The effect of the Rh negative disease on perinatal mortality
Evidence from Skellefteå 1840-1900

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Abstract

Background The Rh-negative gene is a well known cause of perinatal mortality especially before there were any effective treatment. The Rh disease, that is caused by a Rh positive foetus carried by a Rh negative mother, leads to typical patterns of perinatal mortality with an increase of mortality with parity and mortality clustered in families. This effect has been largely neglected in earlier papers trying to explain mortality patterns in historic data.

Objectives This paper highlights the role of this gene in causing these patterns and tries to quantify the effect in a society with a large group of Rh-negative persons and no access to treatment.

Methods The risks of the Rh disease is approximately known from the medical literature. Knowing family sizes and the approximate share of Rh negative genes the "theoretical" patterns of perinatal mortality can be calculated and simulated. Comparing these figures with observed patterns of perinatal deaths the relative importance of Rh factor can be estimated. We have used data from 1840-1900 in the Swedish parish of Skellefteå where we have data on all births and their outcomes as well as good estimates of the Rh negative gene frequency.

Results The results show that the Rh gene is likely to have had an important role in perinatal mortality and the patterns with more dead at high parities and clustering explaining a relatively large part of these phenomenon in high Rh negative gene societies.

Conclusions The paper shows that the Rh-disease is an important factor in understanding mortality patterns. Its great effect on the patterns makes it necessary to take it into account when analysing other factors that can affect perinatal mortality patterns.

Contents

1 Introduction

The decline in mortality in younger age groups has contributed to most of the rapid increase in life expectancy that has taken place during the last centuries. Consequently, many researchers have focused on infant and child mortality in their search for explanations for the improved life expectancy. These scholars have proven the impact of many different factors for the decline, for example improved nutrition, sanitary measures, efficient medical treatment or better childcare. It is however obvious that not one single factor can explain it, but that instead the development was characterised by a complex web of influences.

Recently, several scholars have however pointed out that mortality is unevenly spread between families. Deaths tend to cluster within families. Das Gupta (1990) found in her study of infant mortality in India during the 1980's that a small proportion of families contributed to a large part of the deaths. In historical contexts, Brändström (1984) made the same observation in his thesis on infant mortality in 19th century Nedertorneå, a parish in northern Sweden neighbouring the Finnish border. Edvinsson et al. (2005) took up the theme in a study of death clustering of infant mortality in Skellefteå and Sundsvall region. About 10 % of families contributed to more than half of all infant deaths, while more than half of the families with as many as eight children did not experience any infant death. The analysis shows a clear family clustering. There were thus a specific group of vulnerable high-risk families. Furthermore, Lynch & Greenhouse (1994) has found a strong familial dependence in mortality. Previous infant deaths in the family were one of the main predictors for the death of a newborn child.

This means that many families even in a high mortality regime were successful when it comes to survival of their children, while other families were severely affected. What then characterised these high-risk families? Edvinsson et al. (2005) investigated possible characteristics of these high-risk families. Surprisingly, social class had only marginal effect. The variables that did matter were remarriages of the mother and stillbirths in the family. The first indicate family crisis, while the second points to a possible biological component.

It is such a biological determinant we analyse in this article as a possible important explanation for the patterns of perinatal deaths. That is Rh disease, i.e. a disease that appears in newborn children when the mother is immunized against the child due to incompatible blood groups. The Rh negative disease is in medical literature well-known as a major cause of perinatal deaths, especially before it could be treated in an effective way. However, in earlier studies concerned with perinatal deaths and the historical decline of infant mortality this factor has largely been neglected. In this article, we will study how the disease affects perinatal mortality in a society without efficient treatment. In order to do this, we use historical parish registers with individual records and simulation methods. In our analysis using expected and observed levels of perinatal mortality and stillbirths we address the following questions:

- To what extent does it contribute to the increase of perinatal mortality

with parity?

