OBSTETRICS

Inherited predisposition to stillbirth: an intergenerational analysis of 26,788 mother-daughter pairs

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BACKGROUND: Previous evidence suggests that placental dysfunction, which includes preeclampsia, is inherited from mother to daughter, but heritability of stillbirth has never been investigated.

OBJECTIVE: The purpose of this study was to investigate whether there is an inherited predisposition to stillbirth that is transmitted from mother to daughter.

STUDY DESIGN: We carried out a nested case-control study within the intergenerational cohort held in the Aberdeen Maternity and Neonatal Databank. All mothers who had at least 1 daughter in Aberdeen, United Kingdom, between 1949 and 2000 were included. Mother-daughter pairs were linked with the use of the Scottish Community Health Index number. The main exposure was the mother's history of stillbirth. The primary outcome was stillbirth in any of the daughter's pregnancies. A population average model that used generalized estimating equations with robust standard errors was used to estimate odds of a mother's history of stillbirth in daughters with a stillbirth compared with daughters with only livebirths. This method accounted for clustering of daughters within mothers, and multi-adjusted analyses were performed to include confounders at the daughter's pregnancy level.

RESULTS: Among the daughters, 384 had a history of ≥1 stillbirths (cases); 26,404 only ever had livebirths (control subjects). We found no statistically significant association between mothers' history of stillbirth (adjusted odds ratio, 0.63; 95% confidence interval, 0.24–1.63) or miscarriage (adjusted odds ratio, 1.01; 95% confidence interval, 0.71–1.42) and stillbirth in daughters.

CONCLUSION: This is the first study to investigate an inherited predisposition to stillbirth. There was no evidence of an inherited predisposition to stillbirth transmitted from mother to daughter.

Key words: familial, intergenerational, intrauterine, mother-daughter pairs, stillbirth

In the United States, 23,000 babies were stillborn in 2013 (5.96 per 1000 total births).[1] In 2015, the stillbirth rate per 1000 total births was 4.5 in England and Wales[2] and 18.4 worldwide.[3] Although several risk factors[3–7] have been incriminated, many cases of stillbirth remain unexplained.[6–9] Parents often look for an explanation for this catastrophic life event and are willing to make lifestyle changes to try to improve the outcome of future pregnancies. Women with a history of stillbirth have an increased risk of recurrence of this event[10,11] and other obstetric complications in subsequent pregnancies,[12] which suggests that there may be genetic, lifestyle, or environmental factors that may have a detrimental and repeated impact on future reproductive outcomes.

Familial predisposition to adverse obstetric outcomes such as preterm birth,[13–15] growth restriction,[16–18] and preeclampsia[15,19] suggests that disorders of placental function may be inherited. Because placental dysfunction, growth restriction, and prematurity are all associated with the pathophysiology of stillbirth,[3,6] it is possible that there could be an underlying familial predisposition. Previous studies have investigated mothers with adverse obstetric outcomes;[15,20] however, none have investigated the influence of a mother's history of stillbirth on the risk of a similar event in daughters.

The Aberdeen Maternity and Neonatal Databank (AMND) is a population-based database that holds routinely collected obstetric- and fertility-related data from 1949 to the present day for all deliveries and reproductive outcomes from the only maternity hospital for the geographic area of Aberdeen City, Scotland, UK.[21] Data routinely are collected continuously from hospital medical records by a dedicated data management team and entered into the AMND database at the end of each pregnancy.[21] All pregnancy records are included automatically, and the information is entered routinely for all women under the jurisdiction of Aberdeen Maternity Hospital. Therefore, we can be confident that all stillbirth records for this area are recorded within the database. The AMND provides a rare opportunity to study an intergenerational population with a low outmigration rate,[21] which enables us to explore stillbirth in mother-daughter pairs. This cohort has been used successfully in the past to answer a similar question about inherited predisposition to preterm birth.[14] The objective of this study was to determine whether a history of stillbirth in mothers is associated with an increased risk of stillbirth in daughters.

