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Poster

Conjoint association of first pregnancy gestational diabetes, preeclampsia and birthweight on gestational diabetes in the subsequent pregnancy

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Abstract text

Background: Gestational diabetes mellitus (GDM) and preeclampsia may present as opposite entities with preeclampsia being linked to vascular dysfunction and a small fetus and GDM to metabolic dysfunction and a large fetus. Less is known on the co-occurrence and interactions between diagnoses as most studies investigate one complication at a time. We explored the joint association of first pregnancy GDM, hypertensive disorders of pregnancy (HDP) and offspring birthweight on the risk of GDM in the second pregnancy. **Methods:** In sibling linked data from the population-based Medical Birth Registry of Norway 548,933 mothers with their first and second singleton pregnancies (1985-2020) were analysed. Quartiles (Q) of first pregnancy offspring birthweight by gestational age were combined with GDM (yes/no) and HDP (preeclampsia, eclampsia, HELLP or gestational hypertension, yes/no) into one exposure variable (16 categories), keeping women with offspring in Q2 without GDM and HDP as reference. We estimated relative risks (RR) with 95% confidence intervals (CI) for GDM in the second pregnancy adjusting for chronic hypertension in addition to potential confounders. **Results:** GDM in second pregnancy was 1.3, 2.6, 41.0 and 45.9% in women with none of the exposures, HDP only, GDM only and both HDP and GDM in first pregnancy, respectively. Across all exposures, birthweight in Q4 was associated with the highest risk of GDM in the second pregnancy. Compared to the reference group, women with an offspring in Q4 had an adjusted RR of GDM of 1.8 (95% CI: 1.7-1.9), 4.3 (3.8-4.9), 24.1 (22.0-26.3) and 34.5 (28.5-41.7) in women with none of the exposures, HDP only, GDM only and both HDP and GDM in first pregnancy, respectively. **Conclusion:** Women with a first pregnancy with HDP only, had a cross-over risk to GDM in their second pregnancy. GDM recurrence was high, but women with combined GDM and HDP in first pregnancy had the highest GDM recurrence.

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Understanding international differences in stillbirth socioeconomic inequalities – Harmonised data from Euro-Peristat across 29 European countries

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Abstract text

Background: Reduction in inequalities both within and among countries is a key United Nations 2030 Sustainable Development Goal. Policy and practice to reduce perinatal health inequalities can utilise robust routine data gained from monitoring perinatal health inequalities at a national level.

Methods: The Euro-Peristat network with participants from 31 countries developed a Common Data Model and R scripts to exchange and analyse aggregated consistent data on perinatal indicators. Using data for 2015 to 2019 we explored international socioeconomic inequalities in stillbirth using measures of mother's education, occupation or area level deprivation of residence. We used concentration indices to measure inequality in adverse health outcomes to allow comparisons of inequalities between countries.

Results: The median [range] stillbirth rate (>=24 weeks gestation) in 29 participating countries was 3.1 per 1000 total births [1.9 to 4.7]. Socioeconomic inequalities were observed across all countries, with rates in the most disadvantaged groups ranging from 2.3 to 10.6 stillbirths per 1000 births compared to the least disadvantaged group ranging from 1.0 to 4.4. The concentration index of inequality for stillbirths was negative for 28 out of 29 countries highlighting that generally stillbirth rates in the lowest SES groups were higher than those in the highest SES groups. It showed wide inter-national variability ranging between 0.002 and -0.287 with estimated inequalities being more pronounced in some countries than others. Inequalities were lower in Northern Ireland, Luxembourg, Netherlands, Wales and France, and highest in Slovakia, Malta, Portugal and Estonia.

Conclusion: Exploring between and within-country differences in stillbirth rates can inform and motivate improvements in policy and practice to reduce international inequalities. Analytic challenges include harmonisation of socioeconomic measures and mapping data patterns to prevention and care policies.

A Comparison of Maternal and Neonatal Outcomes in Women with and without Polyhydramnios Undergoing Induction of Labor at Term

Yael Lerner , *Tzuria Peled, Morag Yehushua, Ari Weiss, Hen Y. Sela, Sorina Grisaru-Granovsky,* ***Misgav Rottenstreich***

Abstract text

Background: With the increasing popularity of elective induction after 39+0 weeks, the question of whether induction of labor (IOL) is safe in high-risk women with polyhydramnios has become more relevant.

Objective: To evaluate the pregnancy outcomes associated with IOL among women with and without isolated polyhydramnios.

Study design: A multicenter retrospective cohort study. The study population included women who underwent induction of labor at term. The study compared women who underwent induction of labor due to isolated polyhydramnios to low-risk women who underwent elective induction of labor. The main outcome measure was a composite adverse maternal outcome, while the secondary outcomes included maternal and neonatal adverse pregnancy outcomes.

Results: During the study period, 1,004 women underwent induction of labor during the post-term period and met inclusion and exclusion criteria, 162 had isolated polyhydramnios, and 842 had a normal amount of amniotic fluid. Women who had isolated polyhydramnios had higher rates of prolonged hospital stay. perineal tear grade 3/4, postpartum hemorrhage. There was one case of intrapartum fetal death because of uterine rupture which was diagnosed immediately after labor by laparotomy. The mean neonatal birthweight was significantly higher in the polyhydramnios group as well as higher rates of macrosomia and hypoglycemia. Multivariate analyses revealed that among women with induction of labor at the post-term period, polyhydramnios was associated with composite adverse maternal outcome [aOR 1.98 (1.27- 3.10), $P<0.01$].

Conclusion: Induction of labor in women with isolated polyhydramnios at term was associated with worse perinatal outcomes compared to low-risk women who underwent induction of labor. Women with polyhydramnios cannot be extrapolated from studies of low-risk populations. Further studies are needed to evaluate the optimal management of women with polyhydramnios at term.

A rising tide of polypharmacy in pregnancy: The use of one or multiple prescription drugs in pregnancy in Denmark 1998-2018

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Abstract text

Introduction: Use of multiple medications in pregnancy is common despite limited knowledge of how drug-drug-interactions add to the risk of using drugs in pregnancy. In order to plan future studies on the adverse effect of drug use in pregnancy, a better understanding of the change of medication use in pregnancy over time is needed. This study aims to describe the temporal change of use of drugs in pregnancy in Denmark over the latest decades.

Methods: A Danish nation-wide registry study on all clinical recognized singleton pregnancies with a gestational age ≥ 10 weeks between 1998 and 2018. Use of medication in pregnancy was measured by redemption of prescription drugs in pregnancy.

Results: Among 1,376,269 clinical recognized singleton pregnancies, the redemption of at least one prescription drug in pregnancy increased from 56.6% in 1998 to 63.1% in 2018. This trend was partly explained by an increase in the use of polypharmacy in pregnancy (from 25.8% in 1998 to 34.9% in 2018). Additionally, the redemption of drugs for chronic conditions increased more over the years than drugs for occasional and short-time conditions, reflecting an increased prevalence of comorbid pregnant women. Furthermore, redemption of one or multiple prescription drugs in pregnancy is mostly seen among the oldest pregnant (≥ 35years), while the youngest pregnant (<25years) had the greatest increase over the years and used the most varied combinations of drugs in first trimester.

Conclusions: We observed an increased use of medication in pregnancy, partly explained by polypharmacy. Future studies should investigate the safety of polypharmacy in pregnancy and the importance of associated factors including maternal age and social status.

Antipsychotic use during pregnancy and risk of neurodevelopmental disorders and learning difficulties in children: A multinational cohort study

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Abstract text

Objective: To evaluate whether children prenatally exposed to antipsychotic medication are at increased risk of neurodevelopmental disorders and learning difficulties, including specific developmental disorders and poor academic performance.

Methods: Our population-based cohort study used nationwide register data (2000 to 2020) on pregnant women and their live-born singletons from Denmark, Finland, Iceland, Norway, and Sweden. We defined prenatal exposure to antipsychotics as prescription fills from the first day of last menstrual period to date of birth. To control for confounding, we restricted to children of mothers with a psychiatric disorder and applied propensity score (PS) overlap weights. Cox proportional hazard regression yielded PS-weighted hazard ratios (aHRs) and 95% confidence intervals (CIs) for risk of intellectual developmental-, developmental speech or language-, developmental learning- disorders, and a composite outcome of any of the listed disorders. We defined poor performance as scoring within the lowest quartile on national school tests in mathematics language arts. We estimated PS-weighted risk ratios (aRRs) using Poisson regression. Using a common data model, we analysed data from Denmark separately and pooled results using fixed-effects meta-analysis.

Results: Among 213 302 children (median follow-up: 6.7 years), 11 626 (5.5%) were exposed to antipsychotics prenatally. Adjusted risk estimates did not suggest an increased risk of neurodevelopmental disorders: aHR of 1.06 (95% CI 0.94 to 1.20) for the composite outcome, or for poor academic performance: aRR of 1.04 (95% CI 0.91 to 1.18) in mathematics, and aRR of 1.00 (95% CI 0.87 to 1.15) in language arts. Results were generally consistent across trimesters of exposure, sibling- and sensitivity analyses.

Conclusion: The findings of this large multinational cohort study do not suggest an increased risk of child neurodevelopmental disorders or learning difficulties after prenatal exposure to antipsychotics.

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Antiseizure Medication During Pregnancy and Offspring Neurodevelopmental Outcomes: A Study of Electronic Health Records from the UK and Sweden

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Abstract text

Background: The teratogenic potential of valproate is well documented; however, the safety of other antiseizure medications (ASMs) during pregnancy is not well understood.

Objectives: To determine the relationship between the use of ASMs during pregnancy and neurodevelopmental outcomes in offspring.

Methods: This study utilized routinely collected data from two sources: the UK Clinical Practice Research Datalink (CPRD) GOLD (1995-2018) and the Swedish Developmental Origins of Health and Disease (DOHaD) cohort (1995-2020). The CPRD GOLD database contains primary care data from approximately 9% of the UK population and is representative in terms of age and sex, while the DOHaD cohort contains information on nearly all births in Sweden. We identified maternal prescriptions for ASMs recorded using ATC codes during pregnancy and child neurodevelopmental outcomes using Read codes and ICD-10 codes in the UK and ICD-10 codes in Sweden. We used logistic regressions at each site, controlling for confounders such as maternal indication and other variables, and combined the results using fixed-effects meta-analysis.

Results: We identified 518,050 children in the UK and 2,666,272 children in Sweden. The most common prescription during pregnancy was lamotrigine in both countries (approximately 0.23%). In our pooled analysis across both cohorts, carbamazepine (adjusted odds ratio [aOR] = 1.25; 95% confidence interval [CI] = 1.10-1.41), topiramate (aOR = 1.24; 95% CI = 0.90-1.71), and valproate (aOR = 1.60; 95% CI = 1.39-1.84) were associated with offspring neurodevelopmental outcomes, but not lamotrigine (aOR = 0.88; 95% CI = 0.79-0.99). Moreover, we found that there was a pronounced association between topiramate use and offspring intellectual disability (aOR = 3.30; 95% CI = 2.04-5.36).

Conclusions: These results provide valuable information for pregnant women and their healthcare providers in making informed decisions about the use of ASMs during pregnancy.

Association between One Abnormal Value on 3-Hour Oral Glucose Tolerance Test and Adverse Perinatal Outcomes in Twin Gestation

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Abstract text

AIM: To investigate whether women with twin gestation and one abnormal value on the diagnostic 3-hour oral glucose tolerance test (OGTT) are at an increased risk of adverse perinatal outcomes.

METHODS: This was a retrospective multicenter study of women with twin gestation, comparing four groups: (1) normal 50-g screening, (2) normal 100-g 3-hour OGTT, (3) one abnormal value on the 3-hour OGTT, and (4) GDM. Multivariable logistic regressions with covariate adjustments were used.

RESULTS: The study included 2,597 women with twin gestations, of which 79.7% had a normal screen, and 6.2% had one abnormal value on the OGTT. Women with one abnormal value had higher rates of preterm delivery <32 weeks, large for gestational age, NICU admission, and composite neonatal morbidity of at least one fetus, however, similar maternal outcomes as those with a normal screen.

CONCLUSION: Our study provides evidence that women with twin gestation and one abnormal value on the 3-hour OGTT are at an increased risk of unfavorable neonatal outcomes. Further research is needed to determine whether interventions such as nutritional counseling, blood glucose monitoring, and treatment with diet and medication would improve perinatal outcomes in this population.

ASSOCIATION BETWEEN RISK OF INFANT DEATH AND BIRTHWEIGHT Z-SCORE DEFINED BY INTRAUTERINE OR BIRTHWEIGHT CHARTS ACCORDING TO GESTATIONAL AGE

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Abstract text

BACKGROUND: Fetal growth restriction is associated with higher risk of infant death and other complications.[1,2] Its screening at birth mainly relies on the identification of newborns with a birthweight under the 10th percentile.[3] However, questions persist whether this threshold applies to all gestational ages (GA) and all growth charts.[4,5]

AIMS: To study the association between the risk of infant death and birthweight expressed as z-score using intra-uterine versus birthweight charts, by GA.

METHODS: Using data from the Finnish Medical Birth Register between 2006-2016, we included non-malformed singleton live births at 24-41^{+6} weeks of gestation (WG) (N=530,582). The association between risk of infant death and birthweight z-score, defined as a continuous variable using (1) Marsal's intra-uterine and (2) Sankilampi's birthweight growth charts, was studied using generalized additive models stratified by GA categories (24-27^{+6}, 28-31^{+6}, 32-36^{+6}, 37-38^{+6}, 39-41^{+6} WG). We calculated z-score thresholds associated with a two and three-fold increased risk of infant mortality compared to newborns with a birthweight between 0 and 0.675 standard deviation (SD).

RESULTS: Z-score thresholds (equivalence in percentiles in parentheses) associated with a two-fold increased risk of infant mortality compared to newborns with a birthweight between 0 and 0.675 SD were : -3.77 (0.01) at 24-27^{+6} WG, -3.44 (0.03) at 28-31^{+6} WG, -1.35 (8.9) at 32-36^{+6} WG, -1.18 (11.9) at 37-38^{+6} WG, and -1.29 (9.9) at 39-41^{+6} WG according to the intrauterine growth chart. These values were -2.81 (0.25), -2.39 (1.0), -1.40 (8.1), -1.39 (8.2) and -1.39 (8.2) according to the birthweight chart.

CONCLUSIONS: The association between birthweight z-score and the risk of infant death varies by GA whichever chart is used, suggesting that different thresholds for the screening of growth anomalies could be used across gestations to identify newborns at risk.

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Association of Cumulative Maternal Exposures Related to Inflammation and Child Attention Deficit/Hyperactivity Disorder

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Abstract text

Background: Multiple maternal exposures related to inflammation in pregnancy have been associated with child neurodevelopmental disorders, including attention deficit/hyperactivity disorder (ADHD). The aim of this study was to examine the cumulative association and potential interactions between seven maternal exposures related to inflammation and ADHD.

Methods: We conducted a population-based cohort study of children born from 2001-2011 in New South Wales, Australia and followed up until December 2014. Seven maternal exposures were identified from birth data and hospital admissions during pregnancy: autoimmune disease, asthma, hospitalization for infection, mood/anxiety disorder, smoking, hypertension and diabetes. Child ADHD was identified from stimulant prescriptions before age ten. Multivariable Cox regression assessed the association between individual and cumulative exposures and ADHD and potential interaction between exposures, controlling for potential confounders.

Results: The cohort included **292,478 children,** one-third (98,923) with one or more maternal exposures. ADHD was identified in 8472 (2.9%) children with mean age of 7.5 (SD 1.5) years at first treatment. Each exposure was independently associated with ADHD and odds increased with additional exposures: one exposure (adjusted hazards ratio (aHR) 1.59, 95% confidence interval (CI) 1.51, 1.66), two exposures (aHR 2.28, 95%CI 2.11, 2.46), and three or more exposures (aHR 3.62, 95%CI 3.11, 4.21). Positive interaction was found between smoking and infection and between autoimmune disease and asthma. The largest effect size was found for cumulative exposure of asthma, infection, mood/anxiety disorder and smoking (aRR 8.89, 95%CI 3.68, 21.46).