- How much of the clustering of perinatal and infant mortality can be ascribed to the disease?
- How large is the effect of reduced fertility on Rh disease?

We argue that this disease had significant effect on both the level and the clustering of infant mortality in general and on perinatal mortality in particular in the Skellefteå region in northern Sweden during the period 1815-1900. We thus need to consider more the potential impact of family clustering in our analysis of historical mortality patterns, together with social, economic, environmental, medical and behavioural factors.

2 Rh disease

2.1 Rh disease and demography

Rh disease and its history is of interest in itself, both in order to understand how the disease struck the population and the scientific struggle of finding treatments for the disease. Furthermore, even if effective preventive therapies for the disease now are available, the problem remains that many pregnancies with conflicting blood groups occur. Another question is the possible impact on demographic issues. A sceptic might argue that this is a marginal phenomenon without any practical demographic impact. We believe that such conclusions are completely wrong and we will briefly mention some motives for this statement.

A study of Rh disease deepens our understanding of historical infant mortality in general and perinatal mortality in particular. The decline of infant mortality in Sweden started around 1800, which is earlier than in most other countries. At that time, rates were very high even if the Swedish as well as Danish and Norwegian levels were low in international comparison (Edvinsson et al. 2008). Every fifth child died during their first year of life, a proportion that was higher in unsanitary places such as towns or among vulnerable children such as those born illegitimate. Within the first year, mortality was highest among the youngest infants, i.e. perinatal and neonatal mortality. We lack unfortunately national figures on the age components of infant mortality from the period before 1860, but in the period 1860-1866 neonatal mortality in Sweden was 47/1000. Mortality during the first week was 21/1000 and the first day 10/1000. Information on stillbirths have been registered from the middle of the 18th century, and even if we can be suspicious on how well they differentiated between stillbirths and early deaths in the beginning, the figures seem to be quite reliable. The given number of stillbirths in the 1860's together with a level of first week mortality for the period 1860-66 would give a level on perinatal mortality of approximately 50/1000 (SCB 1999).

A second aspect of Rh disease is that it can explain intergenerational transfers in infant and perinatal mortality. Family effects in mortality are not exclusively found among siblings, they have also been observed between generations Brändström et al. (n.d.). This is the case even after control of socio-economic position and living environment. One possible explanation for transfers when it comes to infant mortality is that child-care behaviour may be socialized between mother and daughter. Accordingly, we find this transfer primarily on the female side. Rh disease is however also a possible cause for intergenerational transfers of mortality. Obviously, Rh negative children to Rh negative mothers (when father is heterozygous) would survive while the Rh positive children would get the disease in sensitized mothers.

2.2 How the disease works

The specific pattern of the Rh disease can be understood by considering how the disease works. In a Rh positive person, the red blood cells have Rh protein

in the surface while a negative persons red blood cells do not. If a Rh negative person gets Rh positive blood in the blood stream he or she will be sensitized, making the immune system prepared to produce antibodies against Rh positive blood. If a mother is sensitized she will also damage the blood of a Rh positive foetus. The most common reason to be sensitised for a woman is because a previous pregnancy with a Rh positive foetus. Normally the pregnancy where the mother gets sensitized will neither damage the mother nor the child. The risk of perinatal mortality is about 50% with a sensitized mother.

This will create a typical pattern in perinatal mortality. The first child is not affected, since the mother is not sensitized yet. The sensitization takes place when blood from the foetus enters into the mother's blood stream, something that could occur during delivery, but also through spontaneous or induced abortion. This does however not take place in all the deliveries at risk. It is estimated that around 13% of all deliveries with the Rh conflict will lead to sensitization. If the mother was not sensitized during the first delivery, she again risked it when the second child was coming. Consequently, the more Rh positive children a Rh negative woman had, the larger the risk to eventually become sensitized. For those having eight children, we could expect every second woman in this risk group to be sensitized. When a woman once had become sensitized, all subsequent Rh positive children will catch the Rh disease or HDN (haemolytic disease of the newborn) as it also is called.

