"Repeater" studies – Development of a new research field

Leiv S. Bakketeig

Division of Epidemiology, Norwegian Institute of Public Health, P.O.Box 4404 Nydalen, NO-0403 Oslo, Norway
Telephone: +47 23 40 82 02 Telefax: +47 23 40 82 52 e-mail: leiv.bakketeig@fhi.no

SUMMARY

The tendency to repeat birth weight in successive birth was first published in 1977. The study was based on 81 400 mothers who had their first and second singleton birth within the study period 1967-73, based on information in the Medical Birth Registry of Norway. The paper was presented at a large NICHD (National Center of Child Health and Human Development, NIH) seminar focusing on preterm birth. This meeting started a creative, international long lasting collaboration, a series of papers and book chapters has been published. It seemed like mothers are programmed to give birth to babies of a certain size and age. And if they depart from this norm the baby is at an increased risk of mortality. Also, the tendency to repeat gestational age and birth weight exists across generations, with the same increased risk if the pattern is departed from. This means that if a mother who herself was of low birth weight give birth to a likewise small baby, then that baby has improved survival compared to a likewise small baby where the mother was relatively heavy. This effect across generations is also present on the paternal in addition to the maternal side. Recently the medical birth registration data set has provided possibilities to examine the effect of changing partners from one pregnancy to the next one. Also, half siblings (maternal and paternal) is another valuable data source to explore. Soon 3 generational repeater studies will become available as the first births in the registry by now become grandmothers and grandfathers.

The medical registration of birth in Norway was established in 1967, but the registry based upon these registrations started towards the end of 1969.

The first report from the registry was published in 1970 (1) and the first international publication based on the registry data appeared in 1973 in Acta Peadiatrica Scandinavica (2). I participated in establishing the registry. In 1975, I was invited as visiting scientist to National Institute of Child Health and Human Development (NICHD), National Institutes of Health in Bethesda, Maryland. The invitation was mainly based on the first publication mentioned above. While at NICHD a large seminar was held focusing on preterm birth (or prematurity as it was then labelled).

This meeting started a creative, international collaboration – first and foremost with the statistician Howard J Hoffman, but also others. This collaboration has been longlasting, and so far more then 30 papers, and numerous book-chapters, have been published.

We started out examining 7 years of data from the medical registration of birth (1967-1973). Our first objective was to examine the tendency to repeat adverse pregnancy outcomes in successive pregnancies (3). This was possible since mothers and children are identified by unique personal identification numbers in the medical birth registry. Previous many studies had shown for example associations between low birth weight and a previous history of low weight deliveries (4-9). However, these studies had mostly been done retrospectively, and the authors had to a limited extend been able to obtain information on gestational age and birth weight on previous births and thus they had been unable to take into account both gestational age and birth weight when studying the tendency to repeat low birth weight or preterm births.

However, we had available 464 067 births and we examined the 81 400 mothers who had their first and second singleton birth within the study period 1967-73 (3).

For 5002 (6.6%) of these mothers birth weight or gestational age were not known for either their first or second birth or for both. These mothers were thus excluded from the analyses, leaving for the analysis 76 398 mothers where birth weight and gestational age were known for both first and second birth.

Three different outcomes of their next pregnancies were studied; low birth weight (LBW) defined as a birth weighing 2500 grams or less, preterm delivery defined as a delivery before 37 completed weeks (16-36 weeks) and growth retardation, defined as births with weight being below the 10^{th} percentile for gestational age.

In the analysis 8 weight groups were established: 1000 grams or less, 1001-1500 grams and 500 gram groups until the upper group being 4500 grams or more. Likewise gestational age was also grouped in 8 groups; less than 28 weeks, 28-30 weeks, 31-33 weeks, 34-36 weeks, 37-38 weeks, 39-41 weeks, 42-44 weeks and 45 + weeks.