Conclusion: This study identifies cumulative effects of multiple maternal exposures related to inflammation on ADHD, most potentially preventable or modifiable. Future studies should measure biomarkers of maternal inflammation and consider gene-environment interactions.

Association of pre-existing maternal cardiovascular disease with cardiovascular disease in offspring: nationwide Swedish cohort study

M Zakir Hossin , *Jonas Faxén, Sarka Lisonkova, Neda Razaz*

Abstract text

Introduction: Maternal heart disease is associated with abnormal placentation and adverse neonatal outcomes, but its impact on long-term health in offspring is understudied. This study aims to determine if pre-existing maternal cardiovascular disease (CVD) is associated with offspring's CVD and if this association is more strongly driven by intrauterine or genetic mechanisms.

Methods: This population-based cohort study included >2.5 million non-malformed live singleton births recorded in the Swedish Medical Birth Register in 1992-2019, with follow up until Dec 2020. The National Patient Register provided data on maternal CVD (e.g., cerebrovascular disease, arrythmia, congenital heart disease) diagnosed before conception and offspring CVD diagnosed between age 1 year and up to 30 years. Cox proportional hazards models were fitted to estimate Hazard Ratios (HRs) for the associations. The maternal-offspring associations were compared with paternal-offspring associations to assess possible genetic confounding. All associations were adjusted for offspring's age, sex, birth year, and mother's age at birth, parity, education, country of birth, cohabitation, smoking, body mass index, psychiatric illness, and pre-gestational diabetes.

Results: Of the 2,529,242 offspring analysed, 33,655 were diagnosed with CVD during follow-up (median 14 years). The adjusted analyses showed that offspring of mothers with CVD had 1.73 times higher HR of CVD (95% CI: 1.57-1.90), 1.51 times higher HR of cerebrovascular disease (95% CI: 1.04-2.20), and 2.29 times higher HR of arrythmia (95% CI: 1.99-2.62) compared with offspring of mothers without CVD. Paternal CVD was associated with 1.38 times higher HR of CVD (95% CI: 1.27-1.50), 1.63 times higher HR of arrythmia (95% CI: 1.43-1.85), and no increased HR of cerebrovascular disease in offspring.

Conclusion: Compared with paternal CVD, maternal CVD showed a stronger association with CVD in offspring.

Associations between laterality of unilateral cleft lip with or without palate and co-occurring structural and functional anomalies

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Abstract text

Orofacial cleft (OFC) subtypes have distinct aetiologies and epigenetic profiles[1]. Laterality in unilateral cleft lip (UCL) and unilateral cleft lip and palate (UCLP) has a 2:1 ratio with a left sided UCL and UCLP being more common[2,3]. This ratio suggests laterality is non-random[3]. Full aetiology of OFC subtypes are unknown, and it is likely that the aetiological and/or pathogenic mechanisms differ between laterality. Evidence suggests co-occurring structural and functional anomalies (SFAs) are more common in right sided UCLP than in left sided UCLP[4]. It is important to further explore associations between laterality and SFAs to help inform clinical management and further our understanding of the aetiological pathways. The aim was to determine whether there is a difference in the prevalence of SFAs according to laterality among UCL and UCLP patients.

The Cleft Collective study is a longitudinal cohort study of children with OFC and their families. Data on a child's SFAs are collected via parental questionnaires. Data on laterality of a child's UCL or UCLP was obtained from multiple sources including parental and clinician report. Data were available for 202 UCL and 245 UCLP children. Logistic regression was used to explore associations between individual SFAs and laterality.

Evidence was found to suggest that children with a right sided UCLP were 3.7 times more likely (Odds Ratio 3.68, 95% Confidence intervals 1.22-11.13) to experience difficulties with their vision compared to those with a left sided UCLP.

We found little evidence to suggest a difference in the prevalence of SFAs between left and right sided UCL and UCLPs. However, we found evidence to suggest a difference in the prevalence of vision problems between left and right sided UCLP, with an increased likelihood of vision problems in those with a right sided UCLP. It is important for paediatric clinicians to be aware of this finding to help inform clinical management.

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Atopic Dermatitis in Childhood and Subsequent Pubertal Development: a nationwide cohort study

Camilla Lomholt Kjersgaard , *Lea Lykke Harrits Lunddorf, Linn Håkonsen Arendt, Nis Brix, Andreas Ernst, Onyebuchi Arah, Mette Deleuran, Cecilia Høst Ramlau-Hansen*

Abstract text

Introduction:
Atopic dermatitis is a chronic inflammatory skin disease, affecting up to 20% of children and is characterized by an enhanced immune response. We hypothesized that atopic dermatitis in childhood may delay pubertal development through chronic stress and sleep disturbances, resulting in dysfunction of the hypothalamic-pituitary-adrenal axis that regulates the hypothalamus-pituitary-gonadal axis. We investigated the association between atopic dermatitis in childhood and subsequent pubertal development.

Methods:
The study is based on the Puberty cohort, a sub-cohort within the population-based cohort, the Danish National Birth Cohort (DNBC). In total, 15,538 boys and girls born between 2000-2003 were included. The mothers provided information about doctor-verified atopic dermatitis when the children were 6 months, 18 months, and 7 years old. Additionally, we included diagnosis codes from the National Patient Registry to identify severe cases of atopic dermatitis. Information on pubertal timing came from children's half-yearly self-reported information given from age 11 years and throughout puberty. We estimated the mean age difference in months at attaining Tanner stage 1– 5 on pubic hair, breast development, genital growth, axillary hair, acne, first ejaculation, voice break, and age at menarche, using an interval-censured regression model.

Results:
In total, 3,449 (22.2%) children had atopic dermatitis. No association was found between atopic dermatitis and pubertal development (boys: 0.11 months, (95% confidence intervals (CI): -0.68; 0.90) and girls: -0.09 months (95% CI: -0.89; 0.72)). Boys with a diagnosis code (i.e., more severe disease) had slightly later pubertal development than boys without atopic dermatitis (5.63 months (95% CI: -2.76; 14.01)).

Conclusion:
We found that a diagnosis code of atopic dermatitis was associated with slightly later pubertal development in boys, whereas milder cases were not. No associations were observed in girls.

Cancer risk among children born after assisted reproductive technology– a cohort study based on the French National Mother-Child Register EPI-MERES

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Abstract text

Background: Assisted reproductive technologies (ART) are suspected risk factors of childhood cancer because of their potential for epigenetic disturbance.

Objective: To assess the risk of cancer among children conceived by ART, compared to those naturally conceived (NC)

Methods: We conducted a nationwide population-based cohort study using the EPI-MERES mother-child register built from comprehensive data of the French National Health Data System. All live births in France from 2010 to 2021 were included and followed until June 30, 2022. The risk of cancer was compared, overall and by cancer type, between children born after fresh (fresh-ET) or frozen (FET) embryo transfer following *in-vitro* fertilization or artificial insemination (AI) and those naturally conceived (NC), using Cox proportional hazards models adjusted for maternal and child characteristics.

Results: Among a total of 8,526,306 children, 133,965 (1.6%) were born after fresh-ET, 66,165 (0.8%) after FET and 60,106 (0.7%) after AI. Overall, 9,256 cancers (NC: 8,964, fresh-ET: 165, FET: 57, AI: 70) were identified over a median follow-up of 6.7 years. The most common cancer type was leukaemia (2,729 cases). The overall risk of cancer did not differ between children born after fresh-ET, FET or AI and those NC (aHR [95%CI]: 1.12 [0.96-1.31], 1.02 [0.78-1.32] and 1.09 [0.86-1.38], respectively). Though, compared to NC children, the risk of leukaemia tended to be higher in children born after fresh-ET (52 cases; aHR 1.19 [0.90-1.56]) -especially those followed ≥6 years (45 cases; aHR 1.42 [1.06-1.92]) - and in children born after FET (23 cases; aHR 1.42 [0.94-2.14]) -especially with regard to the risk of acute lymphoblastic leukaemia (20 cases; aHR 1.61 [1.04-2.50]).

Conclusions: Our findings suggest an increased risk of leukaemia among children born after FET or fresh-ET. This risk, although resulting in a limited number of cases, needs to be monitored in view of the continuous increase in the use of ART.

Cesarean section and the gestational duration of subsequent pregnancies: a nationwide retrospective cohort study

Felix Evers

Abstract text

Intro: Preterm birth (<37+0 weeks) is the world's leading cause of neonatal mortality. Birth rates through cesarean section (CS) increases worldwide, which is troublesome since reports indicate an increased incidence of preterm delivery subsequent to a previous CS. The objective of this study is to determine the impact of previous delivery modes (CS or vaginal delivery), on the gestational duration of a subsequent pregnancy.

Methods: This is a retrospective cohort study using clinical data registered in the Swedish Medical Birth Register. Two cohorts were studied: 512 515 women with their first two pregnancies, and 157 581 women with their first three pregnancies. Multivariable logistic regression models assessed the incidence of spontaneous preterm delivery or postterm delivery after one or two previous term birth(s), depending on previous modes of delivery. Survival analyses handled bias due to differences in obstetrical management between the exposure- and reference groups, related to the previous modes of delivery.

Results: Compared to previous vaginal delivery, a previous CS was associated with increased risk of preterm birth in the second pregnancy (adjusted odds ratio [aOR] 1.67, 95% CI 1.58 - 1.77, P <1E-15), but also with a higher risk of postterm birth in the second pregnancy (aOR 1.55, 95% CI 1.49 - 1.62, P <1E-15). In the survival analyses, previous CS(s) was associated with longer gestational durations of subsequent pregnancies. A vaginal birth after a CS reduced the risk of preterm delivery in the third pregnancy to such an extent that no difference was seen compared to the group of women with two previous vaginal deliveries.

Conclusions: CS is associated with subsequent preterm delivery and at the same time with subsequent postterm delivery. These results give a more complete understanding of possible implications for the gestational durations of pregnancies subsequent to CSs, they also raise questions about which mechanisms might be in play behind these results.

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Completed education level at age 25 after induction of labor at term

Renée J. Burger , *Sanne J. Gordijn, Ameen Abu-Hanna, Wessel Ganzevoort, Anita C. Ravelli*

Abstract text

Introduction A recent study showed that induction of labor (IOL), compared to expectant management, is associated with lower offspring school performance at age 12. We aimed to study the influence of elective induction of labor in uncomplicated pregnancies from 37 to 42 weeks, separately, on offspring academic achievement at 25 years of age.

Material and methods We performed a population-based study among live born children from uncomplicated singleton pregnancies of women, born from 37 to 42 weeks of gestation in cephalic presentation in 1995-1997. Children with congenital anomalies, birthweight ≤p5 or women with hypertensive disorder, diabetes or births after pre-labor cesarean section were excluded. Birth records were linked with national data on completed education level. We compared, using a fetus-at-risk approach and per week of gestation, high level of completed education in those born after induction of labor to those born after spontaneous onset of labor in the same week plus all those born at later gestations. We adjusted for age, parity, deprivation, maternal education, fetal sex, prelabor rupture of membranes, and birthweight centile.

Results 94% of the children could be linked. 40.3% of the 283,986 infants had a high completed educational level. The highest achievement was at 289 days. After IOL fewer children reached a high level; at 37 week 33.0% versus 40.4%. The unadjusted odds ratio (OR) at 37 weeks was 0.73 (95% confidence interval(CI) 0.68–0.78) and the adjusted OR 0.82 95%CI (0.76–0.88). For each gestational age up to 41 weeks, IOL was associated with lower probability to attain a high level of completed education. Neither adjustment nor exclusion of risk groups changed this pattern.

Conclusions In women with uncomplicated pregnancies at term, at every week of gestation from 37 to 41 weeks, induction of labor was associated with lower academic achievement at 25 years of age compared with expectant management. Residual confounding may remain.

Cytogenetic outcomes in pregnancies across a range of nuchal translucency measurements: population-based cohort study in Ontario, Canada.

Kara Bellai-Dussault , *Shelley Dougan, Deshayne B Fell, Julian Little, Lynn Meng, Nan Okun, Mark Walker, Christine Armour, Beth K Potter*

Abstract text
Background

Ultrasound measurement of fetal nuchal translucency (NT) is used in prenatal screening for trisomies 21 and 18. A cut-off of ≥3.5mm is commonly used to identify pregnant individuals to whom follow-up investigations (such as cfDNA screening or cytogenetic testing) are offered. However, with recent studies showing a possible association with chromosomal abnormalities for levels <3.5mm, robust research is required to evaluate alternate cut-offs.

Methods

We conducted a population-based retrospective cohort study using data from the Better Outcomes Registry & Network, the maternal and child provincial registry for Ontario, Canada. Data from all laboratories performing multiple forms of cytogenetic testing prenatally and postnatally in Ontario was available. All singleton pregnancies with a valid NT measurement and estimated date of delivery from September 1, 2016, to March 31, 2021, were included. We used multivariable modified Poisson regression with adjustment for gestational age and robust variance estimation to compare cytogenetic outcomes for pregnancies with varying NT levels to a reference group with NTs <2.0mm.

Results

The study included 643 146 pregnancies, of which 86.9% had an NT <2.0mm, 10.4% from 2.0-2.4mm, 1.8% from 2.5-2.9mm, 0.4% from 3.0-3.4mm, 0.3% from 3.5-4.9mm, 0.1% from 5.0-6.4mm and 0.1% ≥6.5mm. The risk of chromosomal abnormalities increased with increasing NT measurements, with a risk ratio (RR) of 20.3 (95% confidence interval (CI) 17.6-23.5) for pregnancies with NTs from 3.0-3.4mm. This RR was 4.4 (95%CI 3.1-6.3) when assessing only the chromosomal abnormalities outside the commonly screened aneuploidies.

Conclusion

Pregnancies with NT measurements <3.5mm are at increased risk of chromosomal abnormalities, including conditions that are not routinely screened through cfDNA screening in Ontario. Further analysis may inform care, as currently pregnant individuals with NTs <3.5mm are not routinely offered cytogenetic testing.

Days in hospital and surgery as indicators of health care use in children with congenital anomalies up to ten years of age in six European countries.

Maria Loane , ***Ester Garne****, Joan Morris*

Abstract text

Background: Congenital anomalies are a major cause of childhood morbidity. This study evaluates the relative health care utilisation of children born with congenital anomalies up to 10 years of age.

Methods: 79,591 children with congenital anomalies born from 1995 to 2014 in seven regions in six European countries covered by EUROCAT congenital anomaly registries were linked to inpatient electronic health records up to their 10^{th} birthday. A random sample of 2,021,772 children (out of 3.3 million) without congenital anomalies born at the same time and in the same regions was also linked. The number of days in hospital and the occurrence of surgery were used as indicators of health care use.

Results: During the first year of life, amongst the seven regions, a median of 2.4% (IQR:2.3-3.2) of children with a congenital anomaly accounted for 18% (14-24) of days in hospital and 63% (62-76) of surgical procedures. Over the first ten years of life the percentages were 17% (15-20) of days in hospital and 20% (19-22) of surgical procedures. The percentage share of surgical procedures decreased after one year of age, whilst days in hospital decreased after 5 years of age. On average children with congenital anomalies spent 8.8 times longer in hospital during their first year of life than children without anomalies, falling to 8.1 times aged 1-4 years and 5.0 times aged 5-9 years. Children with gastro-intestinal atresia's and abdominal wall defects stayed the longest in hospital.

Conclusion: Although only 1 in 40 children are born with a congenital anomaly and not all require hospitalisation and surgery, they consume a significant proportion of health care resources. Their families should be adequately supported by health care professionals, relevant authorities and health and social policies. Priority should be given to public health primary prevention measures to reduce teratogenic exposures during pregnancy and increase awareness of the use of folic acid preconception.

Detection Rate of Major Congenital Malformations Depends on Length of Follow-Up in Swedish National Health Register Data

Silvia Segovia Chacon , *Pär Karlsson, Carolyn Cesta*

Abstract text
Background: In Nordic observational medication pregnancy safety studies, children are often followed from birth to 1 year of age. However, some major congenital malformations (MCM) may take longer to diagnose. We aimed to investigate the detection rate of MCM at different lengths of follow-up from birth to 3 years after birth, and to compare to the prevalence at 1 year after birth.

