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Mortality in mothers after perinatal loss: a population-based follow-up study

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Objective To assess whether mothers who lost a child from stillbirth or in the first week of life have an increased overall mortality and cause-specific mortality.

Design A population based follow-up study.

Setting Data from Danish national registers.

Population All mothers in Denmark were included in the cohort at time of their first delivery from 1 January 1980 to 31 December 2008 and followed until 31 December 2009 or death, whichever came first.

Methods The association between perinatal loss and total and cause-specific mortality in mothers was estimated with hazard ratios (HR) and 95% confidence intervals (95% CI) calculated using Cox proportional hazards regression analyses.

Main outcome measures Overall mortality and cause-specific mortality.

Results During the follow-up period, 838 331 mothers in the cohort gave birth to one or more children and 7690 mothers (0.92%) experienced a perinatal loss. During follow-up, 8883 mothers (1.06%) died. There was an increased overall mortality for mothers who experienced a perinatal loss adjusted for maternal age and educational level, hazard ratio (HR) 1.83 [95% confidence interval (CI) 1.55–2.17]. The strongest association was seen in mortality from cardiovascular diseases (CVD) with an HR of 2.29 (95% CI 1.48–3.52) adjusted for CVD at time of delivery. We found no association between a perinatal loss and mortality from traumatic causes.

Conclusions Mothers who experience a perinatal loss have an increased mortality, especially from CVD.

Keywords Mortality, perinatal loss, stillbirths.

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Introduction

Parents who have suffered the loss of a child in the perinatal period face a comprehensive mourning process. The impact of a perinatal loss may lead to loss of self-esteem[1,2] and loss of future dreams,[3] and relatives may be reluctant to talk about the dead child, leading to emotional isolation.[2,4] Grief research shows that traumatic and untimely death increases the risk of poor physical and mental health and such factors will often apply to losing a child in the perinatal period.[5] Mothers are usually more affected than fathers.[3,5,6] Although the death of a child is especially stressful,[7,8] only few studies have assessed mortality in bereaved parents.[5,9–12] We identified one study assessing mortality in mothers experiencing a perinatal loss, reporting a 40% increased mortality adjusting for maternal morbidity in pregnancy.[13] Most studies on loss of older children report increased parental morbidity and mortality from both natural and traumatic causes.[9,12,14–19]

For mothers who lose a child in the perinatal period there may be more than one mechanism underlying an increased mortality (Figures 1 and 2). Stressful life events can affect the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in adverse physical health,[20] and thus increase mortality from natural causes such as cardiovascular diseases (CVD). Cardiologists

even talk about the 'broken heart syndrome'.[21] Furthermore, psychological stress might lead to adverse lifestyle or high-risk behaviours, which could affect mortality[22–26] and also raise the risk of traumatic death, such as suicide[22,27] (Figure 1). The hypothesis (H1) of perinatal loss being hazardous to the mother's health *per se* has not been addressed earlier. Alternatively, the stillbirth or neonatal loss could be caused by the same maternal metabolic abnormalities or adverse lifestyle underlying the development of fatal illness in the mother later in life (Figure 2). For example, pre-eclampsia is known to be associated with CVD later in life.[28] Likewise, CVD in pregnancy is associated with restricted placental perfusion, intrauterine growth restriction and preterm birth and thus increased perinatal mortality.[29] This hypothesis (H2) of perinatal loss and mortality in mothers, stemming from the same underlying mechanisms, has previously been addressed in one study.[13]

The objective of this study was to assess mortality in mothers with a perinatal loss and to explore the two hypotheses of underlying mechanisms (Figures 1 and 2). Cause-specific mortality was assessed to explore possible contributing pathways to mortality in mothers with a perinatal loss and pre-existing maternal medical conditions were included in the analyses to explore shared causes.

