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Recurrence of prolonged and post-term gestational age across generations: maternal and paternal contribution

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Objective To estimate intergenerational recurrence risk of prolonged and post-term gestational age.

Design Population-based cohort study.

Setting Norway, 1967–2006.

Population Intergenerational data from the Medical Birth Registry of Norway of singleton mothers and fathers giving birth to singleton children: 478 627 mother–child units and 353 164 father–child units. A combined mother–father–child file including 295 455 trios was also used.

Methods Relative risks were obtained from contingency tables and relative risk modelling.

Main outcome measures Gestational age ≥41 weeks (≥287 days), ≥42 weeks (≥294 days) and ≥43 weeks (≥301 days) of gestation in the second generation.

Results A post-term mother (≥42 weeks) had a 49% increased risk of giving birth to a child at ≥42 weeks (relative risk [RR] 1.49, 95% CI 1.47–1.51) and a post-term father had a 23% increased risk of fathering a child at ≥42 weeks (RR 1.23, 95%CI 1.20–1.25). The RRs for delivery at ≥41 weeks were 1.29 (1.28–1.30) and 1.14 (1.13–1.16) for mother and father, respectively, and for ≥43 weeks 1.55 (1.50–1.59) and 1.22 (1.17–1.27). The RR of a pregnancy at ≥42 weeks in the second generation was 1.76 (1.68–1.84) if both mother and father were born post-term. Adjustment for maternal age in both generations, fetal sex in the second generation, parity, and maternal and paternal birthweight did not influence the risk estimates.

Conclusions There is a familial factor related to recurrence of prolonged pregnancy across generations and both mother and father seem to contribute.

Keywords Generations, post-term pregnancy, prolonged pregnancy.

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Introduction

Gestational age is the most important determinant of perinatal outcome and the majority of scientific attention has focused on understanding and preventing preterm delivery. This is reasonable, as preterm born infants account for approximately three-quarters (75–80%) of perinatal deaths.[1–5] At the other end of the gestational age spectrum, few scientists have shown interest in prolonged and post-term pregnancy. The latter is a condition defined by the World Health Organization and International Federation of Obstetrics and Gynecology as a pregnancy lasting 294 days or more, i.e. ≥42 completed weeks.[6–8] In the 1970s it became clear that post-term births were associated with increased perinatal and neonatal mortality and morbidity.[9,10] The aetiology of post-term pregnancy is not understood, and almost 40 years later, little is known about the recurrence of gestational age across generations through maternal and paternal pathways. There is, however, a small body of evidence indicating that prolonged pregnancies may be biologically determined, possibly through genetic factors.[10–12]

Several birth outcomes, such as birthweight,[13,14] pre-eclampsia[15,16] and congenital malformations[17,18] have been found to recur across generations, indicating that genetic factors may be involved. Previous studies of gestational age have focused on the risk of preterm delivery,[19,20] but recurrence of preterm delivery across generations is low.[21] There is evidence against a major contribution from fetal genes, but in favour of a contribution from maternal genes.[20]

Few studies[22,23] have assessed the recurrence of post-term gestation across generations, and findings have been weak and the studies underpowered. No study has so far explored the conjoint effect of maternal and paternal influence. Clearly, this shows the need for more and larger studies focusing on post-term pregnancy across generations. Such studies need to assess both maternal and paternal pathways to not only increase our understanding of prolonged pregnancy, but also add valuable knowledge to the understanding of generational effects on gestational age in general.

The purposes of the current study were to use high-quality data from the Medical Birth Registry of Norway (MBRN) during the last 40 years to estimate the intergenerational recurrence risk of prolonged and post-term gestational age and to assess both maternal and paternal possible pathways.

