Selective fertility –
the examples of perinatal death and preeclampsia

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ABSTRACT

Introduction. Studies of foetal or perinatal losses are hampered by the fact that a woman's pregnancies are not independent events, making traditional "cross sectional" design and analyses difficult. A complicating issue is the mechanism of "selective fertility". Selective fertility is the tendency for a woman to replace a perinatal loss with a new pregnancy until the desired number of children is attained. We wanted to evaluate the effects of selective fertility related to perinatal deaths and to preeclamptic pregnancies, using data covering four decades. ***Material and Methods.*** We use data from the Medical Birth Registry of Norway, covering the years 1967-2006, altogether 2.3 million births, organized into 1.1 million sibships with the mother as the unit of analysis. ***Results.*** Following a perinatal death, the continuation to a next pregnancy is higher then after a live birth, and this elevation of 'fertility' has increased over time. After two perinatal losses, the continuation is more then doubled. On the other hand, continuing to a next pregnancy is reduced after a preeclamptic pregnancy, and after two preeclamptic pregnancies the reduction corresponds to 25%. ***Conclusions.*** These two examples show that samples of births are strongly hampered by self-selection to pregnancy. Therefore, data organized into sibships should be obligatory for studies in perinatal epidemiology. Perinatal epidemiology is in need for analytical designs that account for dependencies in data.

INTRODUCTION

Members of the same family are associated with each other genetically, and through shared biological and environmental factors. Knowledge about how these inter-individual dependencies modify the risk of different pregnancy outcomes is important for clinicians when providing clinical care in pregnancy, and for researchers when analysing causes of and risk for different adverse pregnancy outcomes.

Such adverse outcomes may be miscarriages and perinatal losses. Several studies have shown that women who have had a miscarriage (first-trimester loss) are at increased risk of another loss in subsequent pregnancies[1-3]. Recurrence risk is also found for perinatal losses. A majority of studies concludes that the risk of experiencing a perinatal loss is higher in women with a prior stillbirth or neonatal loss than in women with surviving infants[4-7].

Studies of foetal or perinatal losses are thus hampered by the fact that a woman's pregnancies are not independent events, making traditional "cross sectional" design and analyses difficult. A complicating issue is the mechanism of "selective fertility". Selective fertility is the tendency for a woman to replace a perinatal loss with a new pregnancy until the desired number of children is attained. James described this tendency as an "artefact" which biased the effect of age and parity when studying risk of miscarriage[8]. He found that women with recurrent miscarriages, had more pregnancies, and at higher ages than women who did not lose their foetuses. Wilcox and Gladen[1] modeled the risk of miscarriage as being influenced by three main factors:

1) an "individual" risk, constant for each woman, but differing between women;
2) the effect of selective fertility, which leads to a spurious effect of parity; and
3) a "true" effect of maternal age.

An alternative to the traditional cross sectional design and analysis is the longitudinal cohort design, where births are linked to their mothers. In previous studies, using data from the Medical Birth Registry of Norway (MBRN) for the period 1967-1984, we organized data in maternal sibships by means of the national identification numbers, so that information from the previous pregnancy could be used to predict future risk, a situation which is similar to the clinical situation[9,10]. We found that women who lost their first birth in the perinatal period had a six times higher risk of perinatal loss in their second pregnancy relative to women without a first loss. After three previous losses the relative risk was 17[9]. The effect of age was dependent on parity, with a strong association between age and perinatal mortality for primigravidae, but not for parous women.

In these previous studies we showed the degree to which selective fertility distorts perinatal mortality when data are organized in a "cross sectional" way, especially in the higher parities. Analyses carried out in

the traditional cross sectional way exaggerated the risk of perinatal death at the third birth by 8-20%, and at the fourth birth by 18-27%[10].

Selective fertility can more generally be thought of as the tendency to adjust reproduction after the outcome of previous pregnancies. For instance, it has been shown that following a twin pregnancy, further reproduction is markedly reduced[11]. On the other hand, as mentioned above, reproduction is in general increased following a perinatal loss[10].

Few studies in perinatal epidemiology focus on selective fertility, most likely because of lack of relevant data to pursue reproduction issues in available epidemiological data. To study reproduction following previous pregnancy outcome, data on sibships are needed. It is now nearly 20 years since our earlier work on selective fertility and the distortion of perinatal mortality. During these years, both perinatal mortality and reproduction have decreased in developed countries. Therefore, more up-to-date analyses on the effect of selective fertility are needed.

