Age at menarche and the risk of operative delivery

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Objectives

We sought to evaluate the impact of later menarche on the risk of operative delivery.

Population

We studied 38,069 eligible women (first labors at term with a singleton infant in a cephalic presentation) from the Norwegian Mothers and Child Cohort Study. The main exposures were the age at menarche and the duration of the interval between menarche and the first birth.

Methods

Poisson regression with a robust variance estimator.

Main outcome measures

Operative delivery, defined as emergency cesarean or assisted vaginal delivery (ventouse extraction or forceps).

Results

A five year increase in age at menarche was associated with a reduced risk of operative delivery (risk ratio [RR] 0.84, 95% CI 0.78, 0.89; $P<0.001$). Adjustment for the age at first birth slightly strengthened the association (RR 0.79, 95% CI 0.74, 0.84; $P<0.001$). However, the association was lost following adjustment for the menarche to birth interval (RR 0.99, 95% CI 0.93, 1.06; $P=0.81$). A five year increase in menarche to birth interval was associated with an increased risk of operative delivery (RR 1.26, 95% CI 1.23, 1.28; $P<0.001$). This was not materially affected by adjustment for an extensive series of maternal characteristics (RR 1.23, 95% CI 1.20, 1.25; $P<0.001$).

Conclusions

Later menarche reduces the risk of an operative first birth through shortening the menarche to birth interval. This observation is consistent with the hypothesis that the pattern and/or duration of pre-pregnancy exposure of the uterus to estrogen and progesterone contributes to uterine aging.

Keywords Menarche, Maternal Age, Cesarean, Operative vaginal delivery.

Introduction

Rates of cesarean section (CS) have risen throughout the developed world over recent years.[1] This rise has multiple significant impacts of healthcare systems, due to increased costs and morbidity and mortality associated with surgical delivery. Rising rates of CS have been paralleled by striking increases in the average age at first childbirth.[2-4] The two trends may be connected, as multiple studies have shown that the risk of emergency CS among women having their first birth increases with increasing maternal age.[5-7]

We previously analyzed nationally collected data from Scotland and found a linear increase in the log odds of both emergency CS and operative vaginal (forceps and vacuum [ventouse]) delivery as the mother's age increased from 16y upwards.[4] We concluded that this was likely to be due to an adverse effect of increasing age at first birth on the performance of the uterus. The rationale for this hypothesis is discussed in detail in that paper. Briefly, it was based on the following observations: (i) there was no effect of statistical adjustment for maternal characteristics; (ii) most operative deliveries in this group are related to poor progress in labour;[5;7] (iii) virtually identical associations were observed for CS and assisted vaginal delivery; and (iv) all associations were strikingly linear, even when the age at first birth range was confined to 20y to 29y, indicating that it was unlikely to be explained by variation in care based on knowledge of the mother's age. Similar observations have been made in other populations.[7;8] Finally, a biological effect of post-menarche aging on uterine function was also supported by the observation that increasing age at first birth was associated with changes in the contractile properties of isolated strips of human uterine smooth muscle, specifically, reduced spontaneous activity and an increased proportion of abnormal multiphasic contractions.[4]

Postponing pregnancy, will result in exposure to cyclical estrogen and progesterone, either endogenous (among women using non-hormonal coils, barrier methods of contraception, or sexual abstinence) or exogenous (the combined oral contraceptive pill). The uterus is profoundly controlled by estrogen and progesterone.[9] Moreover, prolonged pre-pregnancy exposure to cyclical stimulation by the female sex hormones is a manifestation of modern societal and contraceptive developments and would be regarded as un-physiological when considered in an evolutionary perspective.[10] We hypothesized that prolonged, cyclical stimulation of the uterus by estrogen and progesterone prior to the first birth impairs uterine function in such a way as to predispose to operative delivery.[4] This hypothesis would explain the association between age at first birth and operative delivery, as the woman's age at her first birth is the major determinant of the menarche to birth interval (i.e. the duration of pre-pregnancy sex hormone exposure). The hypothesis make a falsifiable prediction, namely, that later menarche would be protective in relation to operative delivery, as it would shorten the interval. Therefore, the aims of the present study were (i) to determine whether age at menarche was associated with the risk of operative delivery, (ii) to determine whether any association was lost following adjustment for the menarche to birth interval, and (iii) to determine whether the menarche to birth interval is associated with the risk of operative delivery independently of potentially confounding maternal characteristics.