Materials and Methods

Study design and conduct

This was a case-control study nested within the intergenerational cohort of mother-daughter pairs from the AMND.[21] The population consisted of all mother-daughter pairs who each had

Cite this article as: Woolner AMF, Raja EA, Bhattacharya S, et al. Inherited predisposition to stillbirth: an intergenerational analysis of 26,788 mother-daughter pairs. Am J Obstet Gynecol 2019;220:393.e1-7.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.01.215

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AJOG at a Glance

Why was this study conducted?

We conducted this study to determine whether daughters were at higher risk of stillbirth if their mother had a history of stillbirth.

Key findings

There does not appear to be an inherited predisposition to stillbirth that is transmitted from mother to daughter.

What does this add to what is known?

This is the first observational study to investigate inherited predisposition to stillbirth between mother-daughter pairs.

pregnancies delivered (livebirths or stillbirths) from 1949−2016 at Aberdeen Maternity Hospital, Scotland. Mothers who delivered babies from 1949−2000, and daughters who gave birth from 1965−2016 were included. Mother-daughter pairs were identified by deterministic matching with the use of unique Scottish Community Health Index numbers, where available, or probabilistic matching on surname (daughters' maiden name), postal code, and dates of delivery by the AMND data management team at the University of Aberdeen, and an anonymized database was given to researchers for analysis. Only singleton births in both the mothers and daughters were included.

Mothers who gave birth to liveborn sons, but not daughters, were excluded. Because the risk of stillbirth is 4-fold higher for multiple pregnancies than singleton pregnancies,[22] multiple pregnancies in both mothers and daughters were excluded. The World Health Organization defines stillbirth as a baby born with no signs of life ≥28 weeks gestation.[23] However in the United Kingdom, including within the AMND, stillbirth is defined as a baby born with no signs of life after the 24th gestational week.[7] Therefore, in this study, we used intrauterine death from 24 weeks gestation as the definition of stillbirth.

Cases were defined as daughters with a history of at least 1 stillbirth in any of their pregnancies. Control subjects were defined as daughters with a history of ever delivering only liveborn infants, with no history of miscarriage or stillbirth. The exposure was (1) a mother's history of stillbirth and (2) a mother's history of miscarriage. The pregnancy record for the first stillbirth (cases) or first livebirth (control subjects) were included in all data analyses.

The following potential confounders were adjusted for in the multivariate model: daughter's age at delivery, smoking status (non-, ex-, and current smoker), deprivation category[24] (most deprived [4−6] and least deprived [1−3]), body mass index (<20, 20−25, 26−30, >30 kg/m^2), preeclampsia (yes/no), antepartum hemorrhage (yes/no), gestation at birth (preterm, <37 week gestation, and term ≥37 weeks gestation), parity (primigravid/parous). Age at delivery is collected routinely by the AMND from the hospital medical records.[21] Smoking status is self-reported at the time of antenatal booking and then documented within the hospital record from which it is collected for the AMND. Gestation at delivery is coded according to the due date that was estimated by the first trimester ultrasound scan when available from hospital records (from 1986 onwards)[21] and otherwise by the last menstrual period date that was recorded at first antenatal booking. Antepartum hemorrhage (APH) is defined in the AMND as vaginal bleeding after 24 weeks gestation; the information is collected from hospital records. Preeclampsia is defined as gestational hypertension and at least 1 episode of proteinuria (0.3 g protein in 24 hours);[25] this information is collected from the hospital records. Deprivation category[24] is a Scottish measure of deprivation that categorizes socioeconomic deprivation by assessing national information on several parameters that include income, employment, health, education, and housing. Deprivation category ranks deprivation from 1−6, where 1 represents the least and 6 the most deprived area. This is entered for all women at their pregnancy booking appointment according to their home address (using postal codes).