In a child with Rh disease, the immune system attacks and destroys its blood cells. This leads to complications as fetal hydrops, jaundice, anemia and other symptoms. Every second children is thus either stillborn or dies no later than after a couple of days if no effective treatment is available.

The characteristics of the disease thus create some specific patterns of demographic nature. First of all, the perinatal mortality related to Rh disease is greater in higher parities among siblings. This deviates from the typical u-shaped pattern in infant mortality, where the risk is highest for the first-born, lowest among the second- and third-born, to increase for every additional birth. An effect of the increasing risks in higher parities for Rh disease is that perinatal mortality is reduced when fertility declines and the number of siblings become smaller. An additional effect is that perinatal mortality tends to cluster in families.

In historical time, nothing could be done when a child got Rh disease. The disease was however observed early, but it was not understood as an entity in itself. The history of how medical science started to understand the disease and to find effective treatment can be said to have started in the 1930's, when Diamond and others described the disease in the blood of the newborn. When the Rh blood group was discovered in the 1940's, the progress towards understanding the disease began. During the 1950's, the researchers found that the disease was caused by immunization when Rh positive blood entered the blood system of the mother. From this time, therapies developed, first through blood transfusion, but later with anti-D immunoglobulin prophylaxis. It has now become praxis to control blood status of the parents during pregnancy in order to take the right measures. The disease is almost extinct in contemporary Europe,

but was a quite common cause for perinatal mortality in earlier times.

2.3 The distribution of the gene and the Rh disease

The appearance of the disease is dependent on the frequency of the blood group Rh negative. Without such mothers, there would be no risks of Rh disease. We do however not find the blood group all over the world; instead there are large geographical differences. It is mainly related to the white population of the world. In America, it is present in 15% of the Caucasian population, while only 1 % of those of Asian or native background have it. Some groups in Europe have a very large proportion of Rh negative in their populations. One example is the Basques where there is around 50%. In other parts of Europe, the proportion is around 15 %.

There are however other parts with comparatively many Rh negative persons. In a study of blood groups in Västerbotten, Beckman et al. (1972) found that the Rh negative individuals were quiet common in the northern parishes along the coast of the county, i.e. the parish Skellefteå and the surrounding parishes or the parishes investigated in this article. For those born in the early 20th century around 22% of the population were Rh negative. This makes the Skellefteå region an interesting study area.

3 Data

The analysis is performed on the 19th century Skellefteå region. This region has many advantages that make it interesting to analyse. As mentioned above, the Rh negative gene occurs frequently in the region. The region is also one of the regions where the Demographic data base has entered all information from the parish registers 1699-1900. It thus covers a long period where the possibility to follow individuals throughout life is good. The effects of migration on the data were limited, partly because the population remained fairly stable and partly because much of the movement that did occur did not result in a registered movement (i.e. crossing the parish border) due to the large geographical size of the parish.

Our data is taken from the Demographic Data Base. It contains information from digitized parish registers. They allow us to follow individuals throughout their lives as long they stay in the parishes. It is also possible to reconstruct families.

The death records are missing before 1815 and stillbirths are missing to a large extent before 1860, and we have thus chosen to study only mothers born in the period 1840-1900. We have identified every woman observed in the region at the age of 18 and followed her to her death, first out-migration or end of registration. Those included has no gaps in the presence summing up to more than one year. In that way, we can control her child-bearing history from the start of her fertile period to the date of censoring. For every child to these mothers, we have collected information on recorded stillbirths on the one hand

and on all perinatal deaths on the other hand. We lack unfortunately cause of death in most cases. However, this is of minor importance because this cause of death could anyhow not be diagnosed at this time.