Methods

Data source

A population-based cohort study was designed using data from the MBRN from 1967 to 2006. The register was established in 1967 by the Directorate of Health and was the first national medical birth registry in the world. It is based on compulsory notification of all live births and stillbirths from 16 weeks of gestation. A standardised notification form is used to collect data on demographic variables, maternal health before and during pregnancy, previous reproductive history, complications during pregnancy and delivery, and pregnancy outcomes. This notification form was almost unchanged from 1967 until 1999, with the exception of the addition of the Apgar score in 1978. In 1999 a new and more detailed form was introduced in which information on maternal smoking habits and ultrasound gestational age determination was included. All records in the MBRN are matched with the files of the Central Person Register, ensuring medical notification of every newborn in Norway.[24]

Study population and formation of intergenerational data sets

Every Norwegian citizen is given a unique personal identification number at birth, which enables linkage of participants. Intergenerational data sets were formed, as the first birth cohorts in the MBRN have almost finished their reproductive careers. Birth records from the first birth cohorts were linked to their own subsequent births, identifying mother (first generation), father (first generation) and child (second generation). We restricted the selections to singleton-born mothers and fathers with gestational age ≥28 weeks and singleton offspring with gestational age ≥22 weeks, excluding all multiple pregnancies. As a result of the acknowledged misclassification of gestational age in the preterm period (<32 weeks), infants with gestational age <32 weeks and *z*-scores for birthweight by gestational age above four standard deviations were excluded in both generations.

Definitions and statistical analysis

The following sources are available to estimate gestational age in the MBRN: (i) last menstrual period (registered from 1967) and (ii) expected date of parturition according to ultrasound (registered from 1999). If not stated otherwise, gestational age was calculated by using the last menstrual period.

We defined post-term pregnancy in accordance with the recommended, standardised and internationally endorsed definition of a pregnancy lasting ≥294 days (≥42 weeks) of gestation.[6,7] The main exposure in the current study was post-term pregnancy in the first generation (mother, father or both). The main outcomes were gestational age at ≥41 weeks (≥287 days of gestation), ≥42 weeks (≥294 days of gestation) and ≥43 weeks (≥301 days of gestation) in the second generation.

Maternal age at delivery in the first and second generation was categorised as <20 years, 20–34 years and ≥35 years. Parity was categorised as nulliparous and multiparous. Maternal and paternal birthweight was categorised as <3000 g, 3000–4499 g and ≥4500 g. These variables were considered as possible confounders.

Relative risks (RR) with 95% CI for the main outcomes in the second generation were obtained using contingency tables (SPSS, version 15.0). Relative risk modelling (STATA, version 9.0) was used to assess risk estimates (RR) when adjusting for the possible confounding factors outlined above and to assess the risk of post-term pregnancy as a function of maternal or paternal gestational age in completed weeks, categorised into the following groups: 28–34, 35–36, 37–38, 39–40, 41 and ≥42 completed weeks.

Results

We identified 478 627 mother–child units and 353 164 father–child units (Table 1) with complete data on gestational age in the MBRN. The lower number of father–child units was the result of the older average age of fathers as well as missing paternal data. In building trios with complete gestational age for mother, father and child, we identified 295 455 mother–father–child units (Table 2).

The RRs of a pregnancy at ≥41 weeks, ≥42 weeks, or ≥43 weeks in the second generation for post-term-born parents compared with parents born <42 weeks are outlined in Table 1. The risks of all categories of prolonged pregnancies were significantly higher in offspring born to post-term mothers than to mothers delivered at <42 weeks, with the highest point estimate for the longest pregnancies

Table 1. Risk of gestational age at ≥41 weeks, ≥42 weeks and ≥43 weeks among singleton offspring when mother or father was born post-term (≥42 weeks) relative mothers or fathers born at 28–41 weeks (<42 weeks), Norway 1967–2006

