)	−0.01
Moderate	390	(30.9)	331	(26.2)	344	(27.6)	350	(28.0)	0.01
Complex	111	(8.8)	121	(9.6)	112	(9.0)	113	(9.1)	0.00
Mean annual number of hospital contacts‡, n (%)									
0	979	(77.6)	765	(60.6)	862	(69.3)	862	(69.1)	−0.01
>0 to 0.3	93	(7.4)	204	(16.2)	142	(11.5)	146	(11.7)	0.01
>0.3 to <1	107	(8.5)	211	(16.7)	159	(12.7)	157	(12.6)	−0.01
≥1	83	(6.6)	82	(6.5)	81	(6.5)	83	(6.6)	0.01
Prior cardiac surgery, n (%)	513	(40.7)	432	(34.2)	463	(37.2)	464	(37.2)	0.00
Heart failure, n (%)	80	(6.3)	49	(3.9)	58	(4.7)	60	(4.8)	0.01
Prior hypertension, n (%)	29	(2.3)	17	(1.4)	22	(1.8)	23	(1.9)	0.01
Prior atrial arrhythmia, n (%)	23	(1.8)	6	(0.5)	9	(0.7)	11	(0.8)	0.02
Prior diabetes, n (%)	17	(1.4)	12	(1.0)	13	(1.0)	13	(1.1)	0.01
Prior renal, n (%)	20	(1.6)	14	(1.1)	17	(1.3)	17	(1.3)	0.00

Values are numbers and percentage unless otherwise stated. IQR indicates interquartile range.
*2 missing.
†14 missing.
‡Yearly average number of contacts during the 5 years prior pregnancy or corresponding date for comparison women.

comparison cohort consisted of 37% women who were included in both cohorts and we therefore did not continue with the analysis.

In order to derive the CHD cohort data management was done using SAS software (version 9.4; SAS Institute Inc, Cary, NC). All analyses were performed using STAT/IC software (version 15.0; StataCorp LP; College Station, TX).

Missing Data

The amount of missing data was low and women with missing data on covariates were therefore dropped before estimation of the propensity score (0.63%; n=16).

Ethics

The study was approved by the Danish Data Protection Agency (2015-57-0008, no.16/48885). In Denmark, written informed consent or ethical approval is not required for register-based studies. All data were provided by Statistics Denmark and because of their data privacy regulation, data with <5 individuals per cell were not reported.

RESULTS

A total of 1262 individuals gave birth at least 1 time during the study period (see study flow in Figure 1). Among the individuals giving birth 116 individuals had obstetric complications during pregnancy. The final IPTW analysis sample included a total of 2492 individuals. In the delivery cohort 730 individuals (58%) gave birth more than once during the study period whereas the rest remained first-time mothers throughout the study period. Most first-time mothers gave birth in the last 3 years of the study period (2013–2015). A total of 1.7% deliveries were twins or triplets and 1% were stillbirths. Among liveborn singletons 9.1% were preterm births (<37 weeks of completed gestation) and 6.9% of the children were born with a low birth weight (<2500 g) (based on fetal outcome data until 2014).

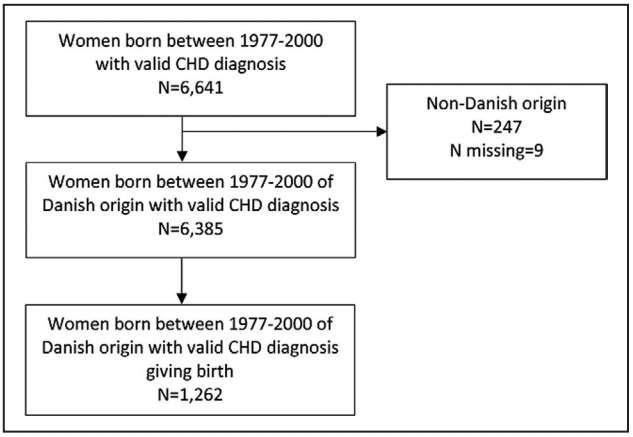

Figure 1. Study flow.
CHD indicates congenital heart disease.