Materials and Methods

The cohort

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[11] The study was approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway. Participants were recruited in early pregnancy from all over Norway from 1999-2008, and 38.7% of invited women agreed to participate. Informed consent was obtained from participants upon recruitment. The study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1), and the Norwegian Research Council/FUGE (grant no. 151918/S10).The MoBA cohort now includes 109,000 children, 91,000 mothers and 71,700 fathers. Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries. The study administered a series of questionnaires but only data from the first questionnaire were used for the present analysis. The current analysis used version six of the quality-assured data files. The study was set up as a resource of data and samples to support diverse research in relation to maternal and child health, and did not have a specific hypothesis. The study organizers accept applications for access to data and/or biological samples that aim to test a specific hypothesis.

The application to request the data from the MoBa investigators for the present study had to pre-specify the primary outcome and the main exposures. This application stated that the primary outcome was operative delivery and the pre-specified main exposures were age at menarche, age at first birth and duration of use of progestogen-only contraception. Age at menarche was self-reported. Use of the progesterone-only contraceptive pill ("minipill") was coded as ever versus none and by duration of use. Ever use of progesterone contraception was defined as any reported use of the minipill, hormonal intra-uterine device, or hormone injection. Unfortunately, the number of women who reported prolonged use of these methods (>4y) of contraception was too small (<1%) for meaningful analysis and this aspect of the analysis was not pursued. Maternal pre-pregnancy height and weight were used to calculate pre-pregnancy body mass index (BMI). Fetal presentation was dichotomized into cephalic versus all other presentations. Gestational age was based on ultrasonic estimate of the due date of delivery and expressed as completed weeks. Smoking status during pregnancy was dichotomized as daily or non-daily: the primary source was MBRN, but where this was missing smoking status was based on self-report from MoBa. Diabetes was defined as either pre-pregnancy or gestational diabetes recorded in the MBRN, or self-report of ever being treated for diabetes in MoBa. Birth weight at each week of gestational age was converted into percentiles, separately for males and females and analyses of birth weight used the pooled sex and gestational age specific percentiles. Previous infertility was dichotomized on the basis of ever use of a range of treatments. Marital status was defined as married, cohabiting and all other relationships. Educational status was dichotomized into degree level or not degree level, either completed or on-going. Income was dichotomized into personal income being above or below 300,000NOK.

Pregnancy outcome data were obtained by linkage to the Medical Birth Registry of Norway (MBRN). The menarche to birth interval was defined as the difference between the age of the mother at the time of the first birth and the age of the same women at menarche. Both were recorded rounded to the nearest year, hence the menarche to birth interval is expressed as whole years. Induced labor was defined as induction by amniotomy, oxytocin infusion or prostaglandins, or any combination of these methods. Intrapartum CS was defined on the basis of induced or spontaneous onset of initiation of delivery combined with cesarean mode of delivery. Pre-labor cesarean deliveries were cases where delivery was initiated by CS. Operative vaginal birth was defined as delivery assisted by vacuum extractor (ventouse) or obstetric forceps. Pre-eclampsia was defined as new onset hypertension and proteinuria in pregnancy, and the coding of this variable in the MBRN has previously been described in detail.[12] We did not adjust for epidural anesthesia or fetal distress as these could be on the causal pathway, as they are both associated with prolonged labor. The term dystocia is used to describe slow progress in labor, not an absolute obstruction to the passage of the fetus caused by true disproportion.