Methods: All singleton liveborn children born in Sweden from 2006-2016 were included. MCM were identified by ICD-10 codes in the Medical Birth Register and National Patient Register, aligned to the EUROCAT classification system. Detection rate (cumulative prevalence) at birth, 90 days, 1, 2, and 3 years was calculated. A detection rate ratio was calculated by dividing the prevalence at each timepoint by the prevalence at 1 year. MCM detection rates among children born at term and preterm were compared.

Results: In 1,139,768 children, the detection rate of any MCM increased from 2.0% at birth to 4.0%, 4.5% and 4.8% at 1-, 2-, and 3-years after birth, respectively, and varied by MCM subgroup. MCMs of the eye, ear-face-neck, nervous system and genitals were detected with the longest delay, with 30-58% more detected at 3- versus 1-year follow-up. Compared to children born at term, the prevalence of any MCM was 2.5 times higher among preterm children, with a higher detection rate over the first 90 days for most MCM subgroups, which is likely due to surveillance bias.

Conclusion: In studies of medication safety in pregnancy, the length of children follow-up should be chosen in accordance with the type of MCM under investigation, balanced by the available data, e.g. eye and genital MCM require longer follow-up for detection than abdominal wall and digestive system MCM. Prenatal exposure to medications/maternal conditions associated with preterm birth may result in biased risk estimates if infant follow-up length is less than 3 months.

Do women with ADHD have increased risk of adverse pregnancy and perinatal outcomes? A nationwide cohort study

Ammal Khan , *Anders Engeland, Berit Skretting Solberg, Kari Klungsøyr*

Abstract text

Objective

Few studies have focused on pregnancy outcomes in women with ADHD. We examined the association between ADHD and adverse pregnancy and perinatal outcomes, focusing on the “total effect” of ADHD on these outcomes.

Methods

Using linked data from four nationwide population-based registries in Norway, we identified a total of 923,701 singleton pregnancies during 2005-2020, where 15,714 (1.7%) were to women with ADHD. ADHD was defined based on a prescription of ADHD medication in the Norwegian Prescription Database and/or a diagnosis of ADHD in the Norwegian Patient Registry. Variables on adverse pregnancy and perinatal outcomes were all from the Medical Birth Registry of Norway. Relative risks (RR) and 95% confidence intervals (CI) were estimated using binary regression models, which were adjusted for time period, maternal age and parity. Clustered analyses using the mother as the cluster unit accounted for correlations between births to the same mother.

Results

Women with ADHD had increased risks of preeclampsia (RR: 1.13, 95% CI 1.03-1.24), induced delivery (1.21; 1.17-1.25) and cesarean section (1.19; 1.14-1.24). Their offspring more often had low birth weight (1.15; 1.06-1.24), respiratory problems (1.30; 1.19-1.42), withdrawal syndrome (9.53; 7.74-11.74), were born preterm (1.19; 1.11-1.27) and were transferred to a neonatal care unit (1.36, 1.31-1.42). Notably, maternal ADHD was associated with a decreased risk of stillbirth (0.64; 0.50-0.83), which will be further investigated.

Conclusion

Maternal ADHD was associated with increased risks of several adverse pregnancy, delivery and infant outcomes, but most risks were only slightly increased. Additionally, ADHD was associated with a decreased risk of stillbirth. Future mediation analyses may identify possible causal paths underlying these associations. Our results will inform clinicians caring for pregnant women and suggest closer follow up for pregnant women with ADHD.

Early life sleep characteristics and their associations with 1 to 5.5 years old respiratory and allergic multi-trajectories in the ELFE birth-cohort

Danielle Saade , *Rosalie Delvert, Chantal Raherison-Semjen, Oriane Dumas, Mohammed Sedki, Blandine de Lauzon-Guillain, Bénédicte Leynaert, Rachel Nadif, Annabelle Bédard,* ***Sabine Plancoulaine***

Abstract text

Sleep troubles have been associated with respiratory and allergic health problems in children, however the timeline of their association is overlooked. We examined the associations between: (1) sleep patterns at age 1 year and respiratory and allergic multi-trajectories between 1 and 5.5 years; (2) respiratory and allergic multi-trajectories between 1 and 5.5 years and sleep patterns at age 5.5 years in a French birth cohort.

Clusters of sleep features at age 1 year (night sleep duration (NSD), day sleep duration (DSD), sleep onset difficulties (SOD), night awakenings (NA)) and at age 5.5 years (NSD, SOD, NA) and respiratory and allergic symptoms multi-trajectory groups between 1 and 5.5 years (wheezing, asthma medication, eczema, allergic conjunctivitis) were identified using unsupervised methods. Associations were assessed using multinomial regressions adjusted for potential confounding factors among 9,577 children.

We identified 2 sleep clusters at each age: C1a (79.9%, age 1 year) and C1b (83.1%, age 5.5 years) characterized by adequate sleep duration and good sleep quality; C2a (20.1%, age 1 year) and C2b (16.9%, age 5.5 years) characterized by shorter sleep duration and poorer sleep quality. We identified 4 multi-trajectory groups: G1 (no/few symptoms, 44.4%), G2 (persistent non-respiratory allergic symptoms, 23.1%), G3 (transient early respiratory symptoms, 25.2%), G4 (persistent respiratory and allergic symptoms, 7.3%). Belonging to C2a was associated with an increased odds of belonging to G3 and belonging to G4 was associated with an increased odds of belonging to C2b.

In conclusion: sleep disturbances at 1 year were associated with poorer respiratory and allergic health between 1 and 5.5 years and respiratory and allergic problems between age 1 and 5.5 years were associated with sleep troubles at 5.5 years suggesting bidirectionality. Further research will explore coevolution of sleep and allergic and respiratory troubles during early childhood.

Early origins of health in young adults of the French Constances cohort

Coralie Amadou-Kerangoarec , *Marie Zins, Marie-Aline Charles*

Abstract text

Introduction

Low or high birth weight (BW) and premature birth are clinical markers of intrauterine conditions that have long-term consequences for health. However, they are little considered in adult care to screen or treat diseases. This work aimed to describe their associations with young adult health in a contemporary French cohort with an outcome-wide approach.

Methods

In participants of the French Constances cohort aged less than 60 years, we studied the association between low or high BW (BW: <10th and >90th sex-specific percentile) (analysis 1) and birth term (analysis 2) with a range of prevalent (>1%) symptoms and diseases. Analyses were performed separately in men and women through modified Poisson regressions adjusted for age, parental socio-professional characteristics and maternal medical history of participants. Mediation analyses quantified the role of education level (analysis 1) and BW (analysis 2) in the observed associations.

Results

Data from 73,315 (analysis 1) and 34,840 (analysis 2) participants were used (mean age 38 years, 60% women). Individuals born with a low BW had an excess risk of metabolic diseases, hypertension, anxiety, and, in women only, asthma. Relative risks compared to normal BW ranged from 1.1 to 1.4. Those born with a high BW had a 20 % excess risk of obesity, without an excess risk of metabolic diseases. These extreme BW were associated with lower educational attainment, which mediated 10-15% of the risk of these conditions. Finally, prematurity (i.e., birth before 37 pregnancy weeks; 6% of births), was associated with an excess risk of metabolic diseases and obesity, as well as asthma (women only), and with a lower level of education. The excess risk of obesity was directly related to prematurity, not to a low BW.

Conclusion

These results quantify the associations between early life conditions and later health. The screening and prevention measures for young adult diseases should account for birth weight and term.

Effects of Endometriosis on Miscarriage: a Doubly Robust Analyses

Amanuel Gebremedhin , *Vera Mitter, Bereket Duko, Gizachew Tessema, Gavin Pereira*

Abstract text

Background: Endometriosis is a chronic condition where endometrial-like tissue grows outside the uterus, leading to inflammation, pain, and subfertility. Although there has been a growing interest in the potential association between endometriosis and miscarriage, the findings to date are inconclusive.

Objective: To estimate the causal association between endometriosis and a miscarriage.

Study design: A population-based retrospective cohort study was conducted among 468,778 eligible women who contributed 912,747 singleton livebirths between 1980 and 2015 in Western Australia. We used probabilistically linked perinatal and hospital separation data from the Midwives Notification System and Hospital Morbidity Data Collection databases. Our exposure of interest (Endometriosis) and all the outcomes were ascertained using ICD-9/10 codes. We used a doubly robust estimator to estimate the effect (*average treatment effect)* of endometriosis on miscarriage.

Results: There were 19,476 singleton livebirths among 8,874 women diagnosed with endometriosis. Using a doubly robust estimator, we found pregnancies in women with endometriosis to be associated with an increased risk of miscarriage (relative risk, 2.16, 95% confidence interval, 1.63 – 2.86)**.** The observed association persisted when stratified by the use of Medically Assisted Reproduction (MAR), with a slightly elevated risk among pregnancies conceived spontaneously. MAR does not modify but mediates the association between endometriosis and miscarriage. Our causal mediation analyses suggest that 34% of the effect of endometriosis on miscarriage was mediated through MAR.

Conclusion: In this large population-based cohort, endometriosis is associated with an increased risk of miscarriage, and the effect is mediated through MAR**.** The study paves the way for future research on mechanisms underlying the relationship between endometriosis and miscarriage.

Effects of exclusive breastfeeding duration on trajectories of grade progression and educational attainment among children in Malawi

Shamsudeen Mohammed , *Emily L Webb, Clara Calvert, Judith R Glynn, Bindu S. Sunny, Amelia C. Crampin, Estelle McLean, Shekinah Munthali-Mkandawire, Albert Lazarous Nkhata Dube, Fredrick Kalobekamo, Milly Marston, Laura L Oakley*

Abstract text

The benefits of exclusive breastfeeding for infant health are well documented. However, its impact on educational outcomes has been contested and poorly researched in Africa. Positive associations in high-income countries have been criticised and attributed to residual confounding by socioeconomic status. Our study investigated whether exclusive breastfeeding duration in infancy is associated with age-for-grade attainment at school-age in rural Malawi. Longitudinal data on 1021 children at the Karonga demographic surveillance site in Malawi were analysed. Breastfeeding data were collected at ages 3 months and 1 year, and school grades recorded up to age 13 years. Age-for-grade was based on whether a child was at, over, or under the expected age for a grade. Generalised estimating equations estimated the average effect of breastfeeding on age-for-grade. Latent class growth modelling identified age-for-grade trajectories, and multinomial logistic regression examined their associations with exclusive breastfeeding. Maternal-child and paternal characteristics, HIV status, and family socioeconomic status were controlled. There was some evidence that exclusive breastfeeding for six months was associated with a lower odds of over-age for grade than exclusive breastfeeding for less than three months (adjusted odds ratio (aOR)=0.82, 95% confidence interval (CI)=0.64-1.06). In subgroup analyses, children exclusively breastfed for six months in infancy were less likely to be over-age for grades between ages six to nine (aOR=0.64, 95%CI=0.43-0.94). Latent class growth analysis also showed some evidence that exclusive breastfeeding reduced the odds of falling behind in the early school grades (aOR=0.66, 95%CI=0.41-1.08) but not later. Our study adds to the growing evidence that exclusive breastfeeding for six months has benefits beyond infant health and survival, supporting the World Health Organization's recommendation for exclusive breastfeeding.

EPI-MERES: A nationwide mother-child register for pregnancy and paediatric pharmacoepidemiology built from the French National Health Data System

Sara Miranda , *Jérôme Drouin, Thien Le Tri, Jérémie Botton, Antoine Meyer, Mahmoud Zureik, Alain Weill, Rosemary Dray-Spira*

Abstract text

Background

Observational data are of major interest for studying drug use, safety and effectiveness during pregnancy and childhood, barely measurable in clinical trials.

Objectives

We describe the French nationwide mother-child register EPI-MERES, a data source set up for conducting pregnancy and paediatric pharmacoepidemiology studies.

Methods

Based on reimbursement and hospitalisation databases of the National Health Data System (SNDS) covering almost the whole French population, EPI-MERES is an unselected register including all identified pregnancies ended from 2010 onwards in France and their offspring (if any). Pregnancies identification is updated yearly, and included children are continuously followed over time from birth.

EPI-MERES contains comprehensive information over time on mothers (sociodemographics, medical history, healthcare use, medication consumption), pregnancies (start and end date, assisted reproduction procedure, ultrasound scans, pregnancy complications and outcome), and offsprings (sex, gestational age at birth, birth weight, medical conditions such as malformations or neurodevelopmental disorders, healthcare use, medication consumption).

Results

As of April 2023, EPI-MERES includes a total of 12,170,915 pregnancies ended between 2010 and 2021 (median maternal age: 29 years). Of them, 8,802,659 (72.3%) ended in a live birth, accounting for 98% of all live births recorded in France; and 2,336,652 (19.2%) were terminated (elective/therapeutic abortion). A total of 8,529,397 infants (94% of live births) successfully linked to their mother are included (median birth weight 3.3 kg, 6.3% born prematurely). Median follow-up from birth is 7.2 years (maximum 12 years).

Among pregnancies ended in 2018-2019, 96% had at least one medication reimbursed, with a median of 6 medications dispensed during pregnancy.

Conclusions

EPI-MERES is a powerful tool for studying drug use, safety and effectiveness during pregnancy and childhood.

Evaluating the impact of guidelines for prophylactic aspirin treatment against preeclampsia using interrupted time series analyses.

Julie Hauer Vendelbo , *Mette Østergaard Thunbo, Tine Brink Henriksen, Zeyan Liew, Agnete Larsen, Lars Henning Pedersen*

Abstract text

Introduction: Preeclampsia increases the risk of both maternal and neonatal death, intrauterine growth restriction, and preterm delivery. There are no causal treatment except delivery of the placenta but aspirin started early in pregnancy reduces the risk of development of preeclampsia for women at high risk. Consequently, 2-10% of pregnant women are treated with aspirin but evaluation of safety is hampered by the inherent risk of confounding by indication.

Aim: Evaluate the effect and safety of prophylactic treatment with aspirin for high-risk pregnancies in Denmark using interrupted time series analyses.

Methods: The study population consist of all clinical recognized singleton pregnancies with a gestational age >10 weeks in Denmark in 1997-2018, a total of 1,479,442 pregnancies. High-risk pregnancies were classified based on the clinical guidelines for prophylactic treatment and defined by diagnosis codes in the Danish national patient registry. It includes women with either/or 1) severe preeclampsia in a previous pregnancy, 2) inflammatory disease as SLE or antiphospholipid syndrome, 3) pregestational hypertension requiring treatment, 4) chronic kidney disease or 5) pregestational diabetes. Low-risk pregnancies was used as a control group. Outcomes: development of preeclampsia, birth complications (maternal bleeding and haematoma, emergency caesarean sections, vaginal assisted delivery (forceps or vacuum) and shoulder dystocia), neonatal brain development (intracranial haemorrhage, epilepsy, cerebral palsy, febrile cramps) and birth weight.

Results: In preliminary data, 29,794 pregnancies were classified as of high risk for development of preeclampsia and 1,449,648 as controls. The high-risk population increased over time reflecting a general increase in the use of these diagnosis codes in pregnancy. In the latter year, as expected, around 3% of the pregnancies were of high-risk. Further results as well as a discussion will be presented at the meeting.

Evaluating the rising prevalence of cerebral palsy in children born preterm in Denmark

Martha Veber Fogh , *Mads Langager Larsen, Tine Dalsgaard Clausen, Lone Krebs, Gorm Greisen, Christina Engel Hoei-Hansen*

Abstract text

Objective

The prevalence of cerebral palsy (CP) among children born preterm has been declining globally during the last decades.[1] However, in Denmark, we have observed a slow but steady rise in the prevalence of CP in children born preterm from 2003-2013. Therefore, we aimed to evaluate this observation and identify important neonatal factors possibly illustrating reasons for the increase.

Methods

A population based cohort study including all live-born children in Denmark from 1997–2013, born before 37 completed gestational weeks. We included validated diagnoses of CP from the Danish Cerebral Palsy Register and Cerebral Palsy Follow-up Program. Additional information was included from the Danish Medical Birth Register. We evaluated changes in the prevalence of CP and relevant factors per 1000 live births using Poisson regression with a 95% Confidence Interval. A p-value <0.05 were considered significant.