Methods

This population-based cohort study comprised mothers with live births or stillbirths in Denmark, identified in the National Birth Register. Perinatal death is defined as stillbirth or death within the first week of life. The mother entered the study cohort on the date of her first childbirth (live- or stillborn, singleton or multiples) during the study cohort period, which began in 1 January 1980 and ended after 31 December 2008. Mothers who had a perinatal loss were considered exposed. In Denmark, reported stillbirths comprised intrauterine death after gestational age (GA) 28 weeks until April 2004 and intrauterine death after GA 22 weeks from April 2004. Perinatal deaths also included live-born children who died within the first week of life. All births were linked to the mother via the unique personal identification number which is given to all citizens in Denmark. Follow-up time ended 31 December 2009 or when the mother died, whichever came first. Our primary outcomes were all-cause mortality and cause-specific mortality. Information on cohort members (date of birth, date of death, cause of death and covariates) was obtained from the National Birth Register, the Causes of Death Register, the National Patient Register and Statistics Denmark. Natural causes of death were categorised as cancer (ICD8 1400-2099 and ICD10 C00-99), cardiovascular diseases (CVD), including all circulatory diseases and coronary heart diseases (ICD8 3900-4299 and ICD10 I00-99), renal diseases (ICD8 5800-5999 and ICD10 N00-N39) and all other natural causes. Traumatic causes were categorised as vehicle accidents (ICD8 8100-8230 and ICD10 V01-89), suicide (ICD8 9500-9599 and ICD10 X60-84) and other traumatic causes. The National Board of Health and The Danish Data Protection Agency approved the study.

The association between perinatal loss and total and cause-specific mortality in mothers was estimated with hazard ratios (HR) and 95% confidence intervals (95% CI) calculated using Cox proportional hazards regression analyses. As mortality is rare in mothers within a follow-up time of 29 years after first delivery (occurrence below 10%), we can interpret the HR as a relative risk.[30] The mother was the study unit of the analyses and could contribute with one or more births within the follow-up time. A multiple birth with one or more dead babies was counted as a perinatal loss. We used the mother's age as underlying timescale, thereby controlling for maternal age in all analyses and the women became at risk (delayed entry) on the date of their first childbirth. The time a mother was in the unexposed group started from the date of her first live childbirth until she experienced a perinatal loss or died, or follow-up ended, whichever came first. The time mothers who experienced a perinatal loss were in the exposed group

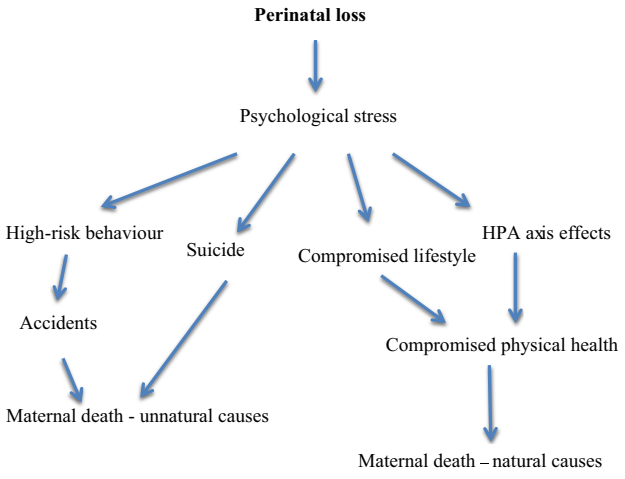

Figure 1. Possible pathways contributing to mortality in mothers who experience perinatal death.

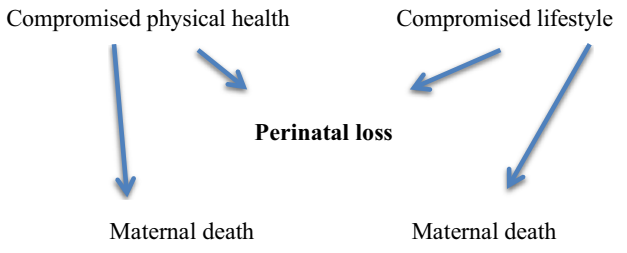

Figure 2. Possible shared causes behind both perinatal death and mortality in the mothers who experienced perinatal loss.

started from the date of their first perinatal loss; the date she gave birth to a stillborn baby or the date she gave birth to a live-born child who subsequently died within the first week of life. Mothers who died on the same calendar day that they gave birth were excluded from the analyses to exclude mother–child pairs dying from traumatic deliveries. Follow-up time was from less than a year to 30 years with a mean follow-up time of 15 years (SD 8 years). Educational level at first delivery (9–12 years/13–16 years/more than 17 years) was included in the adjusted analyses. We assessed total mortality and cause-specific mortality. We conducted stratified analyses to assess whether mortality differed between: (1) mothers who had a stillbirth and mothers who had a loss in the first week of life, and (2) mothers who lost their first child and mothers who lost a child of higher parity.