The mean age at index date was 25.9±4.2 years. Statistically differences in baseline characteristics existed between the delivery cohort and the comparison cohort regarding history of cardiac surgery, heart failure, and atrial arrhythmia; educational level; number of hospital contacts; distribution of CHD severity; and income. After IPTW adjustment, the balance in baseline characteristics in all variables were improved and all standardized mean differences were below 0.02. Table 1 shows baseline characteristics without and with IPTW.

Median (interquartile range) follow-up time for critical cardiovascular events, other cardiovascular morbidity and cardiac surgery was 6.3 (3.5–9.5), 6.0 (3.2–9.2), and 6.1 (3.4–9.3) years, respectively. The overall proportion of critical cardiovascular events, other cardiovascular morbidity, and cardiac surgery was 1.4%, 7.3%, and 4.8 %, respectively. The number of all-cause deaths was low (n=13). Information on cause of death was available for 6 individuals, of whom <5 was due to cardiovascular disease. Most individuals with a given cause of death was included in the critical outcome as they were hospitalized with a critical diagnosis immediately before death.

Long-Term Cardiovascular Morbidity

The crude hazard ratios and the adjusted hazard ratios of critical and other cardiac morbidity as well as cardiac surgery are shown in Table 2. In general crude and IPTW analyses were similar. There were 14, 85, and 53 events of critical and other cardiovascular morbidity and cardiac surgery, respectively, corresponding to an incidence rate per 1000 person-years of 1.6, 10.0, and 6.0 among individuals giving birth. Overall, there was no difference among women giving birth and not giving birth for either critical and other cardiovascular morbidity or cardiac surgery; aHRs were 0.74 (95% CI, 0.37–1.48), 0.88 (95% CI, 0.65–1.19), and 0.78 (95% CI, 0.54–1.12), respectively. However, for individuals who had obstetric complications during pregnancy there was a higher risk of other cardiovascular morbidity with an aHR of 1.85 (95% CI, 1.07–3.20). For cardiac surgery this association was insignificant (aHR, 1.32;

Table 2. Hazard Ratios of Long-Term Critical Cardiovascular Morbidity, Other Cardiovascular Morbidity, and Cardiac Surgery

	N events/N women	Incidence rate per 1000 person-years	Crude HR	aHR*
Critical cardiovascular morbidity†				
No delivery	20/1262	2.3	1 (reference)	1 (reference)
Delivery (all)	14/1262	1.6	0.68 (0.34–1.34)	0.74 (0.37–1.48)
Other cardiovascular morbidity‡				
No delivery	100/1262	12.1	1 (reference)	1 (reference)
Delivery (all)	85/1262	10.0	0.83 (0.62–1.11)	0.88 (0.65–1.19)
Delivery (complications)§	15/116	20.7	1.66 (0.97–2.86)	1.85 (1.07–3.20)
Delivery (without complications)	70/1146	9.0	0.75 (0.55–1.02)	0.79 (0.57–1.09)
Cardiac surgery/intervention				
No delivery	69/1262	8.2	1 (reference)	1 (reference)
Delivery (all)	53/1262	6.0	0.74 (0.51–1.05)	0.78 (0.54–1.12)
Delivery (complications)§	7/116	9.2	1.13 (0.52–2.45)	1.32 (0.59–2.93)
Delivery (without complications)	46/1146	5.7	0.70 (0.48–1.02)	0.73 (0.50–1.07)

aHR indicates adjusted hazard ratio; and HR, hazard ratio.
*Inverse probability weighting based on propensity score.
†Heart failure, aortic dissection, and cardiac arrest.
‡Atrial arrhythmia, valve disease, and ischemic heart disease.
§Hypertension, preeclampsia, and/or gestational diabetes.

95% CI, 0.59–2.93) whereas the number of events was too low to conduct any subgroup analyses for critical cardiovascular morbidity. When all cardiovascular outcomes were analyzed together the HR of any long-term cardiovascular morbidity was 0.77 (95% CI, 0.61–0.97). For the subgroup of individuals having obstetric complications during pregnancy the HR was 1.46 (95 %CI, 0.93–2.29).