	Second generation											
	Pregnancy ≥ 41 weeks				Pregnancy ≥ 42 weeks				Pregnancy ≥ 43 weeks			
	n	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI
Mothers (*n* = 478 627)												
Not post-term (<42 weeks) (*n* = 403 191)	140 776	34.9	1.0	Referent	56 084	13.9	1.0	Referent	16 712	4.1	1.0	Referent
Post-term (*n* = 75 436)	34 004	45.1	1.29	1.28–1.30	15 626	20.7	1.49	1.47–1.51	4 830	6.4	1.55	1.50–1.59
Fathers (*n* = 353 164)												
Not post-term (<42 weeks) (*n* = 301 279)	107 854	35.8	1.0	Referent	43 725	14.5	1.0	Referent	13 274	4.4	1.0	Referent
Post-term (*n* = 51 885)	21 226	40.9	1.14	1.13–1.16	9 236	17.8	1.23	1.20–1.25	2 790	5.4	1.22	1.17–1.27

Table 2. Risk of gestational age at ≥41 weeks, ≥42 weeks and ≥43 weeks among singleton offspring when father alone, mother alone and both mother and father were born post-term (≥42 weeks) relative mothers and fathers born at 28–41 weeks (<42 weeks), Norway 1967–2006

Both parents (*n* = 295 455)	Second generation											
	Pregnancy ≥ 41 weeks				Pregnancy ≥ 42 weeks				Pregnancy ≥ 43 weeks			
	n	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI
None post-term (< 42 weeks) (*n* = 211 664)	72 920	34.5	1.0	Referent	28 629	13.5	1.0	Referent	8 581	4.1	1.0	Referent
Father post-term (*n* = 36 501)	14 582	39.9	1.16	1.14–1.18	6 234	17.1	1.26	1.23–1.29	1 840	5.0	1.24	1.18–1.31
Mother post-term(*n* = 40 271)	18 026	44.8	1.30	1.28–1.32	8 239	20.5	1.51	1.48–1.55	2 554	6.3	1.56	1.50–1.63
Both post-term (*n* = 7 019)*	3 466	49.4	1.43	1.40–1.47	1 669	23.8	1.76	1.68–1.84	551	7.9	1.94	1.78–2.10

**P*-value for interactions; *P* = 0.001 for pregnancy ≥41 weeks; *P* = 0.002 for pregnancy ≥42 weeks; *P* = 0.93 for pregnancy ≥43 weeks.

(≥43 weeks; RR 1.55, 95% CI 1.50–1.59). Likewise, the risks of prolonged pregnancies in the second generation were significantly increased if the father was born post-term compared with at <42 weeks, although the point estimates were significantly lower through fathers than mothers.

We assessed the RR of post-term delivery in the second generation after categorising maternal and paternal gestational age into six categories, and using parental gestational age at 39–40 completed weeks as the reference category (Figure 1). As shown in the figure, the risk of offspring post-term delivery was significantly increased relative to the reference group when maternal gestational age was 41 (RR 1.35, 95% CI 1.33–1.38) and ≥42 completed weeks (RR 1.61, 95% CI 1.58–1.63), and significantly decreased for mothers delivered at 37–38 completed weeks (RR 0.88, 95% CI 0.86–0.91). A similar pattern was found through fathers, although the associations were weaker and also paternal gestational age category 35–36 weeks was statistically significant (RR 0.94, 95% CI 0.89–0.99). The RR for post-term delivery was 0.93 (95% CI 0.90–0.96) for offspring of fathers delivered at 37–38 weeks and 1.17 (95% CI 1.14–1.19) and 1.27 (95% CI 1.24–1.30) for offspring of fathers delivered at 41 and ≥42 completed weeks, respectively. A mother born at ≥42 weeks had a RR of 1.82 (95% CI 1.77–1.87) of giving birth to a post-term infant compared with a mother delivered at 37–38 weeks. For fathers, the corresponding RR was 1.37 (95% CI 1.32–1.41).

The confounding effects of maternal age at childbirth in the first and the second generation, fetal sex in the second generation, parity, and maternal and paternal birthweights were assessed, but did not influence the risk for any of the outcomes.