Results

We included 71,301 live births, of which 824 (1.2%) had CP. The overall prevalence of CP changed from 10.2 in 2002-04 to 12.3 in 2011-13, although not significantly (p=0.33). However, the prevalence of children with CP born extremely preterm (<28 weeks) increased significantly from 46.8 to 63.2 (p<0.01), whereas it did not change among children born very (weeks 28–31) and moderately premature (>31 weeks).

The most notable changes during the study period were admission to neonatal care units (p<0.01) and concurrent increased usage of continuous positive airway pressure and assisted ventilation (p<0.01). Neonatal mortality did not change during our study period (p=0.24).

Conclusion

The observed rise in the prevalence of CP in preterm children in Denmark is only among children born extremely preterm. It seems to be a direct result of more live births at early gestational ages, which could indicate a shift in the general obstetric and neonatal treatment, with increased care, particularly for neonates closer to the margin of viability.

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1
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Exploring the impact of parity and its interaction with history of preterm delivery on gestational duration

Karin Ytterberg , *Bo Jacobsson, Christopher Flatley, Julius Juodakis, Staffan Nilsson, Pol Sole-Navais*

Abstract text

Purpose

Preterm delivery is a major cause of neonatal and under five year of age mortality. Parity is a known risk factor for preterm delivery, but its association with gestational duration and its variability is underexplored. Differences in variance by parity may aid in etiological understanding and suggest modification effects on other well-established risk factors, such as clinical or family history of preterm delivery.

Methods

With 1.1 million spontaneous deliveries (1990-2012) from the Swedish Medical Birth Register, we assessed the marginal effects of parity on the mean and variance of gestational duration and whether it modifies the effect of history of preterm delivery on gestational duration. Pedigrees allowed to account for non-observed, shared confounders using linear mixed models.

Results

Parity has a modest association with mean gestational duration, but a large effect on its variance. For instance, compared to the second pregnancy the gestational duration in the first pregnancy was only observed to be 6-8 hours shorter on average (difference in days: -0.29; 95% CI: -0.33, -0.25 for the linear mixed regression). The largest variance was observed in the first pregnancy (σ^2 =135), and the lowest in the second pregnancy (σ^2 =100) (Levene's test, $P < 1 \times 10^{-15}$). Accounting for shared unobserved confounders highlighted a group effect bias, likely linked to the total number of children a mother will have. Parity modified the effect of other risk factors, including previous preterm delivery, which affects all pregnancies but the magnitude of its effect increases with parity (difference in days: -8.34; 95% CI: -8.58, -8.11; difference in days: -11.0; 95% CI: -11.3, -10.9; difference in days: -13.0; 95% CI: -13.6, -12.4, in parity one, two and three respectively).

Conclusion

Non-shared factors across a mother's pregnancies highlight parity's importance to gain insight into the mechanisms governing the timing of delivery.

Exposure misclassification in studies comparing operative delivery outcomes

Giulia Muraca , *Abirami Kirubarajan, Irina Oltean, Parnian Hossein Pour, Maya Rajasingham, Meejin Park, Anvi Desai, Thilini Wijesekera*

Abstract text

Objective

We performed a quantitative bias analysis to evaluate the influence of misclassification of failed operative vaginal delivery (OVD) attempts as 2nd stage cesarean deliveries (CDs) on the results of studies comparing spontaneous preterm birth (sPTB) in individuals with a previous 2nd stage CD vs OVD.

Methods

We used a deterministic sensitivity analysis approach[1] by adjusting observed odds ratios (ORs) upon ranging the sensitivity and specificity values of 2nd stage CD and OVD among those with and without subsequent sPTB. Bias parameters were obtained using external validation data[2] and assumed a differential misclassification structure. We estimated the standard errors of the bias-corrected estimates of effects using equations[3] that account for the random error from the individual studies as well as the additional error introduced by the bias parameters.

Results

We found 4 studies that provide data to compare the rate of subsequent sPTB among women with previous OVD and 2nd stage CD.[4-7] All studies showed a significantly higher rate of subsequent sPTB in the 2nd stage CD group with ORs from 1.63 (95% confidence interval [CI] 1.47-1.80)[7] to 3.18 (95% CI 2.00-5.05)[4]. Misclassification bias-corrected ORs with specificity parameters varying from 0.99 to 0.92 showed an attenuation of these associations such that when bias parameters were set to correspond to a 7% failed OVD rate, ORs were attenuated to between 1.41 and 1.88, with 2 of the 4 studies showing associations that no longer rejected the null hypothesis. Bias-corrected estimates with bias parameters reflecting an 8% failed OVD rate showed all but one misclassification-adjusted OR failed to reject the null hypothesis.

Discussion

The failure to account for 2nd stage CDs that result from failed OVD attempts can result in underestimates of risk among OVD and a corresponding overestimate of risk among 2nd stage CD that can alter the interpretation of results between operative delivery options.

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Factors associated with failed trial of labor after cesarean, among women with previous two cesarean deliveries

Misgav Rottenstreich

Abstract text

Objective: trial of labor after two cesarean deliveries (TOLAC), is associated with a lower success rate of vaginal delivery than singleton TOLAC and a higher rate of adverse outcomes, in comparison to an elective repeat cesarean delivery. This study aims to investigate the factors associated with failed TOLAC, among women with previous two cesarean deliveries.

Study design: A multicenter retrospective cohort study was undertaken. All women with singletons pregnancies attempting a trial of labor after previous two CDs, between 2005 and 2021 were included. Labor, maternal, and neonatal characteristics were compared. A univariate analysis was undertaken, followed by multivariate analysis (aORs; [95% CI]).

Results: A total of 1181 women attempting a TOLAC after two previous CDs were included. Vaginal birth after cesarean was achieved in 973 (82.4%) of these cases. Longer inter-pregnancy interval, smaller gravidity and parity, smaller rates of previous successful vaginal delivery, higher rates of smoking, a lower cervical dilation on admission, a lower rates of epidural use an earlier gestational age at delivery, higher rates of preterm delivery (<37 gestational weeks) and smaller neonatal birthweight were all found to be associated with failed TOLAC. The multivariate model revealed that the most important risk factor for failed TOLAC was cervical dilation on admission of labor< 3 cm followed by preterm delivery (<37 weeks).

Conclusion: In the investigated population of women with previous two CDs undergoing TOLAC, admission at active labor may reduce the risk of repeat cesarean delivery.

Failed vacuum and preterm delivery risk in the subsequent pregnancy – A multicenter retrospective cohort study

Misgav Rottenstreich

Abstract text

Objective: Second-stage cesarean delivery (CD) is associated with subsequent preterm delivery (PTD). Failed vacuum is a sub-group of second-stage CD in which the fetal head is engaged deeper in the pelvis, thus, associated with increased risk for short-term maternal complications. We aimed to study the maternal and neonatal outcomes of women at their subsequent delivery following a second-stage CD with failed vacuum extraction versus following a second-stage CD without a trial of vacuum.

Methods: A multi-center retrospective cohort study. The study population included all women in their subsequent pregnancy following a second-stage CD who delivered in all university-affiliated obstetrical centers (four) in a single geographic area between 2003 and 2021. Maternal and neonatal outcomes of women who had second-stage CD following a failed vacuum were compared to women who had second-stage CD without a trial of vacuum. The primary outcome of this study was PTD<37 weeks. Secondary outcomes were vaginal birth rate and other adverse maternal and neonatal outcomes. Univariate analysis was followed by multiple logistic regression modeling.

Results: During the study period, 1313 women met inclusion criteria, of whom 215 (16.4%) had a history of failed vacuum at the previous delivery, and 1098 (83.6%) did not. In univariate analysis, women with previously failed vacuum had similar preterm delivery rates (<37, <34, <32, and <28 weeks), a successful trial of labor after cesarean rates, uterine rupture, and hysterectomy. However, multivariate analyses controlling for confounders showed that a history of failed vacuum is associated with a higher risk for preterm delivery<37 weeks (aOR 2.05, 95% CI 1.11-3.79, p=0.02), but not with preterm delivery<34 or <32 gestational weeks.

Conclusion: Among women with a previous second-stage cesarean, previously failed vacuum is associated with increased risk for preterm delivery<37 weeks in the subsequent birth.

Failure to seek maternal consent for interventions during childbirth: frequency and determinants from the French ENP 2021

Marianne Jacques , *Anne Alice Chantry, Anne Evrard, Nathalie Lelong, Camille Le Ray*

Abstract text

Introduction: Although decreasing, interventions during childbirth remains frequent procedures within the framework of legal requirements, including the request for patient consent. Our aim was to assess the frequency and determinants of women who had medical interventions during labour without prior consent being sought.

Methods: We used the *Enquête Nationale Périnatale* (*ENP)* 2021, a cohort population-based study conducted in all maternity units in metropolitan France providing a representative sample of women who delivered in March 2021 with a 2-month postpartum follow-up (n=7,394). Rates of interventions during childbirth (oxytocin administration, episiotomy or emergency caesarean section) without consent were calculated and weighted to account attrition at 2-months. Association with maternal, obstetrical and organizational characteristics was assessed by univariate analyses and multilevel logistic regressions.

Results: Women reported failure to seek consent in 44.7%, [95% confidence interval (CI) 42.6-47.0] of cases for oxytocin administration, 60.2% [55.4-65.0] for performing an episiotomy, and 36.6% [33.3-40.0] for an emergency caesarean. Lack of consent for oxytocin was associated with nulliparity and maternal birth abroad, while women with high education level and who had a birth plan reported less lack of consent. Delivery assisted by an obstetrician-gynecologist rather than a midwife was associated with more lack of consent for episiotomy. Foetal concerns seemed associate with more lack of consent for caesarean section.

Conclusions: Not seeking consent for interventions during childbirth was frequent. The identification of several factors associated with lack of consent suggests that maternal involvement in medical decisions can be improved in many situations.

Family Cash Transfers in Childhood and Maternal and Birth Outcomes Later in Life

Tim Bruckner , *Brenda Bustos, Candice Odgers, William Copeland, Kenneth Dodge*

Abstract text

Much literature in the US documents an intergenerational transmission of maternal and perinatal morbidity in socioeconomically disadvantaged groups. A separate line of work indicates that family cash transfers may improve life chances of low-income families well into adulthood. By exploiting a quasi-random natural experiment of a large family cash transfer among a southeastern American Indian (AI) tribe in rural North Carolina, we examine whether a “perturbation” in socioeconomic status during childhood improved maternal/perinatal outcomes later in life. We acquired birth records on 6,805 AI and non-AI infants, born from 1995 to 2018, in three counties from the North Carolina Office of Vital Records. Difference-in-difference methods tested whether the mother’s American Indian (AI) status and exposure to the family cash transfer during her childhood years corresponds with improvements in maternal and peromatal outcomes. Findings show an increase in age at childbearing (coef: 0.15 years, 95% confidence interval [CI]: 0.05, 0.25) and a decrease in pre-pregnancy body mass index (BMI; coef: -0.41, 95% CI: -0.74, -0.08) with increased duration of cash transfer exposure during childhood. Consistent with the pre-pregnancy BMI findings, infant birthweight is also reduced among AI births whose mother had relatively longer duration of exposure to the cash transfer. We, however, observe no relation with other maternal/perinatal outcomes (e.g., tobacco use during pregnancy, preterm birth). In this rural AI population, cash transfers during childhood precedes several improvements--10 to 20 years later--in maternal and perinatal health.

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Fear of childbirth declines future fertility

Mika Gissler , *Laura Lampio, Terhi Saisto, Elina Silvan, Katariina Salmela-Aro*

Abstract text
Fertility has decreased substantially in Finland. Factors influencing the decision to have children have been investigated from many perspectives, but fear of childbirth has not been studied. About 3-8% of first-time mothers overcome fear of childbirth. Our purpose was to determine whether diagnosed fear of childbirth during first pregnancy affects the probability of having a second birth.

Our study data were based on Medical Birth Register covering all births in Finland. After excluding multiple births (3.0%), perinatal deaths (0.5%) and women with incomplete personal identity code (0.3%), the final data included 317 220 primiparous women giving birth in 2006-2019. In total 11 109 (3.5%) had a record for fear of childbirth (O99.80 in the Finnish ICD-10). We used Cox regression to calculate Hazard Ratio (HR) with 95% Confidence Intervals (CI) for second childbirth in 2006-2021. The HRs were adjusted (aHR) for maternal age, migrant origin and highest education at first birth.

Women with fear of childbirth (47.5%) had fewer second births than the women without the diagnosis (69.0%): crude HR 0.63 (95% CI 0.61-0.65) and adjusted HR 0.70 (0.68-0.72). The results were the same excluding first births with a child with prematurity (aHR 0.70, 0.68-0.72), low birth weight (aHR 0.69, 0.67-0.71) or any congenital anomalies (aHR 0.69, 0.68-0.72). Limiting the analysis to primigravida (aHR 0.69, 0.67-0.71) or limiting the follow-up to five years did not change the results (aHR 0.68, 0.66-0.70).

The likelihood for a second birth was higher for women with spontaneous (aHR 0.76, 0.73-0.79) or instrumental vaginal birth (aHR 0.83, 0.77-0.89) than for women with planned (aHR 0.67, 0.63-0.70) or urgent Caesarean section (adjusted HR: 0.71, 0.67-0.76).

Fear of childbirth is an important factor declining the likelihood to get another child. The phenomenon should be studied further by investigating the likelihood to have an induced abortion or ART treatment after fear of childbirth.

Fetal scalp pH changes in Category II Fetal Heart Rate Tracings

Aude Girault , *Camille Le Ray, Charles Garabedian, François Goffinet, Xavier Tannier*

Abstract text

Background Since the 1970s, fetal scalp blood sampling (FSBS) has been used as a second-line test of the acid-base status of the fetus to evaluate fetal well-being during labor. The usual thresholds that define normal (7.25), sub-normal (7.20-7.24) and pathological pH (<7.20); and guide clinical decisions lack scientific validation.
Objectives Describe the change of fetal scalp pH and the rate of this change among patients with category II fetal heart rate tracing during labor.
Study Design Retrospective study of patients with at least one FSBS for category II FHR and delivery of a singleton cephalic infant during a 2 year period at a tertiary maternity unit. Population's characteristics and outcomes were described. The rate of change in pH value between consecutive samples for each patient was calculated and plotted as a function of pH value. Linear regression analyses were performed to investigate the relevance of commonly used pH thresholds and to identify potentially more relevant thresholds. Finally, multiple linear regression adjusted on age, body mass index, parity, oxytocin stimulation and suspected small for gestational age was performed.
Results The study included 2047 patients and 5514 fetal samples. Median pH values were 7.29 one hour before delivery, 7.26 30 minutes before delivery. The pH drop was steady and slow between 7.40 and 7.30, then became more pronounced, with median rates of 0.0005 units/min at 7.25 and 0.0013 units/min at 7.20. Out of 1035 possible combinations of thresholds tested, 7.26 and 7.20 minimized the standard error. Multiple linear regression yielded similar results.
Conclusion Our study reinforces the current guideline thresholds for fetal pH drop in patients with category II FHR and highlights the importance of adhering to established guidelines for optimal labor and delivery management. The close alignment of our identified thresholds with existing recommendations emphasizes their validity and reliability in clinical practice.

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Fetal size and cardiovascular disease have inverse associations in term and preterm preeclampsia

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Abstract text
Introduction: Preeclampsia is associated with long term maternal cardiovascular disease (CVD) mortality. Risk of CVD mortality is more strongly associated with preeclampsia delivered at preterm rather than term. The differences in CVD risk between term and preterm preeclampsia are still being investigated, and one important factor that has not yet been explored is differences in growth of the fetus.

Objective: To examine what fetal size is associated with greatest risk of CVD death in term and preterm preeclampsia.

Methods: Our data is from the Medical Birth Registry of Norway and the Norwegian Population Registry (1967 – 2013). Our population included mothers with preterm (before 37 weeks) or term (37 weeks or later) deliveries of first pregnancies with or without preeclampsia. Our exposure was fetal size, standardized by gestational age and Z-score, divided into quartiles. Our outcome was death due to atherosclerotic cardiovascular disease. Results were adjusted for year of delivery, maternal age, and maternal education.

Results: Mothers with no preeclampsia, term delivery, and a fetus in the heaviest size quartile served as the reference group and had the lowest CVD risk overall. Mothers with term preeclampsia had higher CVD risk with a smaller fetus (hazard ratio 2.35, 1.95, 1.51, and 1.56 for first, second, third, and fourth quartiles respectively). Mothers with preterm preeclampsia had higher CVD risk with a larger fetus (hazard ratio 2.72, 3.49, 5.00, 7.79 for first, second, third, and fourth quartiles respectively).