Cumulative incidence curves of the different cardiovascular outcomes in the delivery and the comparison cohort are shown in Figure 2, with exception of critical cardiovascular morbidity where number of events was too few to show graphically. In general, the cumulative incidence was similar between women giving birth and women not giving birth in the years after delivery. However, after a couple of years the cumulative incidence started to diverge with a tendency of a lower cumulative incidence in the delivery cohort for all 3 outcomes (Figure 2). However, among individuals having obstetric complications during pregnancy the cumulative incidence was higher throughout follow-up for both other cardiovascular morbidity and cardiac surgery.

Sensitivity Analyses

Analyses conducted using Poisson regression of incidence rates weighted by IPTW gave essentially the same results. Differences in estimates were <0.03. Trimming of the most extreme weights (first and 99th percentile) resulted in exclusion of 48 individuals but did not affect the estimates. Using a missing indicator approach when specifying the propensity score as opposed to exclusion of the missing observations did not affect the estimates either. Censoring individuals from the comparison cohort when giving birth revealed the same pattern as for the main analyses, however, with slightly lower HRs (see Table S3).

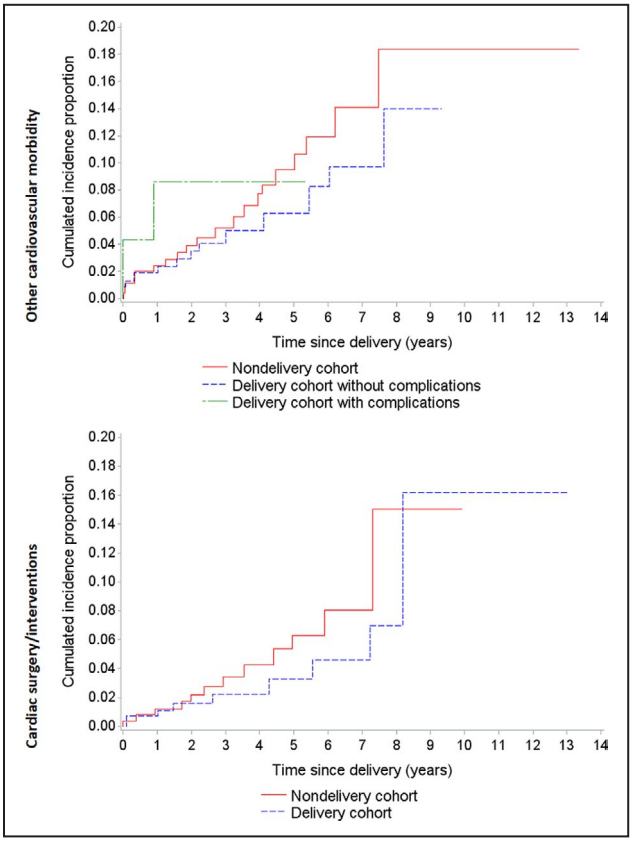

Figure 2. Cumulative incidence curves of other cardiovascular morbidity (upper) and cardiac surgery (lower) according to delivery.
For other cardiovascular morbidity the delivery cohort are subgrouped into women having obstetric complications (hypertension, preeclampsia, and/or gestational diabetes) during pregnancy, and women not having obstetric complications during pregnancy.

DISCUSSION

In this nationwide cohort study among the general population of women with CHD, completing a pregnancy did not seem to be associated with a higher risk of cardiovascular morbidity in the long term. However, in the subgroup of individuals who had obstetric complications during pregnancy, the risk of long-term cardiovascular morbidity seemed to be higher.

Our results are in line with the results by Uebing et al.[21] who did not find an association between pregnancy and, for example, New York Heart Association function class after 1.5 years. However, in a recent study, Son et al.[24] found a higher risk of long-term adverse cardiac outcomes following pregnancy. To our knowledge no other studies have included a broad group of individuals with CHD who have given birth and compared them to a group of women with CHD who had not given birth. Despite differences in the main findings in the studies the estimated association in the study by Son et al. is similar to the association in our study among individuals with obstetric complications. Future research needs to elucidate the relationship between both pregnancy, obstetric complications, and long-term cardiovascular health among women with CHD in order to inform counseling regarding potential long-term implications of pregnancy in individuals with CHD.