Statistical analysis

Numerical data were compared using the Kruskal-Wallis test and categorical data were compared using the χ^2 test. The risk of operative delivery was modelled using Poisson regression with a robust variance estimator. This approach has previously been described to generate adjusted risk ratios (RR) where outcomes are common.[13] Age at menarche, age at first birth and menarche to birth interval were all treated continuously when included as independent variables in Poisson regression. RRs were expressed for a 5 year increase in the given interval to allow a reasonable level of precision when associations were expressed to two decimal places. Linearity was assessed using fractional polynomials.[14] In regression models, continuous variables were truncated for extreme values (the most extreme 0.2 to 0.3% of observations) to avoid overly influential outliers. Covariables were selected on the basis that they were recorded in the data source and that they were known to be, or could plausibly be, associated with both the outcome and the exposure, and were not on the causal pathway. When continuous variables were included as covariables in a model they were categorized and entered as a series of dummy variables. This was due to the relatively large number of continuous covariates and the potential for over-fitting models when using multiple fractional polynomial regression. When data were missing, the most common category was imputed for multivariate Poisson regression analysis. The relationship between age at menarche and maternal height was analyzed using multiple linear regression. Attributable fraction was calculated from a 2 x 2 table[15] where positive was defined >25th percentile of menarche to birth interval. All statistical analyses were performed using Stata v12.1.

Results

A total of 106,926 records were available from the linked MoBa and MBRN databases. 68,857 (64.4%) records had one or more exclusion criteria. Data were excluded (n [%]) where the age at menarche was missing, or outside the range 6 to 24 (6,650 [6.2]), where the age at first birth was missing (478 [0.5]), where the mother was not nulliparous (59,542 [55.7]), where the gestational age was outside the range 37 to 43 weeks (7,400 [6.9]), where the fetal presentation was non-cephalic (6,324 [5.9]), where delivery was by pre-labor cesarean (7,722 [7.2]), where the infant was stillborn (476 [0.5]), and where the birth weight was less than 1kg (511 [0.5]). This left a study group of 38,069, which was 80.3% of all births to nulliparous women recorded in the dataset. There were 28,272 (74.3%) spontaneous vaginal deliveries, 6872 (18.1%) assisted vaginal deliveries and 2,925 Caesarean Sections (7.7%). This gave a total of 9797 (25.7%) operative deliveries, which was our outcome of interest.

The median (inter-quartile range [IQR]) age at menarche was 13 (IQR 12, 14), the median age at first birth was 28 (IQR 25, 31) and the median menarche to birth interval was 15 years (IQR 12, 18). Later menarche was associated with maternal characteristics (Table 1), specifically older age at first birth, shorter menarche to birth interval, being taller, having a lower body mass index (BMI), being less likely to be a daily smoker, a higher level of education, and higher income. Later menarche was also associated with spontaneous onset of labor, non-operative delivery, and slightly smaller birth weight percentile.

A five year increase in age at menarche was associated with a reduced risk of operative delivery (0.84, 95% CI 0.78, 0.89; P<0.001). This was due to a reduced risk of both emergency CS (RR 0.73, 95% CI 0.64, 0.83; P<0.001) and operative vaginal delivery (RR 0.86, 95% CI 0.80, 0.93; P<0.001). Adjustment for the age at first birth slightly strengthened all associations (Table 2). However, adjustment for the menarche birth interval resulted in loss of all associations (Table 2).

There was a progressive increase in the proportion of cesarean deliveries, operative vaginal deliveries, and all operative deliveries with increasing menarche to birth interval (Figure 1). When the relationship was analyzed using fractional polynomial Poisson regression, the best model fit was for a linear association between menarche to birth interval and the risk of operative delivery (test for non-linearity; P>0.9). A five year increase in menarche to birth interval resulted in a 26% increase in the risk of operative delivery (Table 3). This was explained by associations with both emergency CS and operative vaginal delivery. There was no statistically significant interaction between age at menarche and age at first birth for emergency caesarean section (P=0.64), operative vaginal delivery (P=0.98) or all operative delivery (P=0.72). Adjustment for an extensive series of maternal characteristics had a minimal effect. We created a binary variable which indicated that a menarche to birth interval was greater than the lower limit of the inter-quartile range (i.e. >12). 27,758 (73%) women were above this threshold. Their RR for operative delivery was 1.42 [95% CI 1.36 to 1.48] and the attributable fraction was 23.2%.