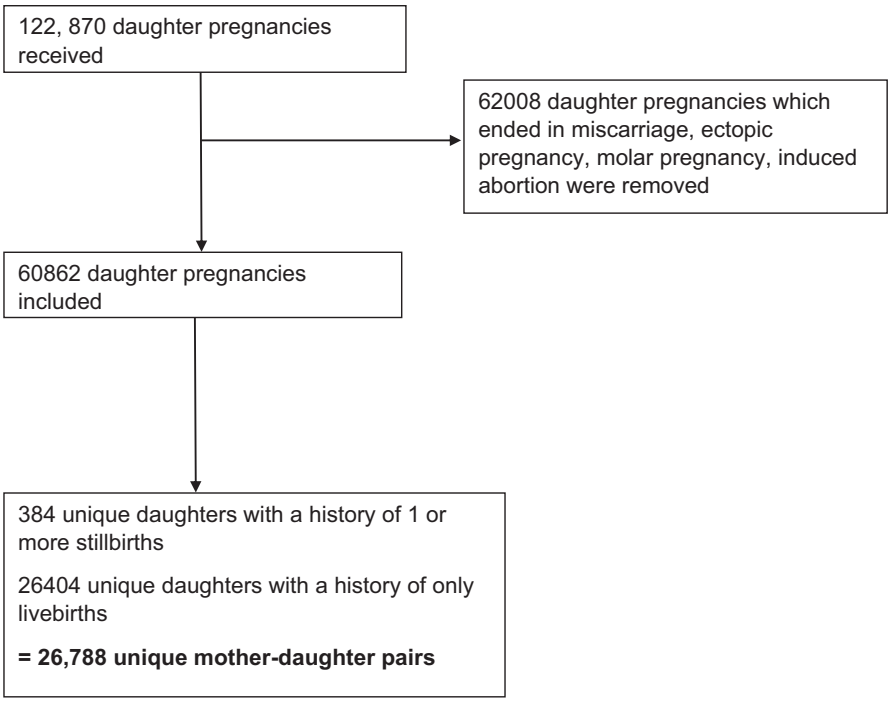
Sample size and power calculation

Assuming a 1% prevalence of stillbirth in the population, a power calculation is made with the use of nQuery advisor software (nQuery [2017]; Stat-Sols, Statistical Solutions Ltd, Cork, Ireland). "Statsols" (Statistical Solutions Ltd, Cork, Ireland) showed that there was 94% power to detect a difference in prevalence of stillbirth of 3% in 576 daughters of mothers with at least 1 stillbirth compared with 1% in 26,212 daughters with a mother with all live births (P=.05 in a 2-sided test). After taking account of the clustered data structure, with large numbers of mothers, small numbers of daughters per mother, and assuming very small intraclass correlation, the power of the study was expected to be at least 80%.

Statistical analysis

All data were stored and analyzed with SPSS software (IBM SPSS Statistics for Windows, version 24.0; IBM Corporation, Armonk, NY). The analyses were carried out under a multilevel framework, with a population average model[26−28] with generalized estimating equations to account for the clustering of multiple daughters (level 1) nested within the same mother (level 2). Specifically, the robust standard errors of the regression coefficients were estimated by the specification of a working exchangeable correlation structure that assumes that the risk of stillbirth is the same in any daughter if the mother had a history of stillbirth. Unadjusted and adjusted analyses were carried out to determine associations between sociodemographic and pregnancy characteristics and a daughter's history of stillbirth. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are presented. Probability values of <.05 were considered statistically significant.

FIGURE 1
Flowchart of selection of mother-daughter pairs



This flowchart shows the population selection for mother-daughter pairs included in this study. Cases were daughters with a history of 1 or more stillbirths and controls were daughters with only a history of livebirths.

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Missing values

Where >5% of covariate data were missing, values were aggregated from complete data in another of the same daughter's pregnancies. Aggregated missing data were used for daughter's body mass index, smoking status, and deprivation category. Complete case analysis was then carried out with the use of the aggregated covariate data. When there was >1 pregnancy record available for the same daughter from which to aggregate data, (1) the maximum recorded body mass index was used, (2) the maximum recorded deprivation category score was used (highest value represented most deprived), and (3) "smoker" was accepted over "ex-smoker" and "nonsmoker".

Ethical considerations

Approval to conduct this study was obtained from the AMND steering committee. The AMND has an overall Research Ethics Committee approval (reference no.:1/0/58-13-NS-0050 North of Scotland Research Ethics committee) that allows data that is recorded within AMND to be used for steering committee–approved research projects. The study is reported in accordance with the STROBE Statement for observational studies.[29]

Results

An anonymized dataset with 122,870 mother and daughter pregnancies was received from the AMND data management team. After cleaning and removal of any ineligible and duplicate records, 26,788 unique mother-daughter pairs were eligible for inclusion in this study (Figure 1). Figure 2 shows the rate of stillbirths over the study time period (as a percentage of total births for mothers and daughters within the AMND population sample). Stillbirth ranged from 0.3–1.1% of all intrauterine pregnancies during this sample. A total of 384 daughters had a history of at least 1 stillbirth; 26,404 daughters had only livebirths. Ten daughters (2.6%) with a history of stillbirth had 2 stillbirths. For this analysis, only the first stillbirth was considered.