Our results indicate that individuals with CHD having obstetric complications during pregnancy have a higher long-term risk of cardiovascular morbidity as compared with women not giving birth. In the general population of pregnant women it is well known that obstetric complications during pregnancy are associated with adverse long-term cardiovascular health.[37–40] We defined the subgroup of individuals having obstetric complications as gestational diabetes, preeclampsia, and/or gestational diabetes as they are common

obstetric complications and were present before start of follow-up (date of delivery). However, fetal outcomes such as preterm birth and infants born small for gestational age, which is also more common among women with CHD,[6–9,41] have also been associated with adverse long-term cardiovascular health in the general population of pregnant women.[37–39] It is, however, debated whether the pregnancy per se causes the higher risk of obstetric complications or the pregnancy unmasks a predisposing condition and the pregnancy thereby acts as a cardiovascular stress-test.[37,39,40] Regardless of the mechanism, identification of individuals with CHD at risk of obstetric complications during pregnancy might also identify individuals at higher risk of long-term cardiovascular morbidity after pregnancy. This is of importance because CHD itself is associated with a 3 times higher risk of cardiovascular disease in later life.[42]

The point estimates for all 3 cardiovascular outcomes are <1, albeit nonsignificant. This might, as discussed later, be due to confounding; that individuals with CHD not having children are sicker. However, it could also reflect a protective effect of pregnancy. A recent Norwegian study has demonstrated that pregnancy is associated with a reduction of blood pressure that persists over decades and suggests that this reduction might be of clinically importance for the risk of long-term cardiovascular disease.[43] Furthermore, becoming a parent might influence health behavior in a positive way[44] that might also lower the risk of long-term cardiovascular disease.

Strengths and Limitations

Using national population-based registries enables inclusion of all women diagnosed with a CHD in Denmark, as opposed to including those from specialized clinics, which limits the risk of selection bias. This enables us to provide data on the association between pregnancy and long-term cardiovascular health among individuals giving birth in nonspecialized clinics. Further, the registries allow for full follow-up among all included individuals.[25] To limit the risk of misclassification of CHD all diagnoses of CHD were validated using an algorithm previously described.[7,8,31] Likewise, the positive predictive value of the included cardiovascular outcomes is in general high in the Danish National Patient Register for both cardiovascular diagnoses[27,45–47] and cardiac procedure and surgery codes.[48]

In our study we included individuals from more than 2 decades. During this period diagnosis and treatment of CHD[49,50] and cardiovascular morbidity in general have changed considerably over time. Likewise, lifestyle risk factors of cardiovascular morbidity as smoking and higher body mass index have changed.[51] However, because we age-matched the individuals we overcame this change over time because individuals who are compared have been born in the same year and therefore have been exposed to the same diagnosis and treatment of CHD, the same prevalence of cardiovascular morbidity, smoking etc.

We find the results to be robust because similar results were found when data were modeled using a Poisson regressions of incidence rates, and when individuals with extreme weights were excluded.

In the current study we were unable to determine the reason for individuals not to become pregnant. It might be that individuals in the comparison cohort are not pregnant because of infertility, recommendations not to become pregnant, or personal decision. Individuals who are foreseen to be at high risk during pregnancy and delivery may because of counseling decide not to become pregnant or pregnancy is simply contraindicated. In the present study this might result in confounding by indication. To handle that we used IPTW and succeeded in balancing the delivery and nondelivery cohort on a comprehensive number of demographic and clinical variables. However, although we tried our best to account for the potential difference between women who gave birth and those who did not, unmeasured confounders likely remain. For example, when individuals were categorized into severity based on diagnoses alone we were not able to account for variability in severity within a given diagnosis because no information on clinical examination was available. Information about use of medication and more detailed clinical data could potentially further help balance the delivery and nondelivery cohort. This type of data, however, was not available for the current study. In case the comparison cohort is sicker than the delivery cohort at baseline, even after IPTW, we will underestimate an association between pregnancy and long-term cardiovascular morbidity.