To assess possible shared mechanisms between perinatal loss and mortality in mothers after perinatal loss, we added pre-existing maternal conditions in two separate models: (1) mortality from all natural causes adjusted for diagnoses of pre-eclampsia, cancer or CVD at time of delivery and (2) mortality from CVD adjusting for a diagnosis of CVD at time of delivery.

To assess whether the association between perinatal loss and mortality in mothers changed over time, we conducted analyses in three age strata; <40, 40–49 and >50 years of age.

For Cox regression analyses, the proportional hazards assumption was evaluated by comparing estimated log-minus-log survivor curves over the categories of variables investigated. STATA version 11.1 was used in processing of data.

Results

Table 1 shows the characteristics of the 838 331 mothers in the cohort (column percentages unless otherwise specified).

In the study cohort, 7690 mothers (0.92%) experienced a perinatal loss: 6658 (0.79%) mothers gave birth to one stillborn or more and 1089 mothers (0.13%) gave birth to one or more children who died within the first week of life. Twenty-two mothers who died at the same date they gave birth were excluded. During the follow-up period, 8883 cohort mothers (1.06%) died. There was an 80% increased overall mortality for mothers who experienced a perinatal loss (HR 1.87; 95% CI 1.58–2.20) compared with unexposed mothers, corresponding to an excess absolute mortality among mothers with a perinatal loss of 87 women.

In the stratified analyses, mortality was assessed in specific strata of mothers with a perinatal loss (using mothers with no loss as the reference group). Comparable mortality was observed in mothers with stillbirths and mothers with an early neonatal loss; 156 (2.34%) mothers with stillbirths died within follow-up time (HR 1.87; 95% CI 1.58–2.22) and seven (0.64%) mothers with an early neonatal loss (HR 1.67; 95% CI 0.76–3.77). There was a higher mortality in multiparous women than primiparous women; 67 (1.95%) mothers who lost their first child died within the follow-up time (HR 1.43; 95% CI 1.10–1.86) and 88 (2.18%) mothers who lost a child of higher parity (HR 2.32; 95% CI 1.88–2.88).

Table 1. Characteristics of 838 331 mothers in the cohort (column percentages unless otherwise specified) in Denmark who gave birth from 1 January 1980 to 31 December 2008 to one or more live or stillborn children. Numbers (percentages) or means (standard deviations)

	Perinatal loss	No perinatal loss
Perinatal loss (row percentages)	7690 (0.92%)	830 641 (99.08%)
Perinatal loss in first delivery	4006 (52%)	NA
Perinatal loss in subsequent delivery	3684 (48%)	NA
Mean age at first delivery*	26 (SD 5)	27 (SD 5)
Mean age at maternal death	37 (SD 8)	41 (SD 9)
Educational level at first delivery		
9–12 years of education	3381 (45.73%)	311 767 (40.37%)
13–16 years of education	3812 (51.56%)	433 848 (56.17%)
More than 17 years of education	201 (2.72%)	26 752 (3.46%)
Diagnosed before or at first delivery		
Cancer	20 (0.26%)	2520 (0.30%)
Cardiovascular disease	151 (1.96%)	11 478 (1.38%)
Renal disease	986 (12.82%)	85 683 (10.32%)
Diagnosed at any pregnancy; pre-eclampsia	1439 (12.9)	56 896 (6.8)
Mean time from 1st delivery, death, years*	12 (SD 8)	15 (SD 7)

*First delivery of live-born or stillborn.

Table 2 shows the overall and cause-specific mortality, adjusted for maternal age and educational level. No associations were seen between perinatal loss and mortality by traumatic causes or cancer, whereas CVD and other natural causes were strongly associated with a perinatal loss. Including maternal educational level did not affect any of the analyses remarkably.

To assess the hypothesis of possible shared causes behind both perinatal death and mortality in the mothers who experienced a perinatal loss (Figure 2), we made two analyses adjusting for pre-existing maternal conditions: (1) mortality from all natural causes adjusting for diagnoses of cancer, CVD or pre-eclampsia at time of delivery, finding an adjusted HR of 1.93 (95% CI 1.62–2.30), and (2) mortality from CVD adjusting for a CVD diagnosis at the time

Table 2. Overall and cause-specific mortality in Danish mothers with or without a perinatal loss between 1980 and 2008, followed through 2009, adjusted for maternal age and educational level