Demographic and pregnancy characteristics were compared between daughters who ever had a stillbirth (n=384 [cases]) and daughters who only ever had livebirths (n=26404, [control subjects]; Table 1). Women with a stillbirth were >3 times more likely to have an APH, more likely to be socioeconomically deprived, and twice as likely to smoke in their first stillborn pregnancy compared with daughters with their first liveborn pregnancy.

We compared reproductive histories in mothers of daughters with and without a history of stillbirth (Table 2). There was no association between a mother's history of stillbirth and stillbirth in the daughter (OR, 0.72; 95% CI, 0.32–1.62; adjusted OR, 0.63; 95% CI, 0.24–1.63) after adjustment for potential confounders. Similarly, there was no association between a mother's history of miscarriage (OR, 0.88; 95% CI, 0.65–1.20; adjusted OR, 1.01; 95% CI, 0.71–1.42) or ≥2 recurrent miscarriages (OR, 0.77; 95% CI, 0.36–1.63; adjusted OR, 0.94; 95% CI, 0.42–2.10) and the outcome of stillbirth in the daughter.

Comment

Principal findings

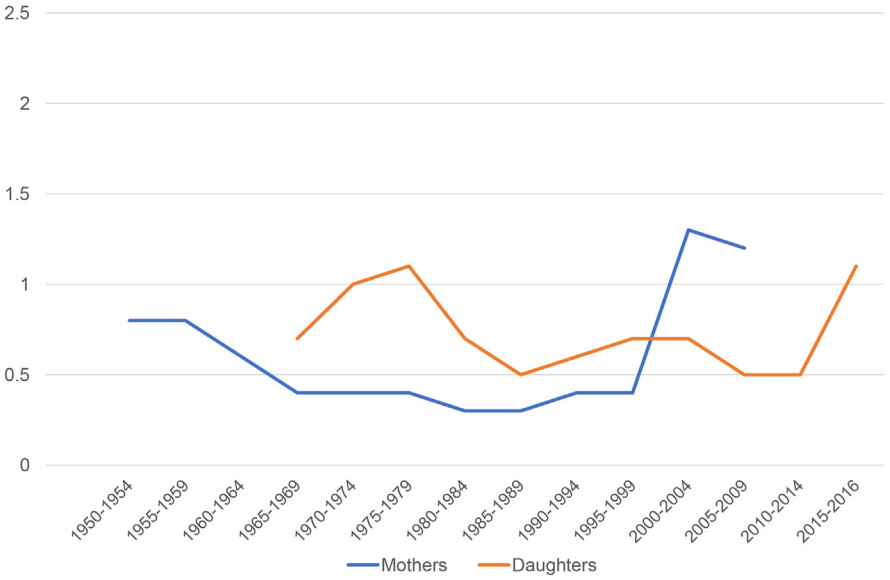
From our analyses, there does not appear to be an increased risk of stillbirth in daughters whose mothers had a history of stillbirth or miscarriage. To the authors' knowledge, this is the first observational study to investigate stillbirth risk transmitted from mother to daughter.

Stillbirths were 17 times more common at <37 weeks gestation. In comparison with those who had only livebirths, daughters who had a history of stillbirth were almost 3 times more likely to have an APH in their first stillbirth. Daughters with a stillbirth were significantly more likely to be socioeconomically deprived and smokers.

Strengths and limitations

Aberdeen has a stable population with a low outmigration rate,[21] which means

FIGURE 2
Stillbirths over time for study mothers and daughters from 1949–2016



Stillbirths in mothers and daughters ranged from 0.3% to 1.1% of all recorded intrauterine pregnancies from 1949 until 2016 in this study population.