Because pregnancy might affect the cardiovascular system already in early pregnancy[52] the cardiovascular system might be affected by pregnancy among individuals whom we were not able to identify because we did not have information about abortions and miscarriages. This information would in particular be of concern among individuals who experience repeated pregnancy losses. We would expect such a bias to lead toward null.

Because we restricted the study population to women born in 1977 and onwards, to allow for full information about hospital contacts, the cohort of women was relatively young. Therefore, despite the use of nationwide registries with the potential of long-term follow-up the median follow-up was only between 6.0 and 6.3 years. Because some of the outcomes, for example, ischemic heart disease, are more common in later life caution should be taken if results are extrapolated to later life.

Previous studies have shown that parity per se is not a factor regarding risk of cardiac complications during pregnancy[53,54]; however, the effect of parity on long-term cardiovascular health has not been addressed. We did not have statistical power to test if completing more pregnancies was more detrimental as compared with completing only 1 pregnancy regarding long-term cardiovascular health. However, because most of the individuals who had only 1 child during the study period mainly gave birth in the end of the study period, this could indicate that many individuals will be having more than 1 child. Because a higher risk after a subsequently pregnancy would have implications for both the mother, the firstborn, and the father it is a highly relevant question to answer. Further research, therefore, should be powered to investigate the association between completing more pregnancies and long-term cardiovascular morbidity.

In the current study it was not possible to stratify the analysis based on CHD severity. However, the severity was included in the propensity score and was thereby accounted for. Because most individuals in the study had a simple CHD and occurrence of long-term cardiovascular complications is relatively infrequent, we cannot ascertain that individuals with moderate and complex CHD do not have a higher risk of long-term cardiovascular morbidity and this need further investigation. As time passes and the cohort of individuals giving birth becomes larger and older a stratified analysis by severity might be possible.

CONCLUSIONS

In conclusion, completing a pregnancy did not seem to be associated with a higher risk of long-term cardiovascular morbidity among women with CHD. However, the subgroup of individuals having obstetric complications during pregnancy had a higher long-term risk of other cardiovascular morbidity.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Distribution of congenital heart disease. Modified from Regitz-Zagrosek et al.[13]

	Disease	ICD-10 code	ICD-8 code	n*
Complex/high risk	Univentricular heart (Complex, mWHO III-IV)	Q201, Q202, Q234, Q226, Q204		41
	Eisenmenger syndrome (Complex, mWHO IV)	Q218A		<5[†]
	Pulmonary arterial hypertension (Complex, mWHO IV)	Q256, Q257		38
	Pulmonary atresia (Complex, mWHO II-IV)	Q255	74739	62
	Transposition of great ateries[‡] (Complex, mWHO III)	Q203	74619	62
	Truncus arteriosus (Complex, mWHO II)	Q200	74609	18
	Other disconnections (ccTGA, isomerisme etc.) (Complex, mWHO III)	Q205, Q208, Q209, Q241		18
Moderate/moderate risk	Atrio-ventricular septal defect (Moderate to complex, mWHO II-III)	Q212	74659, 74641	158
	Ebstein's anomalia (Moderate to complex, mWHO II)	Q225, Q224, Q228, Q229	74661	26
	Pulmonary valve stenosis (Simple to complex, mWHO I-III)	Q220, Q221	74663	162
	Tetralogy of Fallot (Moderate to complex, mWHO II)	Q213	74629	102
	Partly or totally abnormal pulmonary venous connection (Complex, mWHO I)	Q262, Q263, Q242		16
	Coarctatio of the aorta (Moderate to complex, mWHO II)	Q251	74719, 74729	154
	Infundibular right ventricle outflow tract obstruction (Moderate, mWHO II)	Q243		15
	Pulmonary valve regurgitate (Simple to complex, mWHO I-III)	Q222		14
	Subvalvular/supravalvular aortic stenosis (Moderate, mWHO II-III)	Q244, Q252, Q253		27
	Malformation of coronary vessels (ALCAPA, ARCAPA) (Moderate, mWHO II)	Q245		6
	Aortic valve disease (Simple to complex mWHO II-III)	Q230, Q231	74662, 74669	194
	Mitral valve disease (Simple to complex, mWHO II-III	Q232, Q233, Q238, Q239	74660	109
Simple/low risk	Atrial septal defect (Simple, mWHO I-II)	Q211	74649, 74640	568
	Ventricular septal defect (Simple, mWHO I-II)	Q210, Q214, Q218, Q219	74639	794
	Mild pulmonary stenosis (Simple, mWHO I)	Q223		5
	Ductus arteriosus (Simple, mWHO I-II)	Q250	74709	292