In the trio data, we identified 7019 units in which both parents were delivered post-term. Again, the risk of all categories of prolonged gestational age was increased when both parents were delivered post-term compared with

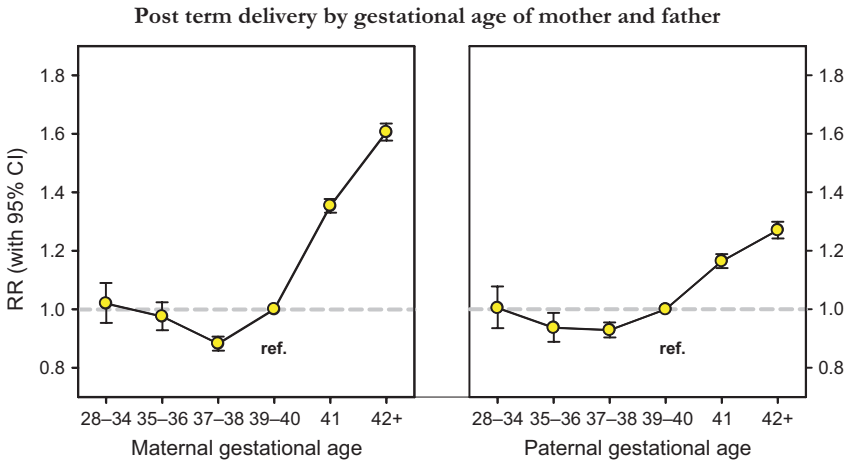

Figure 1. Relative risks for post-term delivery in the second generation as a function of maternal gestational age in weeks, calculated using 478 627 mother–child units and paternal gestational age in weeks, calculated using 353 164 father–child units, obtained using relative risk modelling, Norway 1967–2006.

delivery before 42 weeks, and the risk increased with increasing gestational age in the second generation (Table 2). The maternal alone effect was significantly higher than the paternal alone effect for ≥41, ≥42 and ≥43 weeks. Also, the risks of all the outcomes of prolonged gestation in the second generation were significantly higher when both parents were delivered post-term than when looking at either parent separately. In a separate model, we also assessed the possibility for a conjoint maternal and paternal effect on the RR of ≥41, ≥42 and ≥43 weeks in the second generation by checking for interaction when both parents were born post-term. There was a statistically significant effect of the interaction term in the model for ≥41 weeks ($P = 0.001$) and ≥42 weeks ($P = 0.002$). However, the point estimate was only slightly reduced (RR of ≥42 weeks: 1.74, 95% CI 1.68–1.81) when an interaction term was included in the model compared with no interaction term as are outlined in Table 2.

We also calculated all risk estimates by using gestational age estimated by ultrasound if available for the latter part of the second generation (infants born during 1999–2006). We obtained exactly the same RR estimates as outlined above.

Discussion

The most important finding from the current study is that there is an obvious familial factor related to recurrence of prolonged gestations across generations and that both mother and father seem to contribute to this risk. However, there is clear evidence for a stronger maternal than paternal influence. There also seems to be a generational dose–response relationship, with the lowest risk at parental gestational age 37–38 weeks, having a protective effect on post-term delivery risk, and increasing into the prolonged pregnancy and post-term period.

Strengths and limitations

The current national population-based cohort is based on mandatory reporting of a standardised data set over a period of 40 years, covering two generations of women giving birth in Norway, and the problem of selection bias is therefore minimal. The large size of our mother–child, father–child and mother–father–child cohorts is a major strength, as it enabled us to also study weak relations. Few other data sources are available that enable the preparation of generational data of a similar size. We are also the first to study the paternal effect and the conjoint effect of both parents being post-term in the first generation on the recurrence risk of prolonged gestation in the second generation. The findings of consistent associations across all gestational ages (≥41, ≥42 and ≥43 weeks of gestation) and the fact that adjustments for possible confounding factors did not influence the risk estimates, further strengthens the conclusion of a robust familial effect on the recurrence risk of prolonged gestation. Also, relative risk estimates were not influenced by using ultrasound-based gestational age determination for the latter part of the second generation.