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that many mothers and daughters remain in Aberdeen for their pregnancies and makes this an ideal data source to perform an intergenerational study. There remains a small risk of bias that some mothers and daughters may not have all their pregnancies recorded within the AMND. Standardized coding criteria and regular quality checks means that the AMND is a robust and valid data source[21] and allows many covariates to be included in the model because of the detailed clinical information recorded in the database. Using Scottish Community Health Index identifiers meant that mothers and daughters could be linked easily within the AMND; therefore, it was possible to include all eligible women in the study. Deterministic matching should be 100% accurate with the use of community health index numbers, and probabilistic matching can be up to 97% accurate. The use of retrospective data will always incur risks of bias, but the risk is minimized, given the low outmigration rate;[21] because the data in the AMND is collected routinely, there is no risk of recall bias.

The relative rarity of stillbirth as an outcome meant that a nested case-control approach was the most efficient study design. However, because there were only 384 cases in the sample, we cannot rule out the possibility of a type 2 error.

Because each mother and daughter could have several pregnancies, there was clustering of >1 pregnancy within each daughter and daughters nested within each mother. Including individual daughters (first stillbirth [cases] vs first livebirth [control subjects]), as opposed to including each daughter pregnancy, ensured that cases and control subjects were included only once. This meant that there was no issue of clustering of pregnancies within daughters. To account for clustering of >1 daughter (sisters) within mothers, we used a population average model under a multilevel framework approach.

Stillbirth rates have varied over time in this sample from 0.3–1.1% of all intrauterine pregnancies, which may reflect temporal variations in reporting. There is a sharp increase from 1995 for mothers that may reflect the change in definition of stillbirths to include up to 24 weeks gestation. A similar increase is seen from 2010–2016 in daughters for which there is no clear explanation. This rise could be due to changing population demographics such as increasing obesity or maternal age at conception within daughters Overall, the proportions are generally in keeping with national estimates.[7,30] Therefore, the results are likely to be generalizable to other areas with similar antenatal care in high-income countries. However, the population in the North East of Scotland is primarily white and financially affluent,[21] which may limit generalizability. A formal analysis of ethnicity, however, was not possible because these data were not available. It was not possible to study familial predisposition to stillbirth passed via the male line in this study.

By using aggregated values for missing covariate data, we were able to run all of the planned analyses and maximize the power of the study to answer the research questions that were posed. Given that many sociodemographic characteristics are likely to remain the same for a woman's reproductive life, this approach was deemed appropriate. Furthermore, this meant that data were missing for <10% for all covariates that were included in the multivariate model. Aggregated data were used for body mass index (original missing data, 24%; after aggregation, 6%), smoking (original missing data. 13%; after aggregation, 8%), and deprivation category (original missing data, 14%; after aggregation, 3%). It is possible, however, that some daughters may have had only 1 pregnancy recorded, so this method has limitations in cases in which that single record has incomplete data.

We were unable to differentiate intrapartum from antepartum stillbirth within the dataset. This is a limitation because there may be different pathophysiologic mechanisms involved in the 2 forms of stillbirth for which the results were unable to account. Earlier stillbirths may be less likely to be caused by placental dysfunction and more likely to be caused by infection or congenital anomaly. Therefore, a further analysis was carried out that compared the daughters with a history of preterm (<37 weeks gestation; n=242) and term (≥37 weeks; n=147) stillbirths. Again,

TABLE 1
Comparison of demographic and pregnancy characteristics for daughters with and without a history of stillbirth (N = 26788)