Other malformations in aorta (Right aortic arch, vascular ring) (Simple, mWHO I)	Q254		20
Malformations in large veins without hemodynamic Importance (Simple, mWHO I)	Q260, Q264 , Q268		10
Other specified congenital malformations of heart	Q248	74689, 74699	46

ICD-8: International Classification of Diseases, 8th Revision; ICD-10: International Statistical Classification of Diseases, Tenth Revision; mWHO: Modified World Health Organization

*Women might have more than one diagnosis.

† Exact n is not given due to data privacy policy. The exact number is known by the researchers and used in calculations.

‡ Women with TGA in childbearing age during the study period is predominantly treated with Mustard/Senning operation which is considered mWHO III-IV

Table S2. ICD-8 and ICD-10 diagnostic and procedure codes

PROPENSITY SCORE:		
	ICD-8	ICD-10
Cardiac surgery/interventions	302-329	KFA-KFM KFP KPD
Heart failure	4040 4001 4270 4271	I50
Hypertension	400-404	I10-I15
Arrhythmia	42793 42794	I48
Diabetes	249-250	E10-E11
Moderate to severe renal disease	403-404 580-584 59009 59319 75310-75319 792	I12-I13 N00-N05 N07 N11 N14 N17-N19 Q61
OBSTETRIC COMPLICATIONS:		
Gestational hypertension	63700	O13 O16
Gestational diabetes		O244
Preeclampsia	63703 63709 63799	O140-O142 O149-O159
OUTCOMES:		
Critical cardiovascular morbidity		
Heart failure	See above	See above
Cardiac arrest	4272-4277 4952 4962-7963	I46
Aortic dissection	441	I71
Other cardiovascular morbidity		
Valve disease	3941-3969 4241-4249	I34-I37
Ischaemic heart disease	410-414	I20-I259
Arrhythmia	See above	See above
Cardiac surgery/interventions		
	See above	See above

Table S3. Hazard ratios (HR) of critical cardiovascular morbidity, other cardiovascular morbidity and cardiac surgery after delivery. References are censored at delivery if giving birth.

	N events/N women	Incidence rate per 1000 person-years	Crude HR	aHR*
Critical cardiovascular morbidity†				
No delivery	18/1262	2.9	1 (reference)	1 (reference)
Delivery (all)	14/1262	1.6	0.51 (0.25-1.04)	0.53 (0.25-1.12)
Other cardiovascular morbidity‡				
No delivery	91/1262	15.3	1 (reference)	1 (reference)
Delivery (all)	85/1262	10.0	0.71 (0.53-0.96)	0.74 (0.54-1.02)
Delivery (complications) §	15/116	20.7	1.43 (0.83-2.47)	1.56 (0.90-2.72)
Cardiac surgery/intervention				
No delivery	54/1262	8.9	1 (reference)	1 (reference)
Delivery (all)	53/1262	6.0	0.63 (0.43-0.93)	0.65 (0.44-0.97)
Delivery (complications) §	7/116	9.2	0.98 (0.44-2.15)	1.11 (0.48-2.53)

HR: Hazard ratio

*Inverse probability weighting based on propensity score

†Heart failure, aortic dissection and cardiac arrest

‡Arrhythmia, valve disease and ischemic heart disease

§ Hypertension, pre-eclampsia and/or gestational diabetes