9,797 women had the outcome of interest: i.e operative deliveries comprising of 6872 assisted vaginal deliveries and 2925 Caesarean Sections. Of these, 7,629 (77.9%) had a diagnosis of dystocia (failure to progress). The association between menarche to birth interval and the risk of operative delivery associated with dystocia was much stronger than it was for the risk of operative delivery in the absence of dystocia: adjusted relative risks for a five year increase in interval 1.25 [95% CI 1.22, 1.28] versus 1.14 [95% CI 1.09, 1.21], respectively). The association between menarche to birth interval and the risk of operative delivery was unchanged if the analysis excluded the 2,078 women who had documented ever use of progestogen only contraception (adjusted RR = 1.23 [95% CI 1.20, 1.26]).

Finally, we determined whether the relationships between age at menarche and other maternal characteristics, namely, maternal height and body mass index, were similarly dependent on the duration of the menarche to birth interval. A five year increase in age at menarche was associated with a 2.7cm (95% CI 2.4, 2.9, P<0.001) increase in maternal height. After adjustment for maternal age, the increase was 2.5cm (95% CI 2.3, 2.7, P<0.001) and after adjustment for menarche to birth interval, the increase was 3.0cm (95% CI 2.8, 3.2, P<0.001). A five year increase in age at menarche was associated with a -2.98 kg/m^2 (95% CI -3.13 to -2.82, 2.9, P<0.001) difference in maternal BMI. After adjustment for maternal age, the difference was -3.04 kg/m^2 (95% CI -3.19, -2.89, P<0.001) and after adjustment for menarche to birth interval, the difference was -2.82 kg/m^2 (95% CI -2.97, -2.66, P<0.001). Hence, in contrast to the association between age at menarche and the risk of operative delivery, the associations between age at menarche and maternal height and BMI were not lost following adjustment for the menarche to birth interval.

Discussion

Main findings

In the present study, an increased age at menarche was associated with a decreased risk of operative delivery. The risk of operative delivery progressively increased with the duration of the menarche to birth interval and that this association was unaffected by adjustment for an extensive series of maternal characteristics. The protective effect of later menarche was lost when we performed statistical adjustment for the menarche to birth interval. The effect of adjustment for menarche to birth interval was specific for operative delivery, as there was no similar effect observed when analyzing the relationship between age at menarche and maternal height or body mass index. We interpret these observations as indicating that later menarche reduces the risk of operative delivery because it is associated with a shorter menarche to birth interval. The proposed causal pathway is illustrated in Figure 2. The alternative explanation, i.e. of a confounder, is illustrated by grey lines in the same graph. Our interpretation of the current analysis is that it supports the hypothesis that the menarche to birth interval is causally related to the risk of operative delivery.

The key significance of these observations is that they provide further support for our overarching hypothesis that prolonged, pre-pregnancy stimulation of the uterus by the female sex hormones adversely affects its function and that this underlying property of the uterus explains, at least in part, the increased rates of operative delivery among women who delay first childbirth.

Strengths

The study has a number of strengths and weaknesses. Firstly, the present analysis was the result of a prior hypothesis. We had to pre-state the primary outcome, the main exposure and the analytic approach in order to obtain the data. Moreover, we made a virtually identical observation in a previous much smaller cohort study, and the present study represents validation in a much larger sample.[16] These characteristics make it very unlikely that the results of the present study were a chance finding, or were "data driven". Finally, restricting the analyses to women having their first birth was intentional as the relationship between menarche to birth interval and hormonal stimulation of the uterus would be more complex in women with previous births, due to factors such as the duration of pregnancy and subsequent lactation.