Daughter's pregnancy characteristic	Daughters with history of stillbirth, n (%)[a]	Daughters with only livebirths, n (%)[b]	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)	*P* value
Age at delivery, y					<.001[c]
≤20	88 (22.9)	7,461 (28.3)	0.97 (0.74–1.26)	0.76 (0.55– 1.06)	
21-25	127 (33.1)	8,726 (33.0)	1.00	1.00	
26-30	93 (24.2)	6,678 (25.3)	0.99 (0.75–1.29)	1.36 (0.98–1.88)	
31-35	59 (15.4)	2,900 (11.0)	1.41 (1.02–1.93)	2.22 (1.51–3.27)	
36-40	15 (3.9)	598 (2.3)	1.19 (0.62–2.29)	2.02 (1.09–3.77)	
>40	2 (0.5)	41 (0.2)	3.48 (0.83–14.60)	2.77 (0.54–14.20)	
Smoking status					<.001[c]
Nonsmoker	135 (37.8)	13,154 (54.0)	1.00	1.00	
Current smoker	200 (56.0)	8,671 (35.6)	1.97 (1.57–2.47)	1.93 (1.46–2.56)	
Ex-smoker	22 (6.2)	2,540 (10.4)	1.81 (1.29–2.52)	1.01 (0.61–1.66)	
Missing	27 (7.0)	2,039 (7.7)			
Deprivation category					.004
Least deprived (1-3)	160 (42.7)	13,364 (52.4)	1.00	1.00	
Most deprived (4-6)	215 (56.0)	12,161 (47.6)	1.49 (1.22–1.84)	1.48 (1.14–1.93)	
Missing	9 (2.3)	879 (3.3)			
Body mass index, kg/m^2					<.001[c]
<20	5 (1.4)	57 (1.2)	0.78 (0.32–1.95)	0.68 (0.27–1.72)	
20-25	72 (20.0)	1,066 (21.5)	1.00	1.00	
26-30	140 (38.9)	2,065 (41.7)	1.15 (0.87–1.53)	1.40 (1.00–1.96)	
>30	143 (39.7)	1,760 (35.6)	1.40 (1.05–1.86)	2.06 (1.48–2.86)	
Missing	24 (6.3)	1,639 (6.2)			
Preeclampsia					.560
No	342 (89.1)	24,564 (93.6)	1.00	1.00	
Yes	42 (10.9)	1,693 (6.4)	1.42 (0.99–2.02)	0.89 (0.61–1.31)	
Antepartum hemorrhage					<.001[c]
No	237 (61.7)	23,501 (89.0)	1.00	1.00	
Yes	147 (38.3)	2,903 (11.0)	4.10 (3.30–5.08)	2.82 (2.16–3.69)	
Preterm birth					<.001[c]
Term (≥37 wk)	134 (35.4)	24,524 (93.1)	1.00	1.00	
Preterm (<37 wk)	244 (64.6)	1,818 (6.9)	24.55 (19.78–30.48)	17.58 (13.75–22.48)	

[a] N=384; [b] N=26,404; [c] Denotes statistically significant. Multi-adjusted models were adjusted for age at delivery, smoking, deprivation, body mass index, year of delivery, parity, gestation, preeclampsia, antepartum hemorrhage, and exposure of mother's history of stillbirth. Missing covariates, where possible, were aggregated from other pregnancy records from same daughter for body mass index, smoking, and deprivation; thereafter, complete case analysis was carried out with aggregated values for the covariates that were included. Missing data were not included in the calculation of proportions.

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there was no evidence of a familial association with mother's history of stillbirth and term vs preterm stillbirth in the daughter (adjusted OR, 1.60; 95% CI, 0.25–10.39), which was adjusted for age at delivery, smoking, deprivation category, body mass index, year of delivery, parity, preeclampsia, APH). However, because of the small sample size, these results should be interpreted with caution. Larger intergenerational datasets should aim to investigate

TABLE 2
Comparison of mother's reproductive history for daughters with and without a history of stillbirth (N = 26,788)

Mother's reproductive history	Stillbirths, n (%)[a]	Livebirths, n (%)[b]	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)	*P* value
Stillbirth					.341
No	378 (98.4)	25,834 (97.8)	1.00	1.00	
Yes	6 (1.6)	570 (2.2)	0.72 (0.32–1.62)	0.63 (0.24–1.63)	
Miscarriage					.979
No	338 (88.0)	22,878 (86.6)	1.00	1.00	
Yes	46 (12.0)	3,526 (13.4)	0.88 (0.65–1.20)	1.01 (0.71–1.42)	
Recurrent miscarriage					
≤1	377 (98.2)	25,782 (97.6)	1.00	1.00	.884
≥2	7 (1.8)	622 (2.4)	0.77 (0.36–1.63)	0.94 (0.42–2.10)	
Any pregnancy loss					.589
No	334 (87.0)	22,421 (84.9)	1.00	1.00	
Yes	50 (13.0)	3,983 (15.1)	0.84 (0.62–1.14)	0.91 (0.65–1.28)	

[a] N=384; [b] N=26,404. Multi-adjusted models were adjusted for age at delivery, smoking, deprivation, body mass index, year of delivery, parity, gestation, preeclampsia, antepartum hemorrhage, and mother's reproductive history.