Conclusions: Fetal size in a preeclamptic pregnancy is associated with CVD, but the direction differs between term and preterm deliveries. Preeclampsia is a highly heterogenous disorder, and it is important to consider many factors from the full reproductive history, such as gestational age and fetal size, when evaluating maternal health.

Genome-wide analyses of neonatal jaundice reveal a protective role of the intestines and a marked departure from adult bilirubin metabolism

pol Sole-Navais

Abstract text
Neonatal jaundice affects almost all newborns and is caused by the excess accumulation of bilirubin. While the core biochemistry of bilirubin is well understood, pathways behind neonatal jaundice are assumed to be analogous to those affecting bilirubin levels in adults. Genome-wide association studies provide a unique opportunity to study this, and to clarify why in some newborns bilirubin imbalance is more severe and treatment with phototherapy required.
Here, we present the first genome-wide association study of neonatal jaundice (requiring phototherapy treatment) in nearly 30,000 parent-offspring trios (90,000 samples, 2,000 cases), and compare it to the genetics of adult bilirubin levels. We leverage family structure and eQTL analyzes to provide potential mechanisms for our findings.
The maternal GWAS of offspring neonatal jaundice captured known biology at the ABO gene region, where the association of the parental transmitted and non-transmitted alleles was explained by maternal-fetal blood group incompatibility. We also observed surprising differences between the adult and neonatal genetics of jaundice which may indicate a new, context-specific regulatory aspect of bilirubin clearance in neonates. For instance, the alternate allele of a common missense variant affecting UGT1A4, protected from neonatal jaundice by five-fold. eQTL colocalization results suggest that the association could be through the regulation of UGT1A1 expression in the intestines, but not in the liver. Intestinal UGT1A1 expression is known in adults, but often overshadowed by liver bilirubin metabolism, and has never been investigated in human neonates. Our study highlights how genetics can inform new biology and potential novel therapeutic modalities for neonatal jaundice.

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Genome-Wide Association Study of Breastfeeding Phenotypes

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Abstract text
The mean duration of breastfeeding has changed over the course of human evolution, from over 3 years in prehistoric times to under 1 year in the 21st century in high-income countries. Today, the majority of infants are not breastfed according to WHO recommendations, and breastfeeding rates vary between- and within-countries, adding to health inequalities. Many environmental and maternal factors are known to be associated with breastfeeding patterns, but little is known about the role offspring play themselves. Offspring effects could act through effects on birth and delivery, growth trajectories, suckling ability and behaviour/temperament.

Here we explore the genetic architecture of breastfeeding initiation and duration for term (singleton) babies from the offspring genomes point of view, by performing the first large-scale genome-wide association study (GWAS) of these traits. We integrate and harmonise data from multiple historical cohorts, chosen to complement each other in terms of breastfeeding rates, c-section rates, ethnic background and socioeconomic contexts: the UK Biobank (UKB,N=350k), more contemporary UK-based birth cohorts as the Avon Longitudinal Study of Parents and Children (ALSPAC,N=8k) and Born in Bradford (BiB,N=5k), and the Norwegian Nord Trøndelag health study (HUNT,N=20k), with 80+ years of extreme change in breastfeeding rates.

SNP-based heritability estimates are 2.6% (standard error 0.2%, UKB data), and 6.9% (standard error 1.4%, HUNT data) for initiating and establishing breastfeeding, respectively, in line with other complex traits. We will run separate meta-analyses for the two traits to identify genetic variants of offspring-origin to take forward to post-GWAS analyses. These will investigate functional relevance of hits through bioinformatic approaches and estimating genetic correlation with relevant traits including (offspring-origin components of) gestational age, birthweight, neurodevelopmental disorders.

Gestational age at birth and hospitalizations for infections among individuals aged 0 to 50 years: A population-based study of 2.5 million individuals

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Abstract text
Background: Low gestational age is associated with increased risk of infections in childhood, but it is uncertain whether this risk persists into adolescence and adulthood.

Methods: We linked individual-level data on all subjects born in Norway (1967-2016) to nationwide hospital data (2008-2017). Gestational age was categorised as 23-27, 28-31, 32-33, 34-36, 37-38, 39-41, and 42-44 completed weeks. Analyses were stratified by age at follow-up: 0-11 months and 1-5, 6-14, 15-29, and 30-50 years. Hospitalization rate ratios (RRs) were estimated using negative binomial regression for inpatient hospitalization caused by any infection and infection groups, adjusted for year of birth, maternal age, parity, and sex.

Results: Among 2,485,445 individuals with 313,914 hospitalizations for infections, we found a pattern of higher hospitalization risk in lower gestational age groups, which was strongest in childhood but still evident in adulthood. Comparing those born very preterm (28-31) and late preterm (34-36) to full-term (39-41 weeks), RRs (95% confidence interval) for hospitalization for any infectious disease at ages 1-5 were 3.3 (3.0-3.7) and 1.7 (1.6-1.8), respectively. At 30-50 years, the corresponding estimates were 1.4 (1.2-1.7) and 1.2 (1.1-1.3). The patterns were also similar for the infectious disease groups, including bacterial and viral infections, respiratory tract infections (RTIs), and non-RTIs.

Conclusions: Lower gestational age was associated with increased risk of hospitalizations for all infection groups, most prominent in children but still evident in adolescents and adults. Potential mechanisms and effective prevention strategies should be investigated.

Gestational age at birth and type 1 diabetes in childhood and young adulthood: a nationwide register study in Finland, Norway and Sweden

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Abstract text

Background Preterm birth is linked with an increased risk of type 1 diabetes (T1D), but evidence is scarce on specific exposure groups, like extremely preterm birth. Our aim was to investigate the risk of T1D over the full range of gestational ages.

Methods We used nationwide register data from Finland, Norway and Sweden and included all individuals who were born alive in 1987-2016 to mothers whose country of birth was the respective Nordic country. Gestational age was categorised as extremely preterm (23-27 weeks (wk)), very preterm (28-31 wk), moderately preterm (32-33 wk), late preterm (34-36 wk), early term (37-38 wk), full-term (39-41 wk, reference) and post-term (≥42 wk). Results from country-specific Cox regression models were combined in a meta-analysis.

Results Among the 5,501,276 individuals included in the study 0.2% were born extremely preterm, 0.6% very preterm, 0.8% moderately preterm, 4.3% late preterm, 17.8% early term, 70.2% full term, and 6.2% post term. During a median follow-up time of 15.6, 10.0 and 15.7 years, T1D diagnosis was recorded in 12,326 (0.7%), 6,354 (0.5%) and 16,856 (0.7%) individuals at a median age of 8.6, 13.0, and 10.5 years in Finland, Norway, and Sweden, respectively. Late preterm and early term birth were associated with an increased risk of T1D compared to full-term birth after adjustment for mother’s age, education, parity, diabetes, hypertensive disorders during pregnancy and child’s sex, birth cohort, and birth weight z-score [pooled hazard ratio (HR) 1.12 95% confidence intervals (CI) 1.07-1.18 and HR 1.15 95% CI 1.11-1.18, respectively]. Extremely and very preterm birth were, in turn, associated with a decreased risk of T1D (HR 0.63 95%CI 0.45-0.88 and HR 0.78 95%CI 0.67-0.92).

Conclusion Individuals born late preterm and early term have an increased risk of T1D, while those born extremely or very preterm have a decreased risk of T1D. Our results underline the relevance of perinatal history in risk assessment for T1D.

Gestational diabetes - trends in the Medical Birth Registry of Norway 1999-2020

Thomas Nymo Skogvold , *Linn Marie Sørbye, Rolv Skjærven, Kari Klungsøyr*

Abstract text
Introduction: Gestational diabetes mellitus (GDM) has received more attention in recent years. GDM is a risk factor for preeclampsia, cesarean section and later type-2 diabetes, and studies report increasing prevalence in GDM over time.

Aim: To assess time trends in GDM among women giving birth in Norway 1999-2020. To investigate whether the trend is explained by the following risk factors: maternal age, parity, ethnicity, highest level of attained education, and for births from 2007, pre-pregnancy body mass index (BMI).

Method: Retrospective cohort study using data from 1 296 484 pregnancies (714 381 mothers) registered in the Medical Birth Registry of Norway 1999-2020. Multivariable log-binomial regression models were used to calculate adjusted risk ratios (RR) and 95% confidence intervals to estimate the association between GDM and risk factors, all modelled as categorical variables.

Results: GDM had a six-fold increase in prevalence between 1999 and 2020: 0.8% [0.76-0.83] to 5.3% [5.2-5.4]; RR: 6.75 [6.41-7.11]. The associations between the studied risk factors and GDM were as follows: Women aged 35-39 years versus <20 years: RR 7.20 [6.12-8.46]; South-Asian versus Nordic women: RR 3.09 [2.97-3.23]; low versus high education RR 1.57 [1.51-1.63]; and nulliparous women versus women with one prior birth: 0.89 [0.87-0.92]. Using data from 2007, the RR of GDM for women with BMI 30-34.9 (kg/m^2) versus 18.5-24.9 was 4.65 [4.47-4.85]. After adjusting for the risk factors, the RR of GDM in 2018-2020 versus 1999-2002 was 5.81 [5.51-6.13].

Conclusion: GDM is positively associated with increasing maternal age, non-European ethnicity, low education and obesity. The GDM increase over the study period remains strong after adjusting for known risk factors, suggesting that these factors can only partly explain the time trend. Updated guidelines, increased screening and improved registration routines must be accounted for to understand the severity of the GDM epidemic.

How is the newborn’s weight affected by maternal diabetes?

Thomas Nymo Skogvold , *Linn Marie Sørbye, Nils-Halvdan Morken, Rolv Skjærven, Kari Klungsøyr*

Abstract text
Introduction: While gestational diabetes is a complication of pregnancy, type 1 and type 2 diabetes are chronic conditions. Diabetes during pregnancy is known to increase the average birthweight of the fetus. Less is known about whether different subtypes differentially affect fetal weight.

Aim: To explore how maternal diabetes subtypes differentially affect fetal weight at birth.

Method: We identified 483 346 nulliparous women who gave birth to a viable singleton child between 1999-2020 using the Medical Birth Registry of Norway. We studied newborn size by maternal diabetes subtype (pregestational or gestational) and offspring sex. Offspring to mothers without diabetes were used as reference. Generalized additive models in R were used to describe birthweight (grams) by length of gestation. Mean values and 95% confidence intervals (CI) were evaluated by analysis of variance.

Results: In our population 3% of the women were registered with diabetes during their first pregnancy. Of these women 0.7% had pregestational and 2.1% gestational diabetes. Newborn weight differed by diabetes subtype (pregestational or gestational). Mean birthweight at week 38 for offspring of non-diabetic mothers (3217g, 95%CI 3213-3220g) was lower than for pre-gestational and gestational diabetes (3641g, 95%CI 3612-3671g and 3381, 95%CI 3363-3400g, respectively). The largest relative difference in size was found among those born between gestational week 28 and 38 (day 196 and 266).

Conclusion: In the Norwegian population, maternal pregestational diabetes was associated with higher average birthweight. Gestational diabetes did not affect birthweight to the same degree.

Impact of ambient air pollution on preeclampsia in 2001-2019, Rome, Italy.

Marie Pedersen , *Federica Nobile, Paola Michelozzi, Kees de Hoogh, Jesper H. Christensen, Jørgen Brandt, Massimo Stafoggia*

Abstract text

Background: Preeclampsia can lead to maternal and perinatal morbidity and mortality, but the cause of the condition is not well understood. Ambient air pollution has been associated with preeclampsia, but few studies rely on assessment of fine-scale variation in air quality and the impact on mild and severe preeclampsia, which have been reported to have different pathogenesis, is understudied.

Aim: To study the impact of long-term exposure to air pollution on preeclampsia.

Methods: We obtained data from 440,965 liveborn singletons born by women with residence in Rome during 2001-2019 from hospital, birth and administrative registries. Land-use regression models at 100 m spatial resolution assigned to the maternal residential addresses at birth with temporally adjustment were used to estimate the exposure during the first trimester to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3). Logistic regression models with adjustment for maternal age, education, occupation, origin, parity, season of conception and area-specific socio-economic status were used to estimate the associations.

Results: Increased risk of preeclampsia was observed for all pollutants except for O_3 in adjusted single-pollutant models. For instance, a 5-mg/m^3 increase in $PM_{2.5}$ exposure during the first trimester was associated with an adjusted odds ratio (OR) of 1.16 (95% confidence interval: 1.10, 1.23) for all subtypes of preeclampsia (n=1,815). For $PM_{2.5}$, NO_2 and BC, increased risks were evident for mild preeclampsia (n=1,357), but not for severe preeclampsia (n=337).

Conclusions: The results of our study suggest that maternal exposure to ambient air pollution with $PM_{2.5}$, NO_2 and BC increases the risk of preeclampsia and that the observed risk is driven by mild subtypes of preeclampsia. Although the observed risk is relatively small, the population attributable risk is likely to be large, given the widespread exposure to these pollutants in ambient air.

Impact of Prior Use of Topical Hemostatic Agents on Trial of Labor After Cesarean: Insights from a Multicenter Cohort Study

Romi Levy , ***Misgav Rottenstreich***

Abstract text

Objective: Topical hemostatic agents were found to be associated with post-cesarean infections. We aim to evaluate the association between a topical hemostatic agent used at the time of cesarean delivery to uterine scar disruption (rupture or dehiscence) at the subsequent trial of labor after cesarean delivery (TOLAC).

Methods: This is a multicenter retrospective cohort study (2005-2021). Parturients with a singleton pregnancy in whom a topical hemostatic agent was placed during the primary cesarean delivery were compared to patients in whom no such agent was placed. We assessed the subsequent uterine scar disruption rate following the subsequent TOLAC and the rate of adverse maternal outcomes. Univariate analyses were followed by multivariate analysis (adjusted Odds Ratio (aORs); [95% Confidence Interval]).

Results: During the study period, 7199 women underwent a trial of labor and were eligible for the study, of whom 430 (6.0%) had prior use of a hemostatic agent and 6769 (94.0%) didn't. In univariate analysis, a history of the use of hemostatic agents wasn't found to be significantly associated with uterine scar rupture, dehiscence, or failed trial of labor. This was confirmed on multivariate analysis as well for uterine rupture[aOR 1.91, (0.66-5.54), p=0.23], for dehiscence of uterine scar[aOR 1.62, (0.56-4.68), p=0.37], and TOLAC failure [aOR 1.08, (0.79-1.48), p=0.61].

Conclusion: A history of hemostatic agent use is not associated with an increased risk for uterine scar disruption following subsequent TOLAC. Further prospective studies in other settings to strengthen these findings are needed.

Impact of techniques for managing impacted fetal head in second stage cesarean delivery on subsequent preterm birth

Tzuria Peled , *Giulia M. Muraca, Miri Ratner, Abirami Kirubarajan, Hen Y. Sela, Ari Weiss, Sorina Grisaru-Granovsky,* ***Misgav Rottenstreich***

Abstract text

Background: Second-stage cesarean delivery (CD) is associated with subsequent preterm birth (PTB). Previous studies have shown that reverse breech extraction is associated with lower rates of uterine incision extensions compared to the "push" method.

Objective: We aimed to investigate the association between the mode of fetal extraction during second stage CD and the rate of spontaneous PTB (sPTB), as well as other maternal and neonatal outcomes during the subsequent pregnancy.

Methods: A multi-center retrospective cohort study. The study population included women in their subsequent singleton pregnancy following a second-stage CD between 2004 and 2021. The main exposure of interest was the method of fetal extraction in primary CD ("push" method vs reverse breech extraction). The primary outcome of this study was sPTB<37 weeks. Secondary outcomes were overall PTB, vaginal birth rate and other adverse maternal and neonatal outcomes. Univariate analysis was followed by multiple logistic regression modeling.