Weaknesses

Some of the information used in the present study was self-reported, including the primary exposure, namely, age at menarche. However, a previous US study found a strong correlation between actual age at menarche and the age recalled 30 years later.[17] This suggests that self-reported age at menarche is likely to be a reasonable measure of actual age at menarche. Moreover, prospective collection of this information and following more than 30,000 women through to their first birth would not be practical. A further relative weakness of the present study is that we have used the menarche to birth interval as a proxy measurement of a woman's total exposure to cyclical hormonal stimulation. However, women differ in their cycle length and those with prolonged experience of oligomenorrhoea would have been exposed to fewer cycles for a given duration of menarche to birth interval. Hence, estimating this exposure (number of hormonal cycles experienced by a woman prior to her first birth) using the menarche to birth interval will lead to misclassification. However, the effect of misclassification is generally to mask associations rather than create spurious associations where none truly exists. i.e. it is likely that we made the current observations despite misclassification rather than because of it.

Assessing the indication for CS is complex. However, the cohort consisted of nulliparous women with a singleton infant in a cephalic presentation in labor at term. Consistent with other research studies, almost 80% of the women in our cohort had an operative delivery due to dystocia (i.e. failure to progress in labor).[5;7] Moreover, we found that when we divided operative deliveries by the presence or absence of dystocia, the association with menarche to birth interval was much stronger in the former group. Therefore, operative delivery in this group is likely to be a reasonable measure of impaired uterine function. It is also possible that any effect of menarche is not mediated through the uterine smooth muscle. There are other hormonally responsive tissues in the uterus which are also important in the process of labor, in particular the cervix. Finally, the present study was confined to the outcome of operative delivery. It is plausible that the same factors may be related to other complications of pregnancy which are dependent on uterine contraction, such as postpartum hemorrhage. However, our permission to analyses the current data source was limited to the pre-specified outcomes addressed by the present analysis.

Implications and further work

The over-arching hypothesis that this work addresses is that prolonged, cyclical stimulation of the uterus by estrogen and progesterone prior to the first birth impairs uterine function in such a way as to predispose to operative delivery. We predicted that contraceptive methods employing continuous exposure to progestogens would be protective in relation to operative delivery. This is because these women would be exposed to a constant low level of progesterone, rather than cyclical stimulation and withdrawal of progesterone, as occurs with both the menstrual cycle and the combined oral contraceptive pill. Unfortunately, less than 1% of the cohort had employed prolonged use of progestogen only contraceptives and this could not be tested directly.

Although we have now found supportive evidence in two high quality cohort studies that support the hypothesis, experimental testing of the hypothesis is clearly not feasible in women. The hypothesis is, however, amenable to experimental testing in an animal model such as rodents which have a cyclical pattern of estrogen and progesterone stimulation similar to the menstrual cycle (estrous cycle). Our hypothesis predicts that blocking the estrous cycle would ameliorate the effect of aging on the uterus. We have recently tested this experimentally.[18] The key finding of this work was that preventing cyclical secretion of estrogen and progesterone (by either early oophorectomy or prolonged treatment with progesterone implants) prevented uterine aging, as measured by age-related changes in the mRNA transcript profile. These experiments provide direct experimental evidence that aging of the uterus is associated with exposure to cyclical female sex hormones.

Conclusions

Later menarche reduces the risk of an operative first birth through shortening the menarche to birth interval. Further studies are required to determine whether any effect of reproductive aging of the human uterus can be modified by different hormonal exposure following menarche, and on the mechanistic link between menarche to birth interval and the risk of operative delivery. Specifically, the impact of non-cyclical contraceptives such as progestogen intra-uterine devices and continuous use of combined oral contraceptives warrant further investigation.[19] If the hypothesis is correct, it suggests that these forms of contraception may result in better preservation of uterine function and, hence, reduce the risk of operative delivery among older women. Future studies could include a detailed menstrual diary as well as contraceptive history in order to better assess the impact of cyclical ovarian steroids on mode of delivery. Given that the vast majority of women will plan to delay first pregnancy for many years after menarche, better understanding of the relationship between the pre-pregnancy pattern of hormonal exposure of the uterus and the outcome of the first pregnancy is clearly a critical area for future research.

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Legend for figure.

Figure 1.

Raw data of the relationship between menarche to birth interval and the proportion of operative deliveries (i.e. both cesarean and vaginal), operative vaginal deliveries and intrapartum cesarean deliveries among 38,069 nulliparous women in labor at term with a singleton infant in a cephalic presentation. Cesarean deliveries are expressed as a percentage of all births. Operative vaginal deliveries are expressed as a percent of all non-cesarean births.