	Perinatal loss			
	Yes, *n* (%)	No, *n* (%)	HR (95% CI)*	HR (95% CI)**
Overall mortality	163 (2.12)	8720 (1.05)	1.87 (1.58–2.20)	1.83 (1.55–2.17)
Suicide	2 (0.03)	519 (0.06)	0.42 (0.11–1.69)	0.43 (0.11–1.71)
Motor accident	4 (0.05)	325 (0.04)	1.29 (0.48–3.45)	1.32 (0.49–3.54)
Other unnatural causes	7 (0.09)	525 (0.06)	1.44 (0.69–3.05)	1.41 (0.67–2.96)
All unnatural causes	13 (0.17)	1369 (0.16)	1.02 (0.59–1.77)	1.02 (0.59–1.77)
Cancer	34 (0.44)	3210 (0.39)	1.14 (0.80–1.62)	1.14 (0.80–1.63)
Cardiovascular disease	22 (0.29)	849 (0.10)	2.85 (1.85–4.40)	2.68 (1.72–4.17)
Renal disease	0 (0)	28 (0.00)	NA	NA
Other natural causes	94 (1.22)	3264 (0.39)	2.72 (2.16–3.41)	2.67 (2.12–3.37)
All natural causes	150 (1.95)	7351 (0.88)	2.04 (1.71–2.43)	2.00 (1.68–2.19)

*Adjusted for maternal age.
**Adjusted for maternal age and educational level.
HR, hazard rate with 95% confidence interval (CI), mothers with a perinatal loss compared with mothers without a perinatal loss.

of delivery and finding only a small reduction in the risk estimates, adjusted HR 2.34 (95% CI 1.52–3.61).

To assess whether the association between perinatal loss and mortality in mothers changed over time, we repeated our analysis of overall mortality in three age strata. In the age group of mothers <40 years of age we found an HR of 2.55 (95% CI 2.06–3.16), in mothers 40–50 years of age an HR of 1.47 (95% CI 1.10–1.95) and in mothers over 50 years of age an HR of 0.89 (95% CI 0.46–1.71). The differences were statistically significant, $P < 0.001$.

Discussion

Main findings

Our large population-based cohort study showed 83% increased overall mortality in mothers who lost a child in the perinatal period adjusted for educational level. This is in accordance with precious findings.[13] The mortality from all natural causes of death was twice as high as in women who did not experience a perinatal death, with a 2.3-fold increased risk from CVD specifically and a 1.9-fold increased risk from all natural causes, whereas we found no increased mortality from traumatic causes or from cancer.

Strength and limitations

Due to the unique personal identification number used in Denmark and mandatory reporting to the National Birth Register, the Causes of Death Register and the National Patient Register, we were able to identify and follow all likely cohort members. We do not have information about emigration, but emigration would probably not be associated with the exposure and hence not introduce bias in the study.

We divided the natural causes of death into cancer, CVD and renal disease but refrained from further subgrouping due to small numbers within diagnoses. We present the numbers of renal diseases because renal disease was strongly associated with mortality in mothers with stillbirth in a previous study.[13]

We did not have information on all diagnoses at the time of pregnancy and therefore were only able to adjust for cancer, CVD and pre-eclampsia. We did not have information on cause of perinatal death.

Interpretations

For all natural causes of death there was statistically significant excess mortality in mothers with a perinatal loss (HR 2.04 [95% CI 1.71–2.43]). These findings are consistent with results from a large Danish population-based study with 18 years of follow-up assessing mortality in parents who lost an older child, reporting increased mortality from natural causes in mothers bereaved of a child between 0 and 18 years of age (HR 1.43 [95% CI 1.24–1.64]).[9]

We found no increased mortality from traumatic causes, in contrast to two former Danish studies that found increased mortality in parents who lost an older child from traumatic causes such as motor vehicle accidents and suicide.[9,12] In one of the previous studies the strongest associations were observed shortly after the loss for both mothers and fathers.[9] The other Danish register-based study reported a 50% increased risk of suicide in parents who lost a child between 0 and 18 years of age.[12] Also in the latter study the risk was remarkably higher shortly after the loss. In phenomenological studies, mothers who lost a child at any age describe ambivalence about their own mortality, suggesting some possible motivations behind suicide.[31] For

these bereaved mothers dying was anticipated as alluring in two ways: as a release from the pain of loss and as a reunion with the deceased. Having obligations to other children, however, moderated the desire for death and had a preventive effect on suicide.[31] Quantitative research also reports that responsibility for other children reduces the risk of maternal suicide.[12] In our study, 521 mothers committed suicide but we found no association between suicide and perinatal loss (HR 0.42; 95% CI 0.11–1.69). The lack of an association in our study between a perinatal loss and suicide might be explained by the timing of the loss, as mothers who lose a child in the perinatal period may have other small children for whom they are responsible or they may anticipate having an opportunity to become pregnant again in contrast to the parents in the former Danish studies who experienced the loss of older children.