Results: During the study period, 615 women met inclusion criteria, of whom 275 (44.7%) had fetal extraction using the reverse breech extraction technique, while 340 (55.3%) had the "push" method for extraction. In univariate analysis, women the "push" method had similar rates of sPTB and overall PTB (<37, <34 and <32 weeks), as well as other maternal outcomes except of higher rates of overall CD. This was confirmed by multivariate analyses with adjusted odds ratio of 0.64 (95% CI 0.23-1.75) for sPTB.

Conclusion: Among women with a previous second-stage cesarean, no significant difference was observed in the rates of PTB in subsequent pregnancies following the "push" method compared to the reverse breech extraction technique.

Impaired glucose tolerance, cardiovascular risk and infertility: Mendelian randomization analyses in the Norwegian Mother, Father and Child Study

Alvaro Hernaez , *Yunsung Lee, Christian M. Page, Karoline H. Skåra, Siri E. Håberg, Per Magnus, Pål R. Njølstad, Ole A. Andreassen, Elizabeth C. Corfield, Alexandra Havdahl, Abigail Fraser, Stephen Burgess, Deborah A. Lawlor, Maria C. Magnus*

Abstract text

Background. We aim to establish whether impaired glucose tolerance (as measured by fasting glucose, glycated hemoglobin, and fasting insulin) and cardiovascular disease risk (as measured by LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, and diastolic blood pressure) are causally related to infertility (having tried to conceive for ≥ 12 months or used assisted reproduction technologies to conceive) by Mendelian randomization (MR) analyses in women and men.

Methods. We conducted two-sample MR analyses, in which we used genome-wide association summary data that were publicly available for the cardiometabolic risk factors, and sex specific genome-wide association studies of infertility conducted in the Norwegian Mother, Father, and Child Cohort Study (68,882 women [average age 30, 81,682 pregnancies] and 47,474 of their male partners [average age 33, 55,744 pregnancies]). We applied the inverse variance weighted method with random effects to pool data across variants and a series of sensitivity analyses to explore genetic instrument validity. Findings were corrected for multiple comparisons by the Bonferroni method (8 exposures: p-value < 0.00625).

Results. In women, increases in genetically determined fasting insulin levels were associated with greater odds of infertility (+1 log(pmol/L): OR 1.60, 95% CI 1.17 to 2.18, p-value = 0.003). The results were robust in the sensitivity analyses exploring the validity of MR assumptions and the role of pleiotropy of other cardiometabolic risk factors. There was also evidence of higher glucose and glycated hemoglobin in women (and possibly higher fasting insulin in men) causing infertility, but findings were imprecise and did not pass our p-value threshold for multiple testing. Results for lipids and blood pressure were close to the null, suggesting that these did not cause infertility.

Conclusion. Genetic instruments suggest that higher fasting insulin may increase infertility in women.

Inappropriate care during childbirth and maternity stay: frequency and determinants from the Frenc ENP 2021

Marianne Jacques , *Anne Alice Chantry, Nathalie Lelong, Camille Le Ray*

Abstract text

Introduction: Poor birth experience due to inappropriate care during childbirth has been reported by women and professionals in high-income countries for the past two decades. The objective was to assess the frequency and determinants associated with inappropriate care during childbirth and postpartum.

Methods: This study used data from the *Enquête Nationale Périnatale (ENP)* 2021 which surveyed of all women who gave birth in metropolitan France during one week and allowed a 2-month postpartum follow-up of these women (n=7 394). The rate of inappropriate care (embarrassing, hurtful, or offensive words, gestures, or attitudes) during delivery or postpartum reported by women was calculated and weighted to account for attrition at 2 months. The association with maternal, obstetric, and organizational characteristics was assessed by multilevel logistic regression.

Results: Overall, 24.8% (95% confidence interval -CI- [23.8-26.0], n=1,888) of women reported receiving inappropriate care. Inappropriate care was more common among nulliparous women (adjusted Odds Ratio -aOR- =1.51 [1.33-1.72]), obese women (1.31 [1.09-1.57]), women with high education level (1.39 [1.17-1.64] for ≥ 5 years post-graduation compared with women who attended high school), and women with a birth plan (1.55 [1.29-1.87]). Inappropriate care was reported more frequently by women who had at least one complication (instrumental delivery, caesarean section, episiotomy, 3rd and 4th-degree perineal tears or post partum haemorrhage) during delivery (1.31 [1.15-1.49]). Conversely, inappropriate care was not associated with the woman's country of birth, the child's characteristics, or the maternity hospital.

Conclusions: Inappropriate care concerns one quarter of women who gave birth in France. It seems to be reported more frequently in women who had complications during delivery but also seems to be related to different expectations of women according to their own characteristics.

Induction of Labor in term pregnancies with Isolated Polyhydramnios - is it beneficial or harmful?

Yael Lerner , *Tzuria Peled, Shira Priner Adler, Ari Weiss, Hen Y. Sela, Sorina Grisaru-Granovsky,* ***Misgav Rottenstreich***

Abstract text

Objective: To compare rates of adverse pregnancy outcomes in term pregnancies complicated by polyhydramnios between those who had induction of labor versus those who had expectant management.

Methods:

This multicenter retrospective study included term pregnancies complicated by isolated polyhydramnios . Those who underwent induction of labor were compared to those who had expectant management awaited spontaneous onset of labor The primary outcome was defined as a composite adverse maternal outcome, and secondary outcomes were various maternal and neonatal adverse outcomes.

Results: During the study period, a total of 871 pregnancies complicated by term isolated polyhydramnios met the study's inclusion and exclusion criteria. Of these women, 171 underwent induction of labor (19.6%), while 701 underwent expectant management and developed spontaneous onset of labor (80.4%). Women who underwent induction of labor had significantly higher rates of composite adverse maternal outcome, prolonged hospital stay, perineal tear grade 3/4, intra-partum cesarean, postpartum hemorrhage, blood products transfusion and neonatal asphyxia compared to expectant management. Three women in the expectant management group had a stillbirth (0.4%), while in the induction group one case of intrapartum fetal death occurred due to uterine rupture (0.58%) a non-significant 1statistical difference. Multivariate analyses revealed that induction of labor was associated with higher rate of composite adverse maternal outcome [aOR 2.25 (1.41- 3.59), P<0.01].

Conclusion:

Induction of labor in women with term isolated polyhydramnios is associated with higher rates of adverse maternal and neonatal outcomes. These findings have significant clinical implications and highlight the need for evidence-based decision making in the management of these cases. Further research is needed to determine the optimal approach for the management of isolated polyhydramnios at term.

Intergenerational transmission of hypertensive disorders of pregnancy through the unexposed daughter: a population-based cohort study

Aditi Singh , *Sage Wyatt, Rolv Terje Lie, Liv Grimstvedt Kvalvik, Kari Klungsøyr, Rolv Skjærven*

Abstract text

Background: Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, tend to vary by birth order and recur across generations. It remains unclear how birth order and severity of HDP in a mother's affected pregnancies influence the risk of HDP in daughters who themselves were unexposed to HDP in-utero.

Methods: We conducted a retrospective cohort study using the Medical Birth Registry of Norway. We identified 274785 daughters who were born between 1967-2005, who had siblings from this period, and who had their own first pregnancy in the period 1987-2020. We excluded daughters who themselves were exposed to HDP in-utero, preterm birth or placental abruption.
Relative risks (RR) and 95% confidence interval using log-binomial regression were estimated. Results were adjusted for the highest-attained education and the calendar year of birth. The reference group consisted of daughters born to mothers without any pregnancies complicated with HDP, preterm birth, placental abruption or perinatal loss.

Results: First-born daughters had an increased risk of HDP if their mother had HDP in a second pregnancy that was delivered at term (RR 1.79; 95%CI 1.59-2.01). The association remained unchanged if the HDP pregnancy was delivered preterm (RR 1.69; 95%CI 1.31-2.53). Second-born daughters had increased risk of HDP if their mother had a previous HDP-affected pregnancy that was delivered at term (RR 1.80; 95%CI 1.65-1.96), but the risk was even higher if the previous HDP-affected pregnancy was delivered preterm (RR 2.33; 95%CI 1.83-2.99).

Conclusion: A daughter unexposed to HDP has an increased risk of developing HDP if her mother experienced HDP in another pregnancy. The highest risk was observed for daughters born after a pregnancy that was affected by HDP and delivered preterm. These findings suggest that a more detailed family history of HDP and their own birth order may be valuable in assessing HDP-risk in pregnant women.

Internalizing and externalizing scores of the term born siblings of children born preterm

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Abstract text
The birth of a preterm infant (<37 weeks of gestation) may cause strain on other family members including siblings. However, current evidence on outcomes of term born siblings of preterm born children is sparse and inconsistent. In this study, we hypothesized that term born siblings of children who are born preterm are at an increased risk of having higher internalizing and externalizing scores compared to term born siblings of term born children. We used DataSHIELD to analyse harmonized data across four birth cohorts with available internalizing and externalizing scores of the children: Norwegian Mother, Father and Child Cohort Study (MoBa, n=41,546), Danish National Birth Cohort (DNBC, n=40,914), the Generation R Study (GenR, n=4,729), Nascita e INFanzia: gli Effetti dell'Ambiente (NINFEA, n=4,228). In each participating cohort, three groups of children were created based on the index children's status: the *only child group* (child without sibling, n=76,135); the *reference group* (index cases with term born siblings, n=14,734); and the *risk group* (index cases with preterm born siblings, n=548). We conducted individual participant level meta-analysis of the linear associations using standardised scores. Having a preterm sibling was not associated with increased internalizing (β= -0.092, 95%CI= -0.214-0.029) or externalizing scores (β= 0.023, 95%CI= -0.094-0.140). In contrast, we consistently observed that only child participants had higher internalizing (β= 0.050, 95%CI= 0.023-0.076) and externalizing scores (β= 0.048, 95%CI = 0.022-0.074) than index cases with term born siblings. The results were consistent across analyses in terms of the strength and direction of effects. In view of the strengths and limitations of this study, results do not support that having a preterm born sibling increases the risk of internalizing or externalizing problems of their term born siblings.

Intrauterine drug exposure and the risk of congenital or early-onset hearing loss in children – a systematic review

Asli Sena Kücükyildiz , *Mette Østergaard Thunbo, Christer Zøylner Swan, Therese Ovesen, Lars Henning Pedersen*

Abstract text

Background: Hearing impairment in children is linked to delayed speech, academic achievement, and social and emotional outcomes. Knowledge about the etiology of congenital and early onset hearing loss is crucial to improve early diagnostics and treatment of hearing loss. Several risk factors have been linked to this condition in children, but the cause remains unknown in 25-40% of the cases. Medications are used by >60% of pregnant women and many types could theoretically influence the prenatal development of the inner ear.

Aim: We summarize the available literature on the association between maternal drug intake and early onset hearing loss in children.

Methods: A protocol was registered with the International Prospective Register of Systematic Reviews (CRD42023399514). Literature search was performed on PubMed, Embase and Web of Science. Studies reporting on congenital or early-onset hearing loss in children were included. Studies on children with congenital infections or genetically induced hearing loss were excluded.

Preliminary results: Of 951 articles identified, 78 were retrieved for full text screening and 32 met the inclusion criteria. Studies consisted of two randomized controlled trials, three case-control studies, two cross-sectional studies and twenty-five cohort studies. The studies were heterogeneous in terms of exposition and outcome. Besides a few studies investigating the association between prenatal steroids and hearing loss, all studies examined different types of drugs. The association between drug intake and hearing loss ranged from a protective effect for steroids (odds ratios (OR) 0.31-0.75) to a suggested harmful effect for valproate (OR 5.20). One study showed an OR of 1.53 for acetylic salicylic acid, whereas another study found no significant effect of several widely used antibiotics.

Conclusion: Available studies suggest that some drugs might have ototoxic potential, but more high-quality studies are needed to suggest causality.

Is relationship status in young adulthood programmed by being born preterm?

Suvi Alenius , *Johanna Metsälä, Anna Pulakka, Katriina Heikkilä, Petteri Hovi, Eero Kajantie*

Abstract text

Background: Mother's young age and low education are associated both with preterm birth and teenage pregnancy of the offspring. Those born preterm are, in turn, less likely to have a partner or become parents than those born at term. We used multi-generation nationwide register data (G1-G3) to assess the role of the gestational age (GA) of an individual (G2) on the likelihood of having a child (G3) and/or partner at <25yr, and the impact of parental characteristics, including teenage parenthood (G1), in this association.

Methods: We included 219 898 (4.7% preterm) individuals born in Finland in 1987-1990. We assessed the association between GA (reference: 39-41 completed weeks) and relationship status at 23.4yr [(1) single (reference): (2) living with a partner, no children; (3) living with a partner, own children; (4) single parent; and (5) living with a partner, no common children] by multinomial regression, adjusting for sex, birth year, parental education, mother's smoking in pregnancy, and having had a teenage parent.

Results: Compared to controls, those born preterm were less likely to live with a partner and own child. Unadjusted odds ratios (uOR) with 95% CIs were; 23-27week: 0.59 (0.42-0.82), 28-31week: 0.68 (0.57-0.82), 32-33: 0.83 (0.72-0.97), and 34-36: 0.90 (0.85-0.95). uORs for living with a partner but without children were; 23-27: 0.49 (0.36-0.67), 28-31: 0.69 (0.58-0.81), 32-33: 0.80 (0.70-0.92), and 34-36: 0.90 (0.85-0.95). Covariate adjustment had negligible impact on the estimates. For those born at 32-33wk the uOR for single parenthood was 0.51 (0.36-0.72) and for living with a partner with no common children 0.46 (0.28-0.93). The corresponding adjusted ORs were 0.50 (0.36-0.70) and 0.55 (0.30-1.00). The other GA categories were not associated with these outcomes.

Conclusion: Preterm-born young adults were more likely to live with a partner and/or have a child than their term-born counterparts, regardless of their parents' characteristics.

Isolated orofacial clefts in of children born to immigrant women in Norway, a population-based register study (1990-2021)

Tone Engen , *Roy Miodini Nilsen, Katrine Mari Owe, Vigdis Aasheim, Erica Schytt, Eline Skirnisdottir Vik*

Abstract text

Introduction: Orofacial clefts (OFC) are birth defects caused by midline body structural developmental failures in early pregnancy and are associated to a variety of genetic and environmental factors. Occurrence varies across geographical regions and seems to have a genetic basis with variations between gender and ethnic groups. Further, the occurrence of OFC has been associated to migration related factors.

Objective: To assess associations between maternal country of birth birth (specific country and categorised according to Global Burden of Disease regions (GBD)) and OFC (cleft lip with or without cleft palate and cleft palate only).

Methods: National population-based study including birth to migrant (n=316 719) and non-migrant women (n=1 406 670) in Norway from 1990-2021. Data were retrieved from the Medical Birth Registry of Norway and Statistics Norway. Associations were estimated as crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) using multiple logistic regression. Analyses were adjusted for year of birth, maternal age and parity.

Results: Migrant women were associated with lower odds of OFC compared to non-migrant women (aOR) 0.64; 95% CI 0.55-0.73). Compared to non-migrant women, lower odds were found among women from Vietnam (aOR 0.33; 95% CI 0.12-0.89), Kosovo (aOR 0.24; 95% CI 0.06-0.95), the Philippines (OR 0.29; 95% CI 0.11-0.76), Russia (OR 0.31; 95% CI 0.10-0.95), Iraq (aOR 0.32; 95% CI 0.13-0.78), Poland (aOR 0.42; 95% CI 0.23-0.79) and from Other countries (aOR 0.70; 95% CI 0.55-0.88). Compared to non-migrant women, women from the following GBD regions were found with lower odds of OFC: Central Europe, Eastern Europe, and Central Asia (aOR 0.46; 95% CI 0.34-0.64), North Africa and Middle East (aOR 0.53; 95% CI 0.37-0.77) and Southeast Asia, East Asia, and Oceania (aOR 0.53; 95% CI 0.36-0.76).

Conclusion: No sub-groups of migrant women in Norway were found to have a increased odds of OFC compared to non-migrant women.

Lessons learned from the EUROlinkCAT study on the quality of data in European hospital discharge databases

Ester Garne , *Maria Loane, Joan Morris*

Abstract text

Background: The EUROlinkCAT study investigated morbidity outcomes in children with congenital anomalies by linking data from congenital anomaly registries to hospital discharge databases. We present our experiences and challenges in this work.