Our aim in the present study was to assess the effects of perinatal deaths on further reproduction using data covering 40 years, 1967-2006. Preeclampsia has been tightly linked to perinatal death during the first years of MBRN, less so in current years[12]. We therefore also wanted to evaluate the effects of preeclamptic pregnancies on reproduction during these years. An additional aim of the study was to illustrate the importance of such data when analyzing reproduction issues in general.

MATERIAL AND METHODS

Population based data on pregnancies and births covering the years 1967-2006 were used for the analyses, as available in the MBRN (- year 2006 not complete). All 2.3 million births during these years were linked to their mothers providing sibships with the mother as the unit of analysis, and with a total of 1.1 million units. Of these, 938,207 mothers had their first birth in 1967 or later, and we used these mothers for the analyses. In total, 24% had only one pregnancy, 46% had two, 23% had three, and 7% had four or more pregnancies. Plural births were included when counting continuation to another pregnancy, however all families with plural births in the previous pregnancies were excluded from analyses of recurrence risk and fertility, since plurality in itself is known to dramatically reduce further reproduction.

We compared continuation rates to a next pregnancy according to the outcome of the previous pregnancies for the outcomes perinatal death and preeclampsia. We calculate continuation ratios comparing rates for women with losses relative to rates for women without losses (similarly following preeclampsia). These are analysed as 'risk ratios'.

Primarily, we studied the data using 5-year periods (Figures 2 and 3), however for Figure 1 we divided the period of first births in two time categories, 1967-81 and 1982-96, providing sufficient time for follow-up to a next pregnancy for women in the last period. Additional analyses were also done for the last time period, 1997-2006.

The analyses were performed using SPSS for Windows, version 14.0, and STATA, version 9. Continuation ratio (risk ratio) estimates were obtained through generalized linear models (log link), as available in STATA.

RESULTS

Perinatal deaths and further reproduction

In figure 1 we show risk of a perinatal loss in 1st to 4th births, with continuation to a next pregnancy conditioned on perinatal loss in the previous pregnancies.

The figure shows that the tendency to replace a child that dies in the perinatal period has not decreased from the first to the second time period (1967-81 and 1982-96). The continuation to a next pregnancy after a perinatal loss slightly increased (from 90% to 91%), while the continuation to a next pregnancy following a surviving child was somewhat reduced (from 85% to 83% – thus continuation ratio increased from 1.06 to 1.10, i.e. the continuation rate was 6% (first period) and 10% (second period) higher following a loss then following a livebirth.

Reproduction changed markedly after two surviving children: continuation to a third pregnancy was reduced to 42% and 43% in the two periods. With a loss of either the first or the second child, the continuation to a third pregnancy almost doubled: close to 80%.

The continuation rate to a fourth pregnancy with three previous surviving children, was 25% and 21% in the two periods, 1967-84 and 1985-96, respectively. Thus, this baseline rate was slightly reduced. With one previous loss, the continuation varied between 36% and 39% when the loss was not the most recent pregnancy. However, the continuation to a fourth pregnancy was 68% and 61%, respectively, if the only loss was the third child. With two previous losses, the continuation was generally high and varied between 61% and 71% for all sequences, and in both periods.

Few women have three previous losses, and most of these were in the first period (44 of 57 women, 77%). In the first period, the continuation was 73%. Due to small numbers, the observed reduction in Figure 1 for 1986-96 data was not significant (p=0.20).