In total there were 4943 women having 23067 children. The children are recorded until 1900 so many mothers born during during this period have children born later not included in this study. Consequently we have an underrepresentation of higher parities. Figure 1 shows the distribution of births in different parities. Around 900 were first-born. There were only a few cases in parities 13 and above. We have chosen not to include the highest parities in some figures due to small numbers.

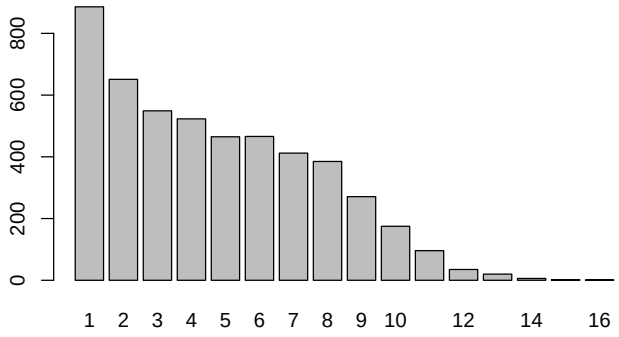

Figure 1: Frequency of number of siblings in the dataset

4 The Skellefteå region – its demographic and socio-economic pattern

The Skellefteå region consists of the parish of Skellefteå and somewhat later also the parish of Byske. Two other parishes, Jörn and Norsjö, were incorporated into the parish of Skellefteå for a number of years at the beginning of the century but became independent in the early nineteenth century. They are however available for research even after the separation and are included in the data files analysed here. The region is situated in the province of Västerbotten in the northern part of Sweden on the Gulf of Bothnia. During the nineteenth century the parish was one of the largest parishes in Sweden both in area and in population. The population began to increase during the seventeenth and eighteenth centuries and by the turn of the nineteenth century about 6,900 inhabitants lived in the region. During the following century the region experienced a rapid population growth. In 1850 the region had approximately 14,000 inhabitants and by 1900 nearly 30,000 (Alm Stenflo 1994).

Fertility was high, not only by Swedish standards but also in an international comparison. The total fertility rate was around five throughout the whole 19th century (Alm Stenflo 1994, Coale & Watkins 1986). Indeed, the fertility transition in Västerbotten occurred first during the second decade of the twentieth century making it one of the last provinces in Sweden to adopt family limitation on a wide scale. Although there was some fluctuation, women in Skellefteå gave birth to about five children on average. Since illegitimate births were not as common as in the rest of northern Sweden, the region's high total fertility was mainly the result of a high marital fertility. Skellefteå as such had not entered the fertility transition during the period under study. Mortality was relatively low (Edvinsson et al. 2005) with the result that population growth was the result of natural increase rather than migration gains. The region experienced some net migration losses in conjunction with the increase in population during the nineteenth century. On the whole migration to and from the region was moderate resulting in a fairly homogeneous population (Egerbladh 1995). Animal husbandry was the mainstay of the local economy and although crofters and other rural landless groups were not uncommon, most of the population consisted of freehold peasants. There were no large estates and industrial development was limited even during the boom period of the sawmill industry during the latter half of the nineteenth century. The town of Skellefteå, founded in 1845, was of little importance with a population of only 1,300 in 1900 (Fahlgren 1956).