Methods: EUROlinkCAT supported 22 EUROCAT population-based congenital anomaly registries in 14 countries to link their data on children with congenital anomalies to hospital discharge databases and vital statistics for the birth years 1995-2014. Each registry transformed their local mortality and morbidity data to a Common Data Model, ran centrally created syntax scripts and produced tables/outputs for meta-analysis. Analyses were performed on 100 congenital anomaly subgroups for three age groups.

Results : The waiting times for ethical and other approvals for the study were very long, taking up to 3 years in one country. Eleven registries linked their data on children with congenital anomalies to regional/national hospital databases. Data on children without a congenital anomaly born during the same time-period and from the same population area (reference population) were available for seven registries. Linkage success was high with 89% of children with a congenital anomaly (n=99,000) and 95% of reference children (n=2 million) being linked. In some countries delays in assigning a permanent ID number resulted in data on deaths and surgeries occurring during the first few days of life, being less complete. Restrictions on the release of small numbers from three databases meant that their data could not be included in analyses concerning rare anomalies or rare events.

Conclusion: Linkage to hospital discharge databases enabled mortality and morbidity outcomes to be investigated for children with over 100 different congenital anomalies across Europe. The quality of the neonatal data in hospital databases would be improved by ensuring that all children are assigned a permanent ID number within the first day after birth.

Leveraging genetics to inform the effect of blood pressure lowering drugs on adverse pregnancy outcomes

Maria Carolina Borges , *Qian Yang, Nancy McBride, Marwa Al Arab, Christy Burden, Katherine Birchenall, Ana Goncalves Soares, Tom Bond, Maria C Magnus, Deborah A Lawlor*

Abstract text

Mendelian randomization (MR) can provide insights into drug efficacy and safety in pregnancy by using genetic variants to mimic pharmacological modulation of proteins targeted by drugs. We used MR to explore the effect of modulating targets of blood pressure lowering drugs [calcium channel blockers (CCB), beta blockers (BB), angiotensin I converting enzyme inhibitors (ACEi), and thiazide diuretics (TZD)]. As proxies for drug target perturbation, we selected genetic variants in the drug target gene region that were strongly ($P < 5*10^{-8}$) and independently ($R^2 < 0.2$) associated with systolic (SBP) or diastolic (DBP) blood pressure, which were used in MR to test the effect of modulating the selected drug targets in 18 adverse pregnancy events in up to 616,175 women. Results for each protein target were estimated using the generalized inverse-variance weighted MR method and are presented as odds ratio (OR) per 1 standard deviation (SD) lower SBP or DBP. Modulating targets of CCB (CACNA1C and CACNA1D) was related to lower risk of hypertensive disorders of pregnancy (HDP) (e.g. OR: 0.87, 95% confidence interval (CI): 0.76, 0.99 for CACNA1C), and preterm birth (OR: 0.84, 95%CI: 0.77, 0.91 for CACNA1C). Modulating a target of BB (ADRB1) was related to lower risk of HDP and preeclampsia (OR: 0.92, 95%CI: 0.88, 0.97). Inhibiting ACE, the target of ACEi, was related to lower risk of gestational hypertension (OR: 0.82, 95%CI: 0.73, 0.92) and delivering a small-for-gestational age baby (OR: 0.87, 95%CI: 0.78, 0.99). In contrast, inhibiting SLC12A3, the target of TZDs, was related to higher risk of low birthweight (OR: 2.3, 95%CI: 1.3, 4.0) and very preterm birth (OR: 3.7, 95%CI: 1.7, 8.2). Our study supports the efficacy of modulating CCB, BB and ACEi targets to control HDP, preterm birth and fetal growth restriction, and raises the possibility of potential on target adverse effects of TZDs, which we are investigating in further analyses.

Life course trajectories of cardiovascular risk factors in women with and without adverse pregnancy outcomes: UK electronic health record data

Abigail Fraser , ***Kate Birnie***, *Laura Howe, Timothy Jones, Paul Madley-Dowd, Flo Martrin, Harriet Forbes, Maria Theresa Redaniel, Maria Magnus, Neil Davies, Kate Tilling, Alun Hughes, Deborah Lawlor*

Abstract text

Background: Women with adverse pregnancy outcomes (APOs) such as preeclampsia are around twice as likely to develop cardiovascular disease (CVD) later in life compared to parous women without a history of APOs. It is not clear if APOs reflect an existing increased propensity for CVD or contribute causally to that risk. We aimed to investigate if women who experienced APOs had worse cardiometabolic health across the life course.

Methods: Cohort study using English primary care data from UK Clinical Practice Research Datalink (CPRD). We included all women whose first pregnancy is recorded in CPRD GOLD Pregnancy Register 1997-2019. We excluded women who were not registered for a minimum of 3 months with an 'up to standard' practice before pregnancy start and women not eligible for Hospital Episode Statistics linkage. We estimated body mass index (BMI), blood pressure, cholesterol and glucose life course trajectories for women with and without a history of APOs (in any pregnancy) adjusting for age first pregnancy, deprivation, multiple pregnancy, and parity.

Results: In a cohort of 187,049 women, preeclampsia was experienced by 7,503 (4.0%), gestational hypertension (GH) by 17,661 (9.4%), gestational diabetes (GDM) by 7,189 (3.8%) and miscarriage by 34,726 (18.4%) women. Levels of all cardiovascular risk factors increased with age in all women. Women with a history of preeclampsia or GH already had higher mean BMI, blood pressure (BP), and glucose 10 years before first pregnancy compared with normotensive women. These differences continued to 15 years post pregnancy. Women with GDM had higher BMI, BP and glucose across the life course and a steeper post-partum rise in glucose than women without GDM. Interestingly, there was no differences between women with and without a history of miscarriage.

Conclusion: Preeclampsia, GH and GDM identify women with pre-existing, more adverse levels of modifiable cardiovascular risk factors.

Long-term maternal cardiovascular mortality after vaginal bleeding: Norwegian population-based cohort.

Nadia Arshad , *Rolv Skjærven, Nils-Halvdan Morken*

Abstract text

Introduction: Vaginal bleeding (VB) without pregnancy loss is a risk factor for multiple complications later in the pregnancy. Few studies have investigated the consequences of first-trimester bleeding on the risk of ischemic heart disease later in life, none has examined the long-term outcome of parity-specific complications with or without VB during pregnancy on maternal cardiovascular (CVD) mortality.

Material and methods: Data was obtained from the Medical Birth Registry of Norway between 1967 and 2020 linked with the Cause of Death Registry and the Educational Database at Statistics Norway. The exposure was parity-specific complications—Preeclampsia, Preterm, Perinatal death and Small for gestational age (PPPS), with or without VB during pregnancy. The outcome was long-term death due to CVD before 70 years. Hazard ratios (HR) with a 95% confidence interval (CI) for CVD mortality were calculated by Cox-proportional regression adjusted for age and year of first birth**.**

Results: Compared to mothers with three PPPS-unaffected pregnancies, two PPPS-affected pregnancies without VB were associated with a higher risk of CVD mortality (HR 4.1, 95%CI 3.4-4.9) than two VB-affected pregnancies (HR 2.7, 95%CI 1.4-5.1). However, in mothers with two pregnancies, the risk of mortality was higher for VB-affected pregnancy if the second pregnancy had any one of PPPS complications (HR 2.6, 95%CI 1.6-4.1), compared with VB-unaffected pregnancy (HR 2.2, 95%CI 1.9-2.6).

Conclusion: Parity-specific complications without VB were associated with a higher risk of maternal CVD mortality, compared to PPPS-VB-affected pregnancy. The results of this study highlight that parity-specific complications should be considered while assessing VB during pregnancy as a risk factor for long-term maternal CVD mortality.

Macronutrient intake in infancy and cardiometabolic health phenotypes in preschool children from the EDEN mother-child cohort

Ana Rita Marinho , *Daniela Correia, Muriel Tafflet, Marie Aline Charles, Barbara Heude, Carla Lopes, Wen Lun Yuan, Blandine de Lauzon-Guillain*

Abstract text

Background: From an early age, understanding the influence of the multiple risk factors contributing to cardiometabolic health is essential. However, the influence of early macronutrient intake on cardiometabolic health during childhood remains relatively unexplored.

Aim: To study the relationship between macronutrient intake in infancy and cardiometabolic health phenotypes in preschool children from the EDEN mother-child cohort.

Methods: Macronutrient intake at 12 months old was assessed from 3-day food records. Four sex-specific cardiometabolic health patterns at 5-6 years old were previously derived by Principal Component Analysis, based on anthropometrics and biological variables (for boys: “Higher Adiposity”, “Higher Insulin Resistance”, “Unhealthier Lipid Profile”, and “Higher Blood Pressure”; and for girls: “Higher Adiposity”, “Higher Insulin Resistance and Healthier Lipid Profile”, “Higher Insulin Resistance and Unhealthier Lipid Profile”, “Higher Blood Pressure”). Multivariable linear regression models assessed associations between macronutrient intake, considered simultaneously in the same models, and cardiometabolic health patterns among 259 boys and 229 girls.

Results: Higher carbohydrate intake was associated with a higher score in the “Unhealthier Lipid Profile” pattern [β=0.25 SD (95%CI 0.06, 0.43)] in boys but not in girls. When monosaccharides and disaccharides were considered separately from other carbohydrates, the association was found only for monosaccharides and disaccharides [β=0.29 SD (95%CI 0.10, 0.48)]. Other macronutrients were not related to cardiometabolic health patterns.

Conclusion: Higher monosaccharides and disaccharides intake in infancy were associated with a less favourable lipid profile in 5-6 years old boys. Replications of these results are warranted to assess their robustness.

Maternal coffee consumption and biomarkers of reproductive health in young, adult sons: a cohort study

Mette Jørgensen Langergaard , *Andreas Ernst, Bodil Hammer Bech, Sandra Søgaard Tøttenborg, Nis Brix, Gunnar Toft, Anne Gaml-Sørensen, Karin Sørig Hougaard, Linn Håkonsen Arendt, Jens Peter Ellekilde Bonde, Cecilia Høst Ramlau-Hansen*

Abstract text
Is maternal coffee consumption in early pregnancy associated with biomarkers of reproductive health in adult sons?

Coffee is a major source of caffeine and other bioactive substances potentially interfering with the gonadal development and subsequent gametogenesis in the sons, resulting in impaired semen quality in adult life.

This study is based on longitudinally collected data from the Fetal Programming of Semen Quality cohort, nested within the Danish National Birth Cohort. In 2017–2019, 5,697 sons born 1998–2000 were invited to participate in the cohort, of which 1,058 (19%) consented. Information on daily coffee consumption was reported by the mothers around gestational week 17. The exposure data was modelled as dichotomized, categorized, and continuous variables. Relative percentages differences for semen characteristics, testes volume and reproductive hormone levels were estimated using negative binomial regression models.

We found tendencies of poorer semen quality in sons of mothers consuming coffee during pregnancy. In the dichotomized analysis, maternal coffee consumption was associated with lower semen volume of -7% (95% CI: -13;-1), lower total sperm count of -7% (95% CI: -18;5), lower proportion of morphologically normal spermatozoa of -8% (95% CI: -17;1), higher proportion of non-progressive and immotile spermatozoa of 4% (95% CI: -2;10), and lower testes volume of -5% (95% CI: -9;0) when compared to unexposed. However, most estimates were small, and confidence intervals overlapped the null. No associations with reproductive hormone levels were observed. We found no strong indication of a dose-response association in the categorized and continuous analyses. Only relatively few participants were exposed to high maternal coffee consumption, limiting our ability to capture potential effects among high consumers.

The study adds to the very limited body of literature on the area. Yet, the clinical significance of these potential differences is unknown.

Maternal glycaemic control in pre-gestational type 1 diabetes and pre-eclampsia risk: A population-based cohort study in Sweden

Nathalie Roos , *Björn Pasternak, Jonas Söderling, Martin Neovius, Soffia Gudbjörnsdottir, Anna Sandström, Jonas F Ludvigsson, Olof Stephansson*

Abstract text

Objective

To study the risk and severity of pre-eclampsia in pregnant women with Type 1 Diabetes Mellitus (T1DM) and the influence of glycaemic control.

Research Design and Methods

Population-based cohort study using nationwide diabetes and birth registries in Sweden 2003-2014, which identified 2,481 (0·21%) singleton pregnancies to 2,035 women with T1DM and 1,167,540 singleton pregnancies to 747,305 women without T1DM (99·79%). With binomial regression we estimated risk differences and crude and adjusted risk ratios (RR) for pre-eclampsia by HbA1c levels in women with and without T1DM around the time of pregnancy start.

Results

Among 2,481 women with T1DM, 15·7% (n=389) developed pre-eclampsia as compared to 2·9% among women without T1DM (n=34,371). Incidence of pre-eclampsia increased across HbA1c level category from 10.3% to 21·5% in women with HbA1C level of ≤6·4% as compared to ≥9·1%. Compared to women without T1DM, the crude and adjusted RR of pre-eclampsia in women with T1DM increased in a dose dependent manner versus women without T1DM with increasing levels of HbA1c from low levels (≤6·4%) of HbA1c (crude RR 3·5 (95% CI 2·7-4·4); adjusted RR 3·1 (95% CI 2·4-4·0)) to high levels (≥9·1%) (crude RR 7·2 (95% CI 5·7-9·2); adjusted RR 5·8 (95% CI 4·5-7·3)).

Conclusions

Poorer glycaemic control around the time of pregnancy start in women with T1DM increases pre-eclampsia risk in a dose-dependent manner as compared to women with good glycaemic control or without T1DM.

Maternal morbidity associated with trial of labor after cesarean of women with antepartum fetal death

Ela Kadish , *Hen Y. Sela, Ari Weiss, Sorina Grisaru-Granovsky,* ***Misgav Rottenstreich***

Abstract text

Objective:

To evaluate maternal morbidity of women with antepartum fetal death attempting vaginal delivery after cesarean delivery (TOLAC).

Methods:

A multicenter retrospective case control study was conducted of singleton pregnancies with trials of labor following a single low-segment cesarean delivery between 24 and 42 weeks of gestations, (2005-2021). Maternal adverse outcomes were compared between women with antepartum fetal death and women with live fetal births, matched by previous VBAC and preterm delivery rate in a 1:4 ratio.

Results:

During the study period, 28,225patients underwent a trial of labor and were eligible for the study, of whom 1, 181 (0.6%) had a pre-labor IUFD who were compared to to 724 matched women with a live fetus. In univariate analysis, parturients with a pre-labor IUFD had a significantly higher rate of successful vaginal birth, but higher rates of chorioamnionitis and shoulder dystocia. However, there were no significant differences in the composite adverse maternal outcome, uterine scar rupture, or dehiscence rates. This was confirmed on multivariate analyses for the composite adverse maternal outcome (aOR= 0.64, 95% CI 0.32-1.26, p=0.19).

Conclusion:

Our study suggests that antepartum diagnosis of fetal death does not increase the risk of adverse maternal outcomes in TOLAC, with high rates of successful vaginal birth. Further research is needed to determine the optimal method of labor induction for this specific patient population.

Maternal pre-pregnancy body mass index and biomarkers of fecundity in adult sons: a cohort study

Anne Gaml-Sørensen , ***Anne Hjorth Thomsen***, *Sandra Søgaard Tøttenborg, Nis Brix, Karin Sørig Hougaard, Gunnar Toft, Siri Eldevik Håberg, Mikko Myrskylä, Jens Peter Bonde, Cecilia Høst Ramlau-Hansen*

Abstract text

Background and aim: Male fecundity may be largely determined through fetal programming and evidence suggests that maternal pre-pregnancy body mass index (BMI) may influence son’s reproductive function later in life. Our aim was to investigate whether maternal pre-pregnancy BMI was associated with semen quality, testes volume and reproductive hormone levels in adult sons.

Methods: In total, 1,058 sons (median age 19 years, 2 months) from the Fetal Programming of Semen Quality (FEPOS) cohort nested in the Danish National Birth Cohort (DNBC) provided a semen and blood sample, measured their testes volume and had height and weight measured at a clinical examination. Maternal pre-pregnancy BMI was obtained by self-report in early pregnancy. Semen quality, testes volume and reproductive hormone levels were analysed according to maternal pre-pregnancy BMI using negative binomial regression models. A mediation analysis examined potential mediation by the sons’ own BMI to separate the indirect from the direct effect.