The continuation ratio (comparing women continuing to a second pregnancy after a loss relative to women with a surviving first birth) increased to 1.33 in the period 1997 to 2006. However, this estimate is not directly comparable with the previous two estimates due to lack of sufficient follow up time for the last years. The interval between pregnancies following a perinatal loss is shorter than following a livebirth. In our data the interval between 1st and 2nd births was
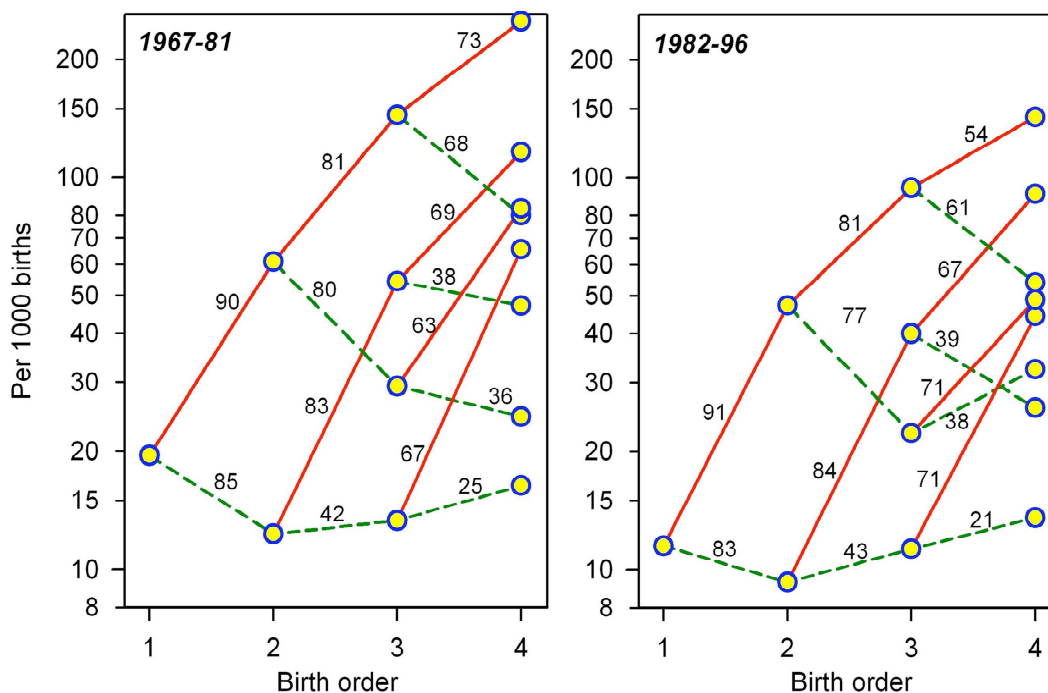
Figure 1. Risk for perinatal death and continuation to a next pregnancy, by outcome of previous singleton births, in two periods of 1st births (1967-81, 1982-96). All women are followed for reproduction to 2006. The numbers in the figure correspond to percent continuing to a next pregnancy. Solid line after a perinatal death, dashed line after a surviving child.

36.3 months following a livebirth, while 17.8 months following a perinatal death (27.3 and 8.9 months, respectively, from birth to conception).

In Figure 2 we show some simple results analyzing continuation ratios, using relative risk modeling. Results are by five-year periods, following 1st, and 1st and 2nd births. Due to insufficient follow-up, results for the last period(s) are not presented.

Perinatal deaths and recurrence risk

Figure 1 also shows recurrence risks of perinatal deaths for the three first singleton pregnancies. Although absolute perinatal mortality rates decreased from the first to the second time period in all birth orders, the relative risk of a recurrent loss in the second pregnancy (i.e. the risk of a loss for mothers with a first loss relative mothers whose first birth survived) did not decrease over time (RR = 4.9 in 1967-84 and RR = 5.1 in 1985-96). However, when comparing relative risks after three pregnancies, we observed a slight reduction.

From Figure 1 we also observe that the risk for another perinatal death to women with one previous loss, regardless of surviving children following the loss, will remain high throughout the reproductive career.

Preeclampsia and further reproduction

Recurrence of preeclampsia is known to be high[13,14], while continuation to a next pregnancy following a preeclamptic pregnancy has been less studied. We esti-

mated recurrence for preeclampsia in singleton pregnancies for 1st to 2nd pregnancies to be between 11 and 13 (OR-values), and for 2nd to 3rd pregnancies between 13 and 20.

In Figure 3 we show continuation to a next pregnancy following preeclampsia in the first pregnancy (panel A) and preeclampsia in both first and second pregnancies (panel B). Again, we divided the period of first births into 5-year periods. Following a first preeclamptic pregnancy there was a small, but significant, reduction in the chance of a second pregnancy. Following two preeclamptic pregnancies, the continuation to another pregnancy was clearly and consistently reduced compared to women without preeclampsia in either pregnancy.

Using rate ratio models, adjusting for period of birth, we found that the overall reduction in fertility following two preeclamptic pregnancies corresponded to a rate ratio (RR) of 0.75 (95% confidence interval 0.72-0.79). Further analyses of the continuation to a third pregnancy, adjusting for maternal age and period of birth (both in 5-year categories), confirmed the results: adjusted RR = 0.82 (95% C.I. 0.78-0.82).