5 Perinatal mortality and the Rh negative disease in the nineteenth century Skellefteå

In this section we try to assess how the Rh negative disease affected a society with high fertility, high levels of the Rh negative gene and no access to treatment, namely the nineteenth century Skellefteå. So, what information are needed to do this? Of course the best information would be if we had blood types of the individuals and death causes which we can derive from the Rh disease. Unfortunately we have neither. Instead we will use estimates of the proportion of Rh negative in the population, risk estimates from the medical literature, parish records to get information about the births and whether they were stillborn or died perinatal. Knowing the risks, frequency of the Rh gene and number of children the mothers have an estimate of number of deaths can be calculated for siblings and for parity. Thus, we get a "theoretical" level of clustering and increase of mortality with parity induced by the Rh disease. This can in turn be compared with the actual levels of mortality from the parish record to assess how much the disease contribute to the total mortality. In the following calculations we have used the figures 48% negative genes, a 13% risk of sensification in a pregnancy, a 50% risk of deaths perinatal and a 16.7% risk of stillbirth. The frequency of Rh negative gene is taken from Beckman et al. (1972). The estimated risk of sensification varies in the literature, here a number in the middle is used (Eklund & Nevanlinna 1973, Ascari et al. 1969). According to Zimmerman (1973) it is between 5 and 20 %. In the calculations no attention has been given to possible effects of if families based the decisions on having more children on the outcome of previous births. Neither to the possibility that the disease gets more deadly at higher parities when the mother can be "re-sensitized".

The levels of perinatal mortality and stillbirths are presented in figures 2 and 3. Perinatal mortality varied between 3 and 6 % except some outliers in the beginning due to small numbers. In comparison with Swedish national rates they are about the same, maybe a little higher towards the end of the century. Stillbirths varied between 1 and 3 %, somewhat lower than the national level. This could be an effect of the under-representation of higher parities in the dataset.

5.1 Perinatal mortality and parity

One of the effects of the Rh disease is the increase of risk over parity. Here the observed perinatal mortality and stillborn are compared to the theoretical level of deaths due to the Rh disease.

Figure 4 compares the observed perinatal deaths in the dotted line with the theoretical level of perinatal deaths that is due to Rh-disease in the solid line. The observed perinatal mortality shows the often encountered J-shape with rather high mortality at parity one, then it goes down in the 3–5 parity and then it rises. The recorded levels are in between 3 and 8% in the parities of substantial size. The expected deaths from the Rh disease can be seen to

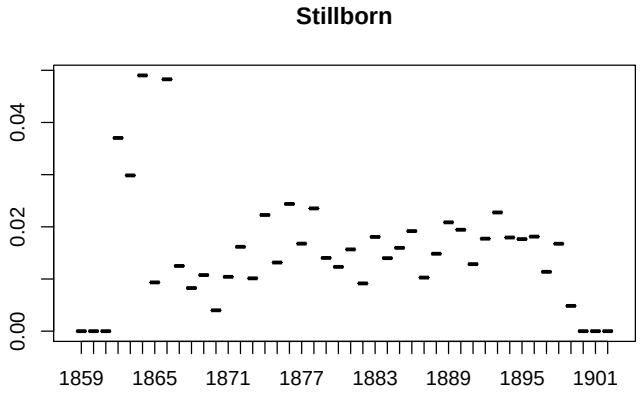

Figure 2: Proportion stillborn over time

be increasing with parity with a diminishing level of increase. The increase is due to the fact that more and more mothers get sensitized and the diminishing level of increase is due to that there are less mothers that can get sensitized at higher parity. It can be established that the Rh-disease contributes to a large part in the observed increase in mortality over parity. From about parity five and higher the expected level is rather similar to the observed.

This can be compared to stillborn shown in Figure 5. The proportion stillborn goes from less than 1 to more than 4 %. The curve for expected level follows the observed increase quite well indicating that most stillborn at higher parities might have Rh disease as cause. The results make it highly plausible that the disease accounts for a large proportion of the perinatal deaths at higher parities and also explains the increase in mortality to a large extent.