The study showed a strong tendency to repeat low birth weight (LBW), preterm birth or small for gestational age births (SGA) as shown in table 1 with data

Table 1. Relative prediction of LBW, Preterm or SGA among second births based on outcome of first births (3).

First birth	Second birth		
	LBW	Preterm	SGA
LBW	**5.6**	3.7	4.1
Preterm	4.0	**4.0**	1.5
SGA	2.8	1.4	**3.9**

extracted from the publication. The table shows the relative prediction of LBW, preterm or SGA births among second births based on outcomes of first birth.

It shows that the low birth weight (LBW) of the first birth is the most powerful predictor of LBW of the second birth, gestational age the best prediction of preterm second birth and growth retardation (SGA) of the second birth is more effectively predicted by growth retardation of the first birth. The study showed that as birth weight and gestational age of the first birth changed from the most favourable to the least favourable combination, the risk of low birth weight, preterm birth and small for gestational age of second birth increased 20-30 times.

In a subsequent study (10) based on the material (all 454 358 singleton births born in Norway 1967-73 it was shown that mothers tended to repeat all combinations of gestational ages and birth weights. Mothers seemed to somehow be programmed to have birth of a certain gestational age and birth weight. This study also demonstrated a cumulative risk for outcomes like preterm, post term, low weight and high weight births. For example, while the risk of the second birth being LBW is 4.1 times as high if the first birth was low compared to if the first birth was not LBW the risk increases to 8.1 times higher for the subsequent birth being LBW if both the mother's first births were LBW.

Later it was shown (11) that when the mother's next baby was rather similar in age and weight then the babies' mortality was lower compared to a baby who differed from the mother's previous birth in terms of gestational age and birth weight. For example, a baby who weighed 2500 grams and whose elder sibling also weighed 2500 grams or lower had a lower perinatal mortality than another baby with the same weight but where the elder sibling weighed 3500 grams or more.

In an extention of these studies (12) we used contour analysis illustrating the bivariate distribution of second births in terms of gestational age and birth weight. This study showed that the mortality is consistently lower where the mother's first birth was rather similar in terms of gestational age and birth weight.

In doing these analyses of perinatal mortality we became aware of the dramatic drop in mortality by parity when we examined within sibships (13). The mortality of second births was less than half of the mortality of the first births within sibships of the two first births. Similar drop was observed for all parities.

In a paper we presented these findings and showed that when the same dataset was analysed cross-sectionally instead of longitudinally the established U-shaped relationship between parity and perinatal mortality reappeared (13). This was a stunning observation and we discussed what types of biases that might explain the longitudinal findings within sibships. But whatever biases, the same biases were behind the cross-sectional findings.

This analysis was criticized by many authors and some of them obviously thought we had claimed that the mortality dramatically fell by increasing parity. Our point, however when presenting the data was that whatever biases that lie behind our findings, the same biases are in the cross-sectional data analysis. But as Mantel correctly claimed in a letter to the editor we had somehow traded one artefact for another one (14).

Later Skjærven and coworkers extended the analysis and showed the weaknesses of doing analysis based on fixed sibship sizes due to the different continuation rates and perinatal mortality by outcome of previous births (15-16).

The sibling studies have recently been extended to generational studies. For example the mean offspring birth weight was related to mothers' and fathers' birth weight. As shown in figure 1 there is a strong association between a baby's birth weight and the mother's and father's own birth weight (17). In order to estimate the recurrence risk of low birth weight and preterm birth across generations 11 092 pairs of mother – first