Two Israeli studies found no overall association between the death of a child and mortality in the bereaved parents,[10,11] but they did report an increased mortality among single mothers[10] and a worse survival in fathers who had a cancer diagnosis.[11] Methodological and study population differences might explain the inconsistencies with findings from Danish studies: the follow-up period in both Israeli studies was only 10 years, the deceased children were older, 18–40 years of age, and most of the children had died in war.

We found only one study specifically assessing mortality in 595 multiparous women who experienced a stillbirth with a follow-up time of 29–41 years, reporting a 40% increased mortality after adjusting for socio-demographic variables, maternal diseases at pregnancy, placental abruption, and pre-eclampsia.[13] The investigators also assessed cause-specific mortality and reported risk estimates for all circulatory causes (adjusted HR 1.70 [95% CI 1.02–2.84]) and renal causes (HR 4.70 [95% CI 1.47–15.0]) (in our cohort no mothers with a perinatal loss died from renal causes). The investigators concluded that stillbirth may be a risk marker for premature mortality among parous women due to metabolic abnormalities underlying both the stillbirth and the mortality in the mother (as in Figure 2) and did not address the possibility that the loss of a child might in fact have affected the health of the mother and thereby caused a higher mortality.

We found increased mortality from CVD among mothers with perinatal loss that was more than twice the risk even after adjusting for a prior maternal CVD diagnosis at time of delivery. There are several potential explanations. The exposure to the loss of a child in the perinatal period could induce chronic stress with feelings of fatigue and demoralization and in consequence increased reactivity of the fibrinogen system and of platelets, both of which increase the risk of myocardial infarction.[20] Alternatively, the reverse could be the case, with mothers with CVD having an increased risk of adverse birth outcomes and CVD being associated with preterm birth and intrauterine growth restriction.[29] Controlling for a diagnosis of CVD at time of delivery did not remove the strong association between having experienced a perinatal loss and eventually dying from CVD, indicating that the loss of a child in the perinatal period may have an independent effect on maternal cardiovascular health. Nevertheless, the higher mortality from CVD among mothers with a perinatal loss may still be due to metabolic abnormalities underlying both the stillbirth and the mortality in the mother but not yet diagnosed at delivery.

Other natural causes of death than cancer, CVD and renal diseases were also associated with a more than two-fold increase in mortality. This again supports both of our hypotheses.

We performed analyses in strata of ages as a marker of time since loss, revealing a decreasing association with increasing age, perhaps due to a rise in competing causes of death with increasing age or a 'healthy worker' selection by age, specifically more vulnerable women being more susceptible to their perinatal loss.

The study was carried out in Denmark and as it was population-based with almost no loss to follow-up, the results can be generalised to populations with similar socio-demographic backgrounds and healthcare systems.

Conclusions

In all probability, the increased mortality following perinatal loss in Danish mothers has multiple underlying mechanisms, supporting both the postulated hypotheses. We were not able to adjust for all co-morbid conditions at the time of pregnancy and hence cannot make firm conclusions. However, based on clinical experience, a perinatal loss most often affects the mother profoundly and the long-term independent effect on maternal health needs to be considered in follow-up studies with more detailed data. Clinically, mothers who have had a perinatal loss should receive adequate care and follow-up that addresses both the psychological stress and potential compromised physical health.

Disclosure of interests

None.

Contribution to authorship

All authors contributed substantially to the design of the study, the interpretation of the data and the revision of the draft. Chunsen Wu cleaned and prepared the data. Erik Parner designed the statistical analysis plan. Tine Brink Henriksen contributed with clinical expertise and Diana Schendel participated in developing the design. Dorte Hvidtjørn is the guarantor, she performed the statistical analyses,

drafted the work and all authors critically revised the draft several times and finally approved the submitted draft.

Details of ethics approval
Not applicable because we used data from Danish Health registers.

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