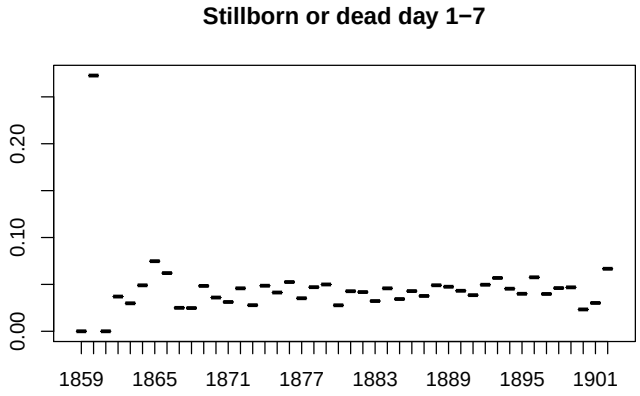

Figure 3: Proportion Perinatal mortality over time

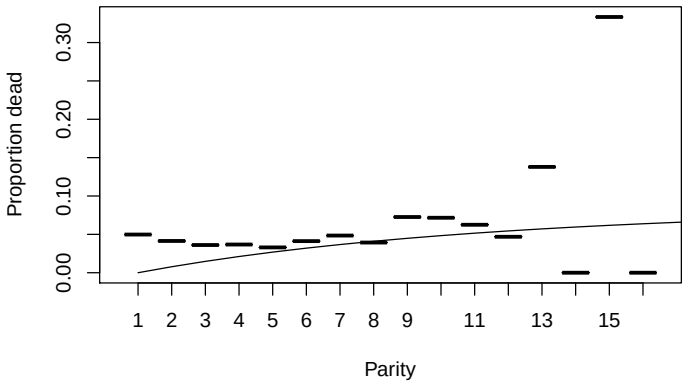

Figure 4: Perinatal mortality and parity compared to theoretical levels

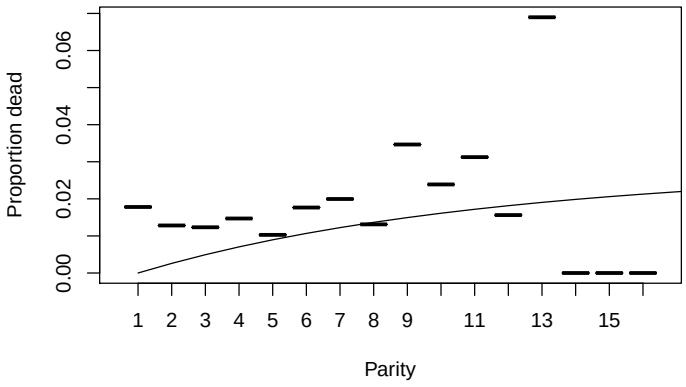

Figure 5: Stillborn and parity compared to theoretical levels

5.2 Stillbirths and clustering within families

Table 1 illustrates the frequencies of specific number of children and number of stillborn a mother has. Table 2 illustrates the frequencies of specific number of children and expected number of stillborn assuming no clustering. The expectations are calculated under the assumption that whether a child is stillborn or not is independent of number of children a mother has and the situation for the siblings. The main conclusion to be drawn from these two tables is that having more than one stillborn child is unusual assuming independence but in practice is observed rather often. This is in line with the Rh disease hypotheses and indicates a strong effect of clustering. Another interesting thing that can be seen in the tables is the high risk for the first and only of a mother where $26/(860+26) = 2.9\%$ are stillborn, much larger than the overall risk for the first-born. For these children there is probably an over-representation of complicated deliveries and maternal deaths.

	0	1	2	3	4	5
1	860	26	0	0	0	0
2	637	12	2	0	0	0
3	526	20	2	1	0	0
4	497	23	2	1	0	0
5	437	26	1	1	0	0
6	429	29	4	1	1	2
7	384	25	2	1	0	0
8	351	29	2	2	1	0
9	237	28	5	1	0	0
10	160	12	2	1	0	0
11	82	9	2	0	2	1
12	30	4	1	0	0	0
13	15	4	0	0	1	0
14	6	0	0	0	0	0
15	2	0	0	0	0	0
16	1	0	0	0	0	0

Table 1: Frequencies of families with a specific number of stillborn (horizontal) and number of children (vertical)