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familial predisposition to stillbirth according to gestational age.

Furthermore, we were unable to include relevant maternal medical conditions, such as chronic hypertension, diabetes mellitus, connective tissue disorders, thyroid disorders, thrombophilias, or substance abuse as confounding factors. These conditions were not all recorded within the database. This is a limitation to the study because these conditions are associated with stillbirth.

Interpretation

This study adds to the body of literature on stillbirth causes. Our results do not suggest a need for extra vigilance for women with a maternal history of stillbirth, but more research is needed to confirm or refute our findings in other populations because there may be a possibility that our study is underpowered.

The lack of association is in keeping with the findings of other studies that investigated the inheritability of placental dysfunction. Wikström et al[15] found that being born small for gestational age led to a higher risk of disorders of placental dysfunction. The findings suggest that there could be a genetically inherited predisposition to placental dysfunction transmitted from parents. However, in the adjusted analyses in this large population-based cohort study, the risk of stillbirth in offspring was not statistically significant (adjusted OR, 1.24; 95% CI, 0.84–1.82).[15] The results suggest that there is no inherited predisposition to stillbirth if born small-for-gestational-age.[15] Conversely, an animal study found that Rhesus monkey daughters had a higher risk of stillbirth if their mothers were born small-for-gestational-age.[31] A population-based study found that mothers of Pakistani descent who lived in Norway were at greater risk of stillbirth and infant death than mothers born of Norwegian descent, which suggests that there could be a genetic predisposition, although other socioeconomic or environmental factors could be responsible for this ethnic variation.[20]

The recurrence risk of stillbirth supports the theory that some women may possess a predisposition to stillbirth;[10] however, this may not be an inherited familial predisposition. It is possible that daughters with a maternal or family history of stillbirth may be more aware of modifiable risk factors for stillbirth and may be more vigilant to seek obstetric care, for example, with reduced fetal movements. This could potentially lead to a reduction in the risk of stillbirth in daughters. However, there was no statistically significant association found in our study.

Future research

This study sets a model for the same research question to be answered with larger datasets and, where possible, with the use of national datasets in different populations. National intergenerational datasets with enough longevity to capture the reproductive history of mothers and daughters should be used to confirm or refute our findings. The outmigration rate should also be quantified in future research to minimize bias from attrition when mothers and daughters have pregnancies recorded in different geographic areas and hospitals. Placental abruption was associated independently with a history of stillbirth in daughters in this study. An intergenerational study found placental abruption was more common in women who were born small-for-gestational-age.[15] This suggests an association with placental dysfunction and a risk of abruption. More research is needed to determine whether there is a familial predisposition

to APH and specifically placental abruption. If a familial predisposition to placental abruption were found, this could be associated with consequent higher risk of stillbirth in these women.

Stillbirth can cause significant psychologic stress in a subsequent pregnancy[32] and an increased risk of future adverse obstetric outcomes.[12] This emphasizes the need to improve our ability to identify women who are at risk of stillbirth and to develop prevention. Although this study presents no evidence of a familial predisposition to stillbirth, more research is needed to identify potential genetic or epigenetic factors that are associated with disorders of placental dysfunction, including stillbirth.

Conclusion

There does not appear to be an inherited predisposition to stillbirth transmitted from mother to daughter. More research is needed to understand the causes of stillbirth. ■

Acknowledgments

Thank you to the Aberdeen Maternity and Neonatal Databank data management, University of Aberdeen, for their efforts in data extraction and management for the study and to Dr Gordon Prescott, Medical Statistician at the University of Aberdeen, for providing statistical advice.

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Received Aug. 30, 2018; revised Dec. 27, 2018; accepted Jan. 16, 2019.

Supported by internal funding that was received for the costs of data extraction from the Aberdeen Maternity and Neonatal Databank from the Fetal and Perinatal endowment fund, NHS Grampian, Aberdeen, UK.

The authors report no conflict of interest.

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