Figure 2.

Schematic outline of proposal causal pathway (solid black arrows) and alternative pathway, mediated through confounders (grey arrows). The causal pathway is supported by two statistical observations. 1. The protective effect of later menarche on the risk of operative delivery is completely lost following adjustment for menarche to birth interval. 2. The positive linear relationship between menarche to birth interval and the risk of operative delivery is unaffected by adjustment for a range of maternal characteristics.

Figure 1

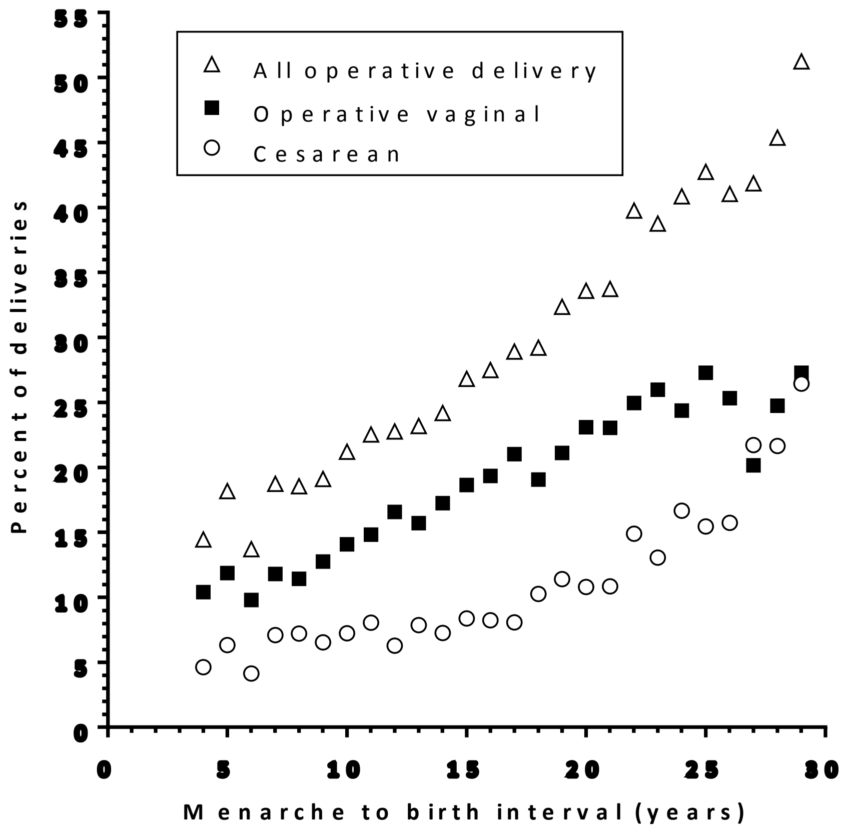
All operative delivery
Operative vaginal
Cesarean
Percent of deliveries
Menarche to birth interval (years)
0
5
10
15
20
25
30
35
40
45
50
55