	0	1	2	3	4	5
1	872.2	13.8	0.0	0.0	0.0	0.0
2	630.9	19.9	0.2	0.0	0.0	0.0
3	523.8	24.8	0.4	0.0	0.0	0.0
4	491.2	31.1	0.7	0.0	0.0	0.0
5	429.9	34.0	1.1	0.0	0.0	0.0
6	424.1	40.2	1.6	0.0	0.0	0.0
7	369.2	40.9	1.9	0.1	0.0	0.0
8	339.6	43.0	2.4	0.1	0.0	0.0
9	235.3	33.5	2.1	0.1	0.0	0.0
10	149.6	23.7	1.7	0.1	0.0	0.0
11	80.8	14.0	1.1	0.1	0.0	0.0
12	29.0	5.5	0.5	0.0	0.0	0.0
13	16.3	3.4	0.3	0.0	0.0	0.0
14	4.8	1.1	0.1	0.0	0.0	0.0
15	1.6	0.4	0.0	0.0	0.0	0.0
16	0.8	0.2	0.0	0.0	0.0	0.0

Table 2: Frequencies of families with a specific number of stillborn (horizontal) and number of children (vertical), expected values assuming no clustering

5.2.1 Clustering likely due to Rh negative disease

Clustering within family, disregarding family size, is illustrated in Table 3. The first column shows the expected frequencies of occurrences of different number of stillborn assuming random occurrences of stillborn. The middle column shows the observed numbers. The third shows the expected frequencies of occurrences of different number of stillborn assuming that the Rh disease is the only cause of stillborn deaths. This is estimated by simulation using the same figures as earlier, 48% Rh-negative genes, 13% risk of sensitization, and 25% risk of stillbirth in a risk pregnancy. The genetic set-up of the parents are randomized according to the proportion of Rh genes in the population. In the simulation each simulated pair corresponds to a real family and their number of siblings. This is repeated 1000 times and the mean from these simulations are used as estimates. The estimated number of cases of Rh disease related deaths is 127 of a total of 359 i.e. about 35% of all stillbirths.

A Chi-2 test to test if the observed data follows the expected distribution assuming independence gives a observed value of the test statistic 77.1 with 2 degrees of freedom (stillborn groups with expected value < 5 merged) which gives us a p-value close to zero. Thus, there seems to be clustering present. The Rh only column shows a pattern for the higher numbers of stillborn that conform with the observed.

	Independent	Observed	Rh only
0	4599	4654	4850
1	329	247	66
2	14	25	21
3	0	9	5
4	0	5	1
5	0	3	0

Table 3: Frequency of number of stillbirths

5.3 The effect of reduced fertility on perinatal mortality

The Rh disease causes a higher risk of perinatal death for higher parities. It can therefore be part of the explanation that the number of perinatal deaths have dropped when fertility has gone down, as suggested by Joseph & Kramer (1998) on the 20th century decline:

"In summary, changes in birth order distribution and in the quality of perinatal care have been responsible for an important fraction of the decline in incidence and mortality from Rh hemolytic disease of the newborn. These results provide a historical perspective on the conquest of a once major cause of perinatal mortality and long-term disability."

In Table 4 it is shown what would happen with the deaths by the Rh disease if the fertility had been lower. For each column to the right the last child among the siblings are removed if the number of siblings remaining exceeds 2 and the resulting number of stillborn per family recorded. In table 5 the corresponding theoretical pattern of the stillborn due to the Rh disease is displayed. It can be seen that with high fertility the Rh disease cause a large proportion of the stillbirths while the numbers are considerably reduced with low fertility. By reducing sibship size with one child 31 cases less of the disease would occur, with two children 60 cases and so on. There is no sign of fertility transition during the studied period. The fertility decline, that is considered to have started in the 1910's, should according to our estimates have resulted in fewer deaths caused by the Rh disease.