DISCUSSION

Cross-sectionally derived data are the basis for most studies in perinatal epidemiology. Births rather then mothers are the units of analysis, since linkage of births to mothers is often not possible on a routine
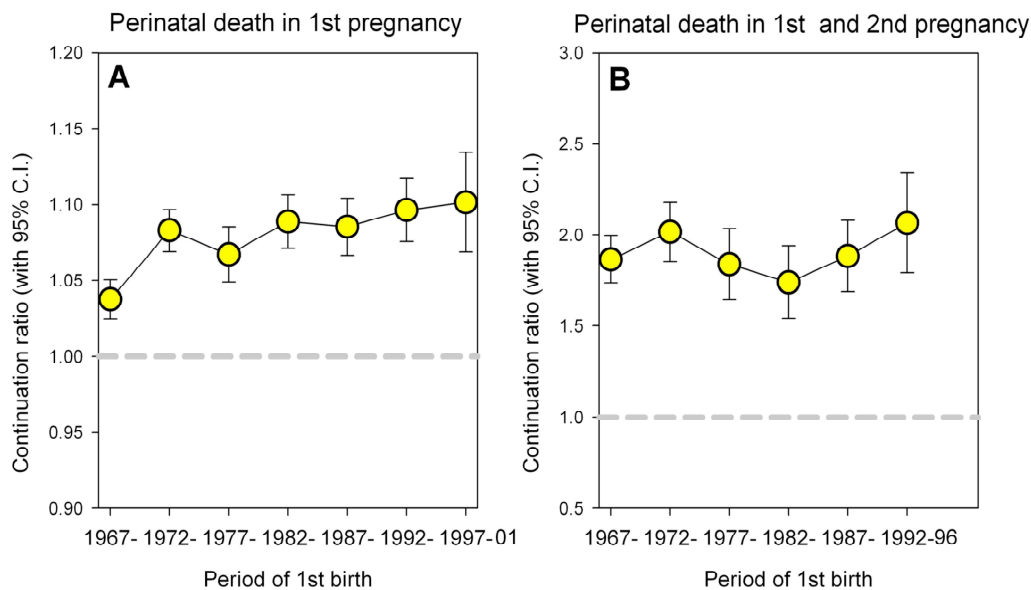
Perinatal death in 1st pregnancy

Perinatal death in 1st and 2nd pregnancy

Figure 2. Continuation to a next pregnancy after perinatal death, 1967-2006. All women are followed for reproduction to 2006.
Panel A: Ratio of continuing to a 2nd pregnancy, comparing women with a perinatal death in 1st birth with other women.
Panel B: Ratio of continuing to a 3rd pregnancy, comparing women with perinatal deaths in 1st and 2nd births with women without perinatal deaths.
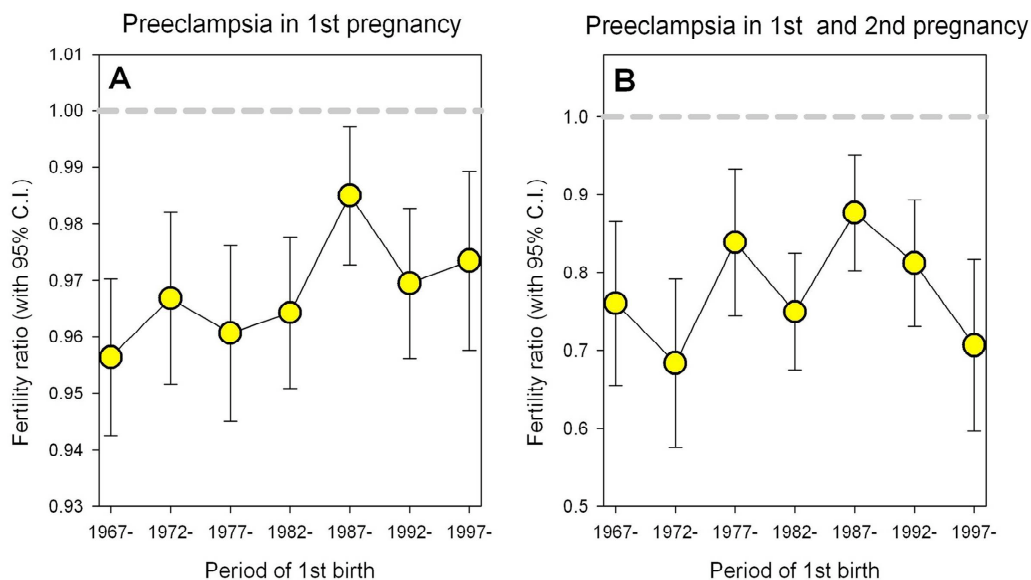
Preeclampsia in 1st pregnancy