Figure 2

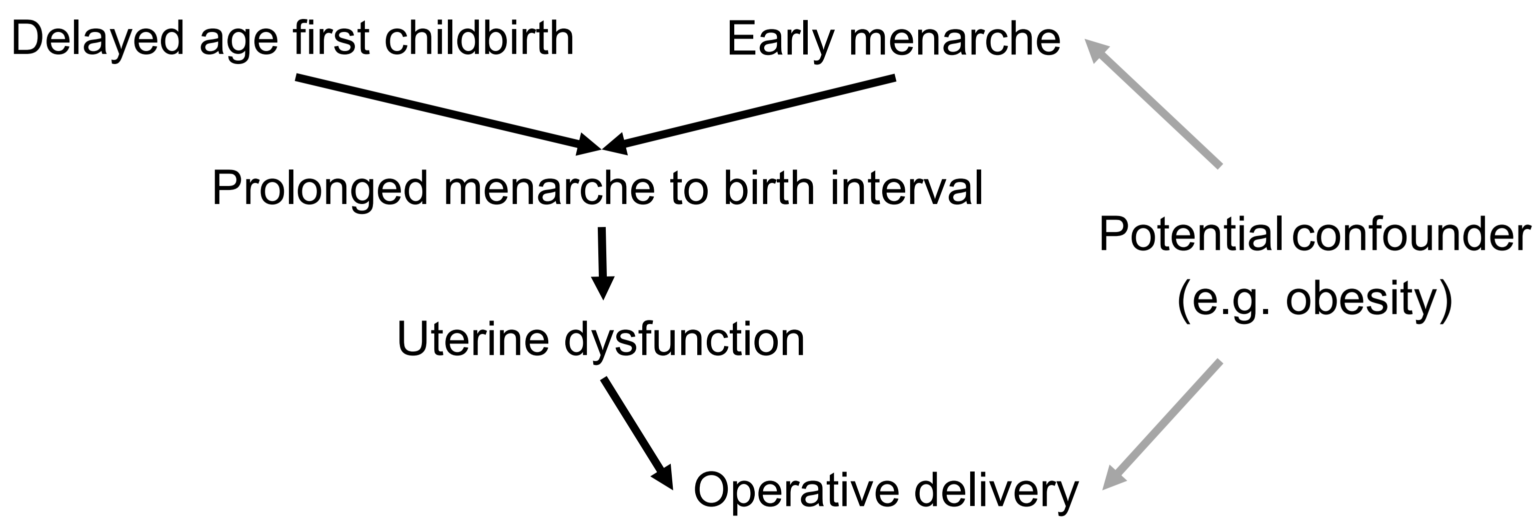
Delayed age first childbirth
Early menarche
Prolonged menarche to birth interval
Potential confounder
(e.g. obesity)
Uterine dysfunction
Operative delivery

Table 1. Characteristics of the cohort by age of menarche

Maternal & Obstetric Characteristics	*Menarche aged ≤11y (n=4,521)*	*Menarche aged 12y to 14y (n=28,673)*	*Menarche aged ≥15y (n=4,875)*	**P=*
Maternal characteristics				
Age at first birth				
Median (IQR)	28 (25-31)	28 (25-31)	29 (26-32)	<0.001
Menarche to birth interval				
Median (IQR)	17 (14-20)	15 (12-18)	14 (11-16)	<0.001
Height (cm)				
Median (IQR)	167 (163-170)	168 (164-172)	169 (165-173)	<0.001
Missing	48 (1.1)	267 (0.9)	46 (0.9)	0.7
Body mass index				
Median (IQR)	24.2 (22.0-27.5)	22.8 (20.9-25.3)	21.9 (20.3-23.9)	<0.001
Missing	127 (2.8)	637 (2.2)	104 (2.1)	0.04
Smoking status				
Not daily smoker	3,970 (87.8)	25,462 (88.8)	4,401 (90.3)	
Daily smoker	511 (11.3)	2,856 (10.0)	409 (8.4)	<0.001
Missing	40 (0.9)	355 (1.2)	65 (1.3)	
Marital status				
Married	1,603 (35.5)	9,780 (34.1)	1,708 (35.0)	
Cohabiting	2,606 (57.6)	17,362 (60.6)	2,933 (60.2)	<0.001
Other	293 (6.5)	1,440 (5.0)	222 (4.6)	
Missing	19 (0.4)	91 (0.3)	12 (0.2)	
Education				
Less than degree	1,399 (30.9)	7,924 (27.6)	1,238 (25.4)	
Degree	2,782 (61.5)	18,881 (65.8)	3,359 (68.9)	<0.001
Missing	340 (7.5)	1,868 (6.5)	278 (5.7)	
Income				
<300,000NOK	2,879 (63.7)	17,233 (60.1)	2,713 (55.7)	
>300,000	1,486 (32.9)	10,658 (37.2)	2,034 (41.7)	<0.001
Missing	156 (3.5)	782 (2.7)	128 (2.6)	
Previous miscarriage				
1 or more	594 (15.3)	3,530 (14.2)	615 (14.4)	0.19
Missing	628 (13.9)	3,753 (13.1)	593 (12.2)	0.045