Unfortunately, body mass index and ethnicity that at least theoretically may influence risk estimates are not registered in the MBRN. The majority of immigration to Norway happened after the mid-1980s, so it is unlikely that ethnicity is a confounding factor in our data.

The proportion of post-term delivery is influenced by the rate of induction of birth. In Norway post-term has been considered to be 296 days of gestation and the

majority of obstetric departments have, during the entire study period, performed expectant management at ≥42 weeks.[25] Pregnancies proceeding to 42 weeks are followed from 42 to 43 weeks every other day. This implies an unchanged and consistent policy of post-term surveillance that gives us the opportunity to study true post-term pregnancies that are difficult to access in other populations with a more aggressive induction policy. We have deliberately not restricted the analyses to spontaneous deliveries as this would exclude a significant proportion of post-date pregnancies where induction was performed with the indication of being post date. This restriction will probably lead to an important bias, as we would lose the post-date pregnancies with higher risk (those induced).

The calculation of risk estimates in our data is clearly complicated by the fact that regular ultrasound estimation of gestational age was only available for the latter part of the second generation (infants born during 1999–2006). The fact that RRs were the same when gestational age based on ultrasound was used for the later part of the data, may indicate that the occurrence of post-term is shifted, but the RR of recurrence across generations is not influenced by the different methods of estimating gestational age. It would of course have been beneficial if data on both methods (last menstrual period and ultrasound) were available for both generations; however, ultrasound dating was not an established method for gestational age assessment during most of the first generation. Therefore, we decided to report manly based on calculations using one method of gestational age determination i.e. last menstrual period.

Comparison with other studies

We are not aware of any population-based cohort study of similar size that has assessed the effect of both maternal and paternal influence across generations on recurrence risk of prolonged gestation. Two previous studies have assessed recurrence of prolonged/post-term pregnancy across generations.[22,23] The data from the British Birth cohort of 1958 found an increasing post-term birth proportion in the second generation with increasing gestational age in the first generation; however, the cohort included only 7501 mother–daughter pairs, with obvious limitations.[22] The second study, by Mogren et al.[23] from Sweden used a cohort of 48 076 mother–daughter pairs and found a relative risk of post-term pregnancy in the daughters of 1.3, below our estimate and only with borderline significance. There is also one previous twin study on the issue that concluded with influence from maternal genes, but did not find any paternal influence.[11]

In a recent paper, Lie et al.[26] calculated gestational age of infant in the second generation as a function of maternal and paternal gestational age in the first generation. One could argue that the risk estimates in our paper could have been calculated had the standard deviation for mean gestational age been given. Such estimation would have been based on the assumption of gestational age as a normally distributed variable. However, gestational age, contrary to birthweight, is not normally distributed because of negative skewness and, most importantly, high kurtosis.

Associations across generations, similar to ours, with both paternal and maternal contribution, but with a stronger maternal component, may indicate that genetic factors or persistent environmental factors are important. Another explanation is that both genes and environment contribute. In generational studies, persistent environmental factors are less likely to contribute than in studies analysing sib-ship data. However, associations from generational studies are not a specific method to estimate genetic effects, but are clearly important by indicating at which areas more specific population-based genetic models are best applied.

Conclusions

Our study shows that there is a familial factor related to recurrence of prolonged gestation across generations. Both mother and father seem to contribute to this risk and the estimates are robust. The current study suggests an importance of genes on gestational duration in the prolonged period.

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Disclosure of interest

There are no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject of this manuscript.

Contribution to authorship

The investigators of this study had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NHM designed the study, performed the analyses of data and was responsible for interpretation of data analysis and completion of the manuscript. KKM contributed to the interpretation of data analysis and the completion of the manuscript. RS designed the study, performed analyses, interpreted data, contributed to completion of the manuscript and is guarantor.

Details of ethics approval

The study was based on anonymous data and was therefore exempt from ethical institutional review board approval according to Norwegian legislation.

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