Preeclampsia in 1st and 2nd pregnancy

Figure 3. Continuation to a next pregnancy after preeclampsia, 1967-2006. All women are followed for reproduction to 2006.
Panel A: Ratio of continuing to a 2nd pregnancy, comparing women with preeclampsia in 1st pregnancy with other women.
Panel B: Ratio of continuing to a 3rd pregnancy, comparing women with preeclampsia in 1st and 2nd pregnancy with women without preeclamptic pregnancies.

basis. With this study we show that cross-sectional data may lead to errors in interpretation. Data on reproduction, using the mother as the unit of analysis, holds unique qualities, shown here by studying reproduction following the outcome of previous pregnancies. A perinatal loss in the previous pregnancy increases further reproduction, and this "selective fertility" has not decreased during the 40 years time period of the MBRN. On the other hand, we find that preeclampsia is related to a reduced continuation to further pregnancies throughout the study period. Further, this effect seems to be independent of survival of the child (results not shown).

The retrospective design of many studies on recurrence of foetal or perinatal losses is another problem in this field, as data on previous pregnancy outcomes are

often based on the women's own report. Studies have shown that women who have experienced a perinatal loss tend to "forget" these losses, resulting in a discrepancy between results from retrospective and prospective studies on associations with previous losses[15,16]. By the present method, linking birth records to the mothers, such recall bias is avoided.

With the extension of the study period from 18 to 40 years we conclude that the tendency to replace previous losses is stronger in the second than in the first period. These two first periods (1967-81, 1982-96) are comparable in terms of follow-up length, while the third period (1997-2006) is not directly comparable with the two previous periods due to right truncation. However, enforcing the same truncation on the two previous periods and re-estimating the continuations, results seem to indicate that the force of selective fertility has increased by time. The general reproduction is reduced, so the net effect is that the continuation ratio (comparing families with previous losses with those without losses) has increased during these years.

In perinatal epidemiology, conclusions may be wrong or seriously biased if these effects of selective fertility are not accounted for. One example of such bias is the interpretation of parity-specific perinatal mortality where the higher risk observed at high parity is attributed to 'parity' or 'gravidity', while it to a large extent is due to the forces of selective fertility – since women who have lost their previous children will tend to have more pregnancies then other women. Due to selective fertility, combined with the high recurrence risks, studies based on strata of fixed sibship size[17,18] will in particular introduce confusion and bias – trading one artefact with another[19-21]. In our previous study we recalculated the parity-specific perinatal

mortality, adjusting for the forces of selective fertility[10]. Selective fertility, will give disproportionally many women with previous losses in the higher parity levels since recurrence of deaths is high. Due to these two mechanisms we will observe increased overall risk for perinatal losses in third and fourth pregnancies, leading to a spurious parity effect. In the study we adjusted these risks for maternal age and period of birth. Although fertility in general is reduced by increasing age, the selective fertility mechanisms lead to higher fertility ratios when age increases.

Also in a generational perspective, the studies of reproduction in subgroups of women and men has proved valuable[22,23]. A full understanding of recurrent pregnancy outcome between generations is not possible without an evaluation of the strong forces of selection between generations.

Selective fertility is a neglected topic in perinatal epidemiology. The contrasting effects we find for perinatal deaths and preeclampsia show the importance of studying variation in reproduction to understand biological and social selection to pregnancy. This variation in reproduction will, both due to conditions of the fetus (i.e. congenital malformations) as well as of the mother (i.e. diabetes), in different ways impact the total sample of births. Automatic selection of confounders in adjusted analyses for perinatal outcome, without a proper understand of the forces of selective fertility, will easily bias conclusions and lead 'into blind alleys'[21].

These two examples show that samples of births are strongly hampered by self-selection to pregnancy. Data organized into sibships should as often as possible be the source for studies in perinatal epidemiology. Also, perinatal epidemiology is in need for analytical designs that account for dependencies in data.

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