	No. children reduction									
No. stillborn	0	1	2	3	4	5	6	7	8	9
0	4654	4688	4716	4756	4774	4789	4802	4807	4807	4809
1	247	220	199	168	155	146	134	130	130	128
2	25	23	19	16	14	8	7	6	6	6
3	9	6	8	3						
4	5	5	1							
5	3	1								

Table 4: Number families with a specific number of stillborn with reduction of fertility

6 Conclusions

In this paper we have looked into the role of a specific type of mortality, perinatal mortality. A substantial part of all infant deaths takes place during the first week, especially in the contemporary world but also in historical settings. Before or during the mortality transition both neonatal deaths and stillbirths were

No. stillborn	0	1	2	3	4	5	6	7	8	9
0	4850	4872	4889	4903	4914	4922	4927	4930	4932	4933
1	66	53	41	32	24	19	15	12	11	10
2	21	15	10	6	4	2	1	0	0	0
3	5	3	2	1	1	0	0	0	0	0
4	1	1	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0

Table 5: Number of families with a specific number of stillborn with reduction of fertility, expected values if the Rh disease is the only cause of death

quite frequent. In earlier research, there have been indications of a biological factor playing a role in the clustering of deaths within families (Edvinsson et al 2005). Here we have been able to highlight a possible mechanism, contributing to clustering of perinatal mortality and stillbirths in particular. Our knowledge about the composition of the Rh factor in this area together with qualified estimates on the risks of sensitization and the mortality risks for those getting the disease, have made it possible for us to estimate the expected number of cases in our area of study. When comparing the expected number to the observed numbers, we make the conclusion that Rh disease represented a large part of the all stillbirths and perinatal deaths. This is especially the case in higher parities. Without Rh disease, the stillbirth rate would have been about a third smaller and in higher parities even more.

The increased risks at higher parities thus have the consequence that a decline in fertility would lower the frequency of Rh disease in particular but also of perinatal mortality in general. During the period we are studying there was no sign of declining fertility. This took place in the 20th century. The effect of Rh disease had strong impact in Skellefteå both due to a large proportion of Rh negative mothers and the very high fertility in the region. Families with ten children or more were not rare in Skellefteå. The Rh negative mothers having that many children most probably became sensitized at the higher parities.

We can not establish the exact level of Rh disease in Skellefteå - we can only make probable its impact through estimations. It is however possible that we underestimate its impact. It is a well known fact that mothers loosing their children shortly after delivery have a shortened birth interval to the next. This could be due to compensation but usually it is an effect of no lactation after the death of a child and consequently an earlier onset of ovulation. Those having high infant mortality, especially perinatal and neonatal mortality, thus had more children and more children of higher parities. Mothers that became sensitized could be expected to have more children, which would lead to more children with Rh disease. This effect may be possible to include in the model, but we have not considered this in the present paper.

We are not arguing that the studied disease explains all or even the most of the death clustering among infants. Without the disease infant mortality

would have been lower and the effect would have been even stronger in perinatal mortality. Still, much of especially the infant mortality can not be explained by Rh disease. It is only one component in the risk panorama of newborn infants at this time. Nevertheless, it is a factor that has significant impact that needs to be considered in the analysis of infant mortality. Our estimates indicate a considerable number of cases related to the disease. We can thus safely conclude that it had a substantial impact on the survival at the time. Even if it was a rather small part of the risks for the foetus, it was a factor that had impact at the time and killed many children.

Rh disease was furthermore an important factor explaining some of the clustering of mortality we find. If a sensitized mother continued to give birth to children, they would by necessity constitute a cluster. Without the disease, clustering would have been less significant even if it was not the only aspect that caused this in Skellefteå.

As far as we know, the role of Rh disease has not been discussed in historical contexts, partly because it is difficult to establish its extension, partly because we lack causes of death and partly because we tend to underestimate its possible role since infant mortality was so high and to the highest degree was caused by socio-economic conditions such as poverty, overcrowding or behavioural aspects such as artificial feeding or neglect. We argue that we need to know more about its role in societies with the potential risks of the disease. We hope that our results have illustrated the impact of the disease in historical settings.

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