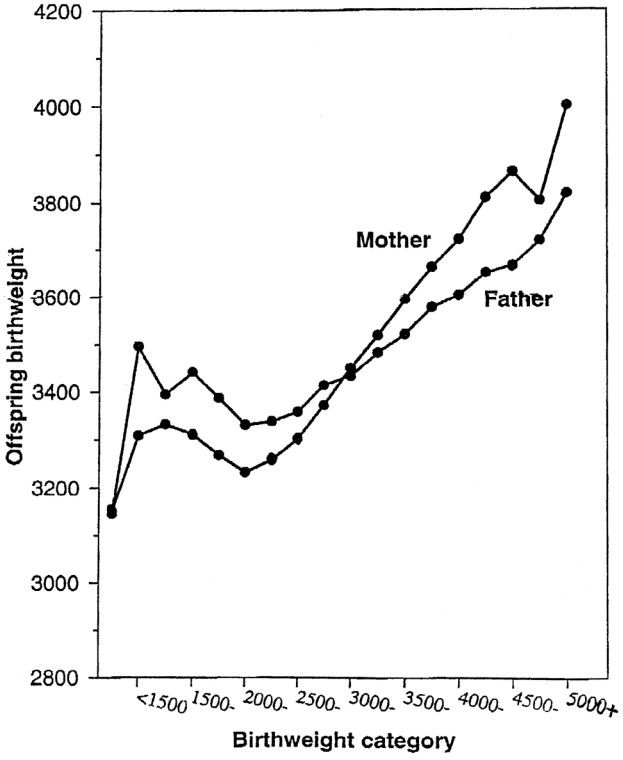

Figure 1. Mean offspring birthweight by categories of maternal and paternal birthweight (grams), Norway, 1967-98.

born offspring were obtained through linkage of births in 1967-69 and their offspring in 1986-89 (18). A low correlation coefficient of 0.086 was found for gestational age across generations whereas the correlation was 0.242 for birth weight. Thus, in contrast to birth weight, human variation in gestational age does not appear to be influenced by genetic factors to any large extent. Recently, a more comprehencive family study on birthweight and gestational age, estimating maternal and fetal effects, as well as shared sibling environmental effects using path analysis, was published (19).

The strong birthweight relations between siblings, but also between a mother and her offspring, led to new standards for birth weight by gestational age using family data (20).

One study (21) focused on whether a baby's survival is related to its mother's birth weight. They linked births during 1981-94 to data on all mothers born from 1967, thereby forming 105014 mother-offspring units. Mother's birth weight was strongly associated with the weight of her baby. Mortality among small babies was much higher where the mothers were born large. For example, babies weighing between 2500 and 3000 grams had a threefold higher perinatal mortality if their mothers' birth weight has been 4000 grams or higher compared to where the mother herself had been small at birth (between 2500 and 3000 grams).

The "repeater studies" have proved valuable in different perinatal epidemiological projects. For example the interval between pregnancies has been related to the risk of preeclampsia (22). And the childbearing was studied among females with birth defects, as well as reproduction to males with birth defects, with focus on the risk of recurrence in their children (23-24). Also, the recurrence risk of birth defects was studied in 1st to 2nd pregnancies to a woman (21). Also, it has been shown that the father has a contributing effect to preeclampsia (26), and that preeclampsia recur between generations, both from mothers and fathers, as well as from unaffected sisters, to their offspring (27).

The "repeater studies" have so far provided new insights, first based on studies of outcomes of successive pregnancies to the same mother, next recurrence to the next generation, both from the maternal and paternal side. Recently the medical birth registration data set has provided possibilities to examine the effects of changing partners from one pregnancy to the next one. Half siblings (maternal and paternal) is another valuable data source to explore. Also, soon 3 generational repeat studies will become available as the first births from late 1960'ies by now becomes grandfathers and grandmothers.