Maternal & Obstetric Characteristics	*Menarche aged ≤11y (n=4,521)*	*Menarche aged 12y to 14y (n=28,673)*	*Menarche aged ≥15y (n=4,875)*	**P=*
Infertility	407 (9.0)	2,282 (8.0)	424 (8.7)	0.02
Diabetes	84 (1.9)	360 (1.3)	58 (1.2)	0.003
Obstetric characteristics				
Pre-eclampsia	235 (5.2)	1,217 (4.2)	152 (3.1)	<0.001
Congenital anomaly	200 (4.4)	1,354 (4.7)	207 (4.2)	0.27
Gestational age at delivery				
Median (IQR)	40 (39-41)	40 (39-41)	40 (39-41)	0.9
Onset of labor				
Spontaneous	3,723 (82.3)	24,348 (84.9)	4,206 (86.3)	<0.001
Mode of delivery				
Spontaneous vaginal	3,279 (72.5)	21,280 (74.2)	3,713 (76.2)	
Assisted vaginal	839 (18.6)	5,228 (18.2)	805 (16.5)	<0.001
Cesarean	403 (8.9)	2,165 (7.6)	357 (7.3)	
Birth weight percentile				
Median (IQR)	51 (25-77)	50 (25-75)	49 (24-74)	0.02
Missing	0 (0.0)	14 (<0.1)	5 (0.1)	0.08

*P values from Kruskal-Wallis test or χ^2 test, as appropriate

IQR denotes inter-quartile range. NOK denotes Norwegian Krone

Table 2. Poisson regression analysis of age at menarche and the risk of operative delivery

	Associations for a 5y increase in age at menarche			
	Adjusted for age at first birth†	*P=*	*Adjusted for menarche to birth interval*	*P=*
Risk ratios for operative delivery [95% CI]				
All operative delivery	0.79 [0.74, 0.84]	<0.001	0.99 [0.93, 1.06]	0.81
Cesarean	0.68 [0.60, 0.78]	<0.001	0.89 [0.78, 1.02]	0.10
Operative vaginal*	0.81 [0.75, 0.87]	<0.001	1.03 [0.95, 1.12]	0.48

In all analyses, age at menarche was truncated at 9y and 17y, age at first birth was truncated at 16y and 42y, menarche to birth interval was truncated at 4y and 29y. The correlation between menarche to birth interval and age at menarche was weak (r= -0.22), hence both could be included as covariables in the same model.

*Analysis of the risk of operative vaginal delivery was confined to women who were not delivered by cesarean.

†The corresponding risk ratios (95% CI) for a 5y increase in maternal age at the time of the first birth, adjusted for the age at menarche, were 1.26 (1.24, 1,28) for all operative delivery, 1.31 (95% CI 1.25, 1.36) for cesarean section, and 1.27 (1.24, 1.30) for operative vaginal delivery.

Table 3. Poisson regression analysis of menarche to birth interval and the risk of operative delivery.

	Associations for a 5y increase in menarche to birth interval			
	Unadjusted	*P=*	*Fully adjusted*†	*P=*
Risk ratios for operative delivery [95% CI]				
All operative delivery	1.26 [1.23, 1.28]	<0.001	1.23 [1.20, 1.25]	<0.001
Cesarean	1.32 [1.27, 1.37]	<0.001	1.29 [1.23, 1.34]	<0.001
Operative vaginal*	1.27 [1.24, 1.30]	<0.001	1.24 [1.21, 1.28]	<0.001

Menarche to birth interval was truncated at 4y and 29y

*Analysis of the risk of operative vaginal delivery was confined to women who were not delivered by cesarean.

†Adjusted for maternal height, BMI, smoking status, marital status, onset of labor, week of gestational age, birth weight percentile, infertility treatment, diabetes, educational status, household income, previous miscarriages, pre-eclampsia, and congenital anomalies. Adjustment could not be performed for age at first birth due to the high degree of collinearity between menarche to birth interval and age at first birth (r=0.95).