REFERENCES

1. Bjerkedal T, Bakketeig LS. Medical Registration of Birth – Report No. 1. Bergen: University of Bergen, 1970.
2. Bjerkedal T, Bakketeig LS, Lehmann E. Percentiles of birth weights of single, live births at different gestation periods. *Acta Paediatr Scand* 1973; **62**: 449-57.
3. Bakketeig LS. The risk of repeated preterm or low weight delivery. In: Reed DM, Stanley FJ, eds. *The Epidemiology of Prematurity*. Baltimore-Munich: Urban & Schwarzenberg, 1977.
4. Karn MN, Langbrown H, Mackenzie H, Penrose LS. Birth weight, gestation time and survival in sibs. *Ann Eugen* 1951; **15**: 306-22.
5. Ounsted M. Maternal constraint of fetal growth in man. *Develop Med Child Neurol* 1965; **7**: 479-91.
6. Collaborative Perinatal Study of the National Institute of Neurological Disorders and Stroke: The women and their pregnancies. US Dept of Health Education and Welfare, Publich Health Service, Publ no (NIH) 73-379, Washington, DC, 1972.
7. Habicht JP, et al. Maternal nutrition, birth weight and infant mortality. In: Ciba Foundation Symposium 27 (new series), *Size of birth*. Amsterdam: Associated Scientific Publishers, 1974.
8. Fedrick J, Anderson ABM. Factors associated with spontaneous pre-term birth. *Brit J Obstet Gynecol* 1976; **83**: 342-50.
9. Kaltreider DF, Johnsen JWC. Patients at high risk of low birth weight delivery. *Am J Obstet Gynecol* 1976; **124**: 251-6.
10. Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. *Am J Obstet Gynecol* 1979; **135**: 1086-1103.
11. Bakketeig LS, Hoffman HJ. The tendency to repeat gestational age and birth weight in successive birth related to perinatal survival. *Acta Obstet Gynecol Scand* 1983; **62**: 85-92.
12. Hoffman HJ, Bakketeig LS. Heterogeneity of intrauterine growth retardation and recurrence risks. *Semin Perinatol* 1984; **8**: 15-24.
13. Bakketeig LS, Hoffman HJ. Perinatal mortality by birth order within cohorts based on sibship size. *BMJ* 1979; **2:** 693-6.
14. Mantel N. Perinatal mortality by birth order. *BMJ* 1979; **2** (6198): 1147.
15. Skjærven R, Irgens L, Lie RT, Bjerkedal T. Parity specific perinatal mortality. A longitudinal study based on sibships. *Paediatric Perinatal Epidemiol* 1987; **1**: 163-83.

16. Skjærven R, Wilcox AJ, Russell D. Birthweight and perinatal mortality of second births conditional on weight of the first. *Int J Epidemiol* 1988; **17**: 830-8.
17. Lie RT, Wilcox AJ, Skjærven R. Maternal and paternal influences on length of pregnancy. *Obstet Gynecol* 2006; **107** (4): 880-5.
18. Magnus P, Bakketeig LS, Skjærven R. Correlations of birth weight and gestational age across generations. *Ann Hum Biol* 1993; **20**: 231-8.
19. Lunde A, Melve KK, Gjessing HK, Skjærven R, Irgens LM. Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. *Am J Epidemiol* 2007; **165**: 734-41.
20. Skjærven R, Gjessing HK, Bakketeig LS. New standards for birth weight by gestational age using family data. *Am J Obstet Gynecol* 2000; **183**: 681-96.
21. Skjærven R, Wilcox AJ, Øyen N, Magnus P. Mothers birthweight and survival of their offspring: population based study. *BMJ* 1997; **314**: 1376-80.
22. Skjærven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002; **346** (1): 33-8.
23. Skjærven R, Wilcox AJ, Lie RT. A population based study of survival and childbearing among female subjects with birth defects and the risk of recurrence in their children. *N Engl J Med* 1999; **340** (14): 1057-62.
24. Lie RT, Wilcox AJ, Skjærven R. Survival and reproduction among males with birth defects and risk of recurrence in their children *JAMA* 2001; **285** (6): 755-60.
25. Lie R, Wilcox AJ, Skjærven R. A population-based study of the risk of recurrence of birth defects. *N Engl J Med* 1994; **331** (1): 1-4.
26. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ* 1998; **316** (7141): 1343-7.
27. Skjærven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ* 2005; **331** (7521): 877.