Results: We found no consistent associations between maternal pre-pregnancy BMI and semen characteristics or testes volume. Sons of mothers with higher pre-pregnancy BMI had higher oestradiol and lower sex-hormone binding globulin levels, both in a dose dependent manner. Sons of mothers with pre-pregnancy obesity had higher luteinizing hormone levels and a higher free androgen index than sons born by mothers with normal pre-pregnancy BMI. The mediation analysis suggested that the effect of maternal pre-pregnancy overweight or obesity on reproductive hormone levels was partly mediated by the sons’ own BMI.

Conclusion: Maternal pre-pregnancy BMI was associated with an altered reproductive hormone profile in young adult sons. The potential effects of maternal pre-pregnancy obesity on a son's reproductive hormone profile may be prevented through approaches aimed at avoiding adult overweight and obesity before pregnancy.

Maternal pre-pregnancy body mass index and risk of preterm birth: a collaboration using large routine health datasets

Rosie Cornish , *Maria Magnus, Stine Urhoj, Gillian Santorelli, Lisa Smithers, David Odd, Abigail Fraser, Siri Haberg, Anne-Marie Nybo Andersen, Kate Birnie, John Lynch, Kate Tilling,* ***Deborah Lawlor***

Abstract text

Background and aims

Preterm birth (PTB), is a leading cause of child morbidity and mortality. Evidence suggests an increased risk with both maternal underweight and obesity, with some studies suggesting underweight might be a greater factor in spontaneous PTB (SPTB). Previous studies have largely explored established body mass index (BMI) categories. Our aim was to compare associations of maternal pre-pregnancy BMI with any PTB, SPTB and medically indicated PTB (MPTB) across populations with differing characteristics, and to identify the optimal BMI with lowest risk for these outcomes.

Methods

We used three UK datasets, two US datasets, and one each from South Australia, Norway and Denmark, together including over 22.5 million pregnancies resulting in a live birth or stillbirth after 24 completed weeks gestation. Fractional polynomial multivariable logistic regression was used to examine the relationship of BMI with any PTB, SPTB and MPTB. The results were combined using a random effects meta-analysis. The estimated BMI at which risk was lowest was calculated via differentiation and a 95% confidence interval (CI) obtained using bootstrapping.

Results

We found non-linear associations between BMI and all three outcomes, across all datasets. The adjusted risk of any PTB and MPTB was elevated at both low and high BMIs, whereas the risk of SPTB was increased at lower levels of BMI but remained low or increased only slightly with higher BMI. In the meta-analysed data, the lowest risk of any PTB was at a BMI of 24.5 kg/m^2 (95% CI: 23.1, 30.3), with a value of 21.3 kg/m^2 (20.8, 21.9) for MPTB; for SPTB, the risk remained roughly constant above a BMI of around 25-30 kg/m^2.

Conclusions

Consistency of findings across different populations, despite differences between them in terms of the time period covered, BMI distribution, missing data and control for key confounders, highlight the importance of promoting pre-conception BMI between 21 to 30 kg/m^2 to prevent PTB.

MATERNAL PSYCHOTROPIC DRUG USE AND OTHER PERINATAL FACTORS ASSOCIATED WITH PHYSICAL ABUSE IN INFANTS: A PROSPECTIVE NATIONWIDE COHORT STUDY IN FRANCE

Flora Blangis , *Jérôme Drouin, Elise Launay, Sara Miranda, Mahmoud Zureik, Jérémie Cohen, Alain Weill, Rosemary Dray-Spira, Martin Chalumeau*

Abstract text

Background: Understanding the factors associated with child physical abuse (CPA) is crucial to defining targeted preventive interventions. We aimed to identify perinatal factors associated with CPA, including maternal psychotropic drug use.

Methods: This was a prospective nationwide cohort study based on comprehensive data from the EPI-MERES mother–child register built from the French National Health Data System. All infants liveborn between 2010 and 2019 were included. CPA was identified based on a previously validated algorithm using hospital discharge codes during the first year of life. We calculated the relative risk (RR) of CPA associated with 28 maternal and perinatal characteristics using crude RRs and their 95% confidence intervals (CIs).

Results: Among the 6,920,602 included children, 2,994 (0.04%) had a diagnosis of CPA (median age 4 months; 60% boys). The factors most strongly associated with CPA were maternal age < 20 years (versus 30-35 years: RR 8.4 [95% CI 7.4-9.5]), low maternal income (versus high income: RR 4.0 [95% CI 3.5-4.5]), alcohol use disorder (RR 5.6 [95% CI 4.6-6.9]), opioid use disorder (RR 5.3 [95% CI 4.0-7.0]), intimate partner violence (RR 8.7 [95% CI 6.2-12.3]), hospitalisation during pregnancy for a psychiatric disorder (RR 7.9 [95% CI 5.6-11.2]), and extremely preterm birth (versus full-term birth: RR 5.0 [95% CI 4.1-6.2]). Regarding maternal psychotropic drug use during pregnancy, CPA was associated with ≥ 2 dispensations of hypnotic (RR 4.54 [95% CI 3.1-6.6]), anxiolytic (RR 3.4 [95% CI 2.8-4.3]), antipsychotic (RR 2.8 [95% CI 1.9-4.2]) and antidepressant (RR 1.5 [95% CI 1.1-2.1]) drugs.

Conclusions: At the national level in France, we identified perinatal factors associated with CPA and report for the first time a strong association between CPA and maternal psychotropic drug use during pregnancy. Ongoing multivariate analyses will help identify factors independently associated with CPA.

Maternal Stress and Anxiety and Adverse Pregnancy Outcomes: A population-based Study in Canada

Shiliang Liu , *Kaylee Ramage, Chantal Nelson, Susie Dzakpasu, Ian Colman, Russell Kirby*

Abstract text

OBJECTIVE: To respond to the need for more clarity in the relationship between prenatal exposure to maternal mental health disorders and pregnancy outcomes, we sought to examine the association between major stress and anxiety disorder before and during pregnancy and selected infant, pregnancy, and maternal outcomes.

METHODS: We conducted a population-based study of mother-infant dyads (N=3 655 345 singleton births) using linked infant and maternal data from the Discharge Abstract Database in Canada between 2006 and 2020. Mothers with stress and anxiety disorders (n=18 139) were identified, and compared to mothers without this condition. Outcomes included intrauterine growth restriction, non-chromosomal anomalies (NCA), neonatal seizures, respiratory distress syndrome (RDS), and severe maternal morbidities. We used log-binomial regression models to estimate adjusted risk ratio (RR) with 95% confidence intervals (CI) for the infant, pregnancy, and maternal outcomes.

RESULTS: After adjusting for maternal age, parity, substance use, depressive disorder and other mental illness, and chronic conditions before and during pregnancy, maternal stress and anxiety disorder was associated with several adverse infant outcomes, including neontal seizures (RR 2.04, 95% CI 1.60-2.59), RDS (RR 1.59, 95% CI 1.52-1.66), preterm birth (RR 1.36, 95% CI 1.30-1.42)), NCA (RR 95% CI 1.26-1.2.39), low birth weight (RR 1.27, 95% CI 1.21-1.34), and maternal outcomes such as acute psychosis (RR 11.9, 95% CI 6.9-22.6), early idiopathic preterm delivery (RR 1.28, 95% CI 1.21-1.36) and severe preclampsia (RR 1.25, 95% CI 1.04-1.50).

CONCLUSION: Our findings indicate that maternal stress and anxiety disorder is associated with an increased risk of several severe neonatal and maternal morbidities. Women who are identified as having maternal stress and anxiety disorder should be closely monitored and given appropriate psychological and clinical support during the pregnancy and postpartum periods.

Mode of birth after previous caesarean section and risk of undergoing pelvic floor surgery: A population-based record linkage cohort study

Kate Fitzpatrick , *Mohamed Abdel-Fattah, Joris Hemelaar, Jennifer Kurinczuk, Maria Quigley*

Abstract text

OBJECTIVE: To investigate the association between planned as well as actual mode of birth after previous caesarean section and woman's subsequent risk of undergoing pelvic floor surgery.

METHODS: A population-based cohort study of 47,414 singleton term births in Scotland bewteen 1983 and 1996 to women with ≥1 previous caesarean sections was conducted using linked Scottish national datasets. Cox regression was used to investigate the association between mode of birth and women's subsequent risk of having any and specific types of pelvic floor surgery adjusted for sociodemographic, maternal medical, and obstetric-related factors.

RESULTS: Over a median of 22.1 years of follow-up, 1,159 (2.44%) of the study population had pelvic floor surgery. Planned vaginal birth after previous caesarean (VBAC) compared to elective repeat caesarean section (ERCS) was associated with a greater than 2-fold increased risk of the woman undergoing any pelvic floor surgery (adjusted hazard ratio[aHR]:2.38, 95%CI:2.03-2.80) and a 2- to 3-fold increased risk of the woman having surgery for pelvic organ prolapse (aHR:3.17, 95%CI:2.47-4.09) or urinary incontinence (aHR:2.26, 95%CI:1.79-2.84). Analysis by actual mode of birth showed these increased risks were only apparent in the women who actually had a VBAC. Women who needed an in-labor non-elective repeat caesarean had a comparable risk of pelvic floor surgery to those who had an ERCS.

CONCLUSIONS: Planned VBAC compared to ERCS is associated with an increased risk of woman subsequently undergoing pelvic floor surgery including surgery for pelvic organ prolapse and urinary incontinence. However, these risks appear to be only apparent in women who actually give birth vaginally as planned, highlighting the role of vaginal birth rather than labour in pelvic floor dysfunction requiring surgery. The findings provide new information to counsel women with previous caesarean about the risks and benefits associated with their future birth choices.

Multi-trajectory modelling of children’ sleep characteristics between 1 and 5.5 years and their correlates in the French ELFE birth-cohort

Mihyeon Kim , *Danielle Saade, Marie-Noelle Dufourg, Marie-Aline Charles,* ***Sabine Plancoulaine***

Abstract text
Early sleep disturbances are associated with short- and long-term health problems. Most studies report sleep disturbances separately, whereas they may be related. We aimed at identifying longitudinal sleep multi-trajectories in children between 1 and 5.5 years and their early correlates.

The French ELFE birth-cohort included 18,327 newborns in 2011. Early family, maternal, and child characteristics including children's nighttime (NSD) and daytime (DSD) sleep durations, night waking (NW), and sleep onset difficulties (SOD) were collected by parents’ phone interviews at 2 months, 1, 2, 3.5 and 5.5 years. Sleep multi-trajectory groups were identified using group-based multi-trajectory modeling. Associations with early factors were assessed using multinomial logistic regressions.

We identified 5 groups with distinct sleep multi-trajectories for NSD, DSD, NW and SOD among the 9,273 included children. The G1 (31.6%) and G3 (31.0%) multi-trajectory groups were characterized by low NW and SOD prevalence, and shorter NSD but longer DSD in G1 than in G3. G2 (10.3%) was characterized by long NSD and DSD but a SOD peak at age 3.5 years; G4 (9.6%) by short but rapidly increasing NSD to a plateau and high but decreasing NW and SOD; and G5 (17.5%) by persistent high NW and SOD. Maternal depression during pregnancy, and sleep habits at age 1 year (e.g., parental presence or feeding required to fall asleep, sleeping at least part of the night away from own bed) were the common risk factors associated with the most disordered sleep multi-trajectory groups.

In conclusion, we identified distinct groups of sleep multi-trajectories and early life associated factors in preschoolers. Most of the factors associated with the most sleep-disordered multi-trajectory groups are likely modifiable and provide clues for early prevention interventions.

Neighbourhood socioeconomic status and preterm birth: a nationwide register study in Finland

Basho Poelman , *Jaana I. Halonen, Eero Kajantie, Sylvain Sebert, Anna Pulakka*

Abstract text

Background: Low neighbourhood socioeconomic status has been associated with increased risk of preterm birth, independent of individual level risk factors. We further explored this association within the context of Finland, a well-developed welfare state.

Methods: We combined data for 1,608,630 births in the Finnish Medical Birth Register between 1990 – 2016, with residential address at birth and other background information from other registers. A standardized neighbourhood disadvantage-score for 250m map grid cells was calculated from education, income, and employment variables available 5-yearly for the period 1990-2015 from Statistics Finland. We used urban-rural classification made by the The Finnish Environment Institute in 2018 as a moderator. We excluded from analysis multiple births, stillbirths, mother-child pairs with faulty home GPS-coordinates, and those with missing exposure (19.7%). Our outcome was being born preterm (<37 completed weeks gestation). We used logistic regression and adjusted the models for child's sex and birth year, and the mother's smoking, diabetes, hypertension, and education.

Results: Among 1,285,225 singletons included in the analysis (4.3% preterm), a model adjusted for child sex and birth year only showed an increased risk in PTB with 1 standard deviation higher neighbourhood disadvantage (odds ratio (OR) 1.09, 95% confidence interval (CI) 1.08-1.11). In the fully adjusted model, the risk was reduced but remained significant (OR 1.05, 95%CI 1.04-1.06). There was no interaction between neighbourhood SES and rural/urban dichotomy (p=0.34), but stratified analyses showed a slightly higher PTB risk in urban (OR 1.06, 95%CI 1.04-1.07) than in rural neighbourhoods (OR 1.03, 95%CI 1.01-1.06) in the fully adjusted models.

Conclusion: Home neighbourhood disadvantage was related to the risk of PTB in Finland both in rural and urban areas regardless of mother's education that was used as an indicator of individual socioeconomic status.

Obesity and risk of cesarean section

Jamie Lynn Ontiveros , *Kristjana Einarsdóttir, Þóra Lucrezia Bettaglio, Jóhanna Gunnarsdóttir,* ***Heiðdís Valgeirsdóttir***

Abstract text

Introduction: Excess adipose tissue can have a disruptive effect on metabolic and inflammatory processes during pregnancy and thus affect birth outcomes. The aim of this study was to investigate the relationship between severe obesity and the risk of cesarean section, as well as to examine the frequency of pregnancy complications among severely obese women that could also be an indication for induction of labor.

Materials and methods: The study was a retrospective cohort study that included all singleton births in Iceland from 2013 to 2020, a total of 33,004 births. Statistical analysis was performed using the chi-square test, Fisher‘s exact test, and multiple logistic regression.

Results: The cesarean section rate among women with a BMI (Body Mass Index) ≥40 (n=1,258) was 26.3% compared to 15.9% among women with a BMI<40 (n=28,199). The odds ratio for cesarean delivery among women with a BMI≥40 was OR =1.89 (95% confidence interval 1.66-2.15, p<0.001) compared to women with a BMI<40. Among women with a BMI≥40, 52% had one of the most common pregnancy complications indicating labor induction. Among women with a BMI≥40, 22.1% (n=109) had an emergency cesarean section after induction of labor compared to 13.8% (n=1,012) among women with a BMI<40 (p<0.001).

Conclusion: Women with a BMI≥40 were at increased risk of delivering with cesarean section and more likely to deliver by emergency cesarean section if labor was induced, compared to women with a BMI<40. The majority of severely obese women had at least one of the most common pregnancy complications. This underscores the importance of promoting a healthy lifestyle among women of childbearing age to reduce the risk of obesity-related pregnancy complications.

Operative delivery in the second stage of labour and preterm birth in a subsequent pregnancy: a systematic review and meta-analysis

Abirami Kirubarajan , *Nila Thangavelu, Misgav Rottenstreich, Giulia Muraca*

Abstract text

Objective

To quantify the association between of mode of operative delivery in the second stage of labour (cesarean delivery versus operative vaginal delivery) and spontaneous preterm birth (sPTB) in a subsequent pregnancy.

Methods

A systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted of MEDLINE, EMBASE, Emcare, CINAHL, Cochrane Library, Web of Science: Core Collection, and Scopus until April 1st 2023. We included original research with participants who had a second-stage cesarean delivery (CD; defined as CD at full cervical dilation) or operative vaginal delivery (OVD; including forceps or vacuum delivery), and reported PTB rate (either spontaneous or not specified) in subsequent pregnancy. Both descriptive analyses and meta-analyses were conducted. Meta-analysis was performed for dichotomous data using the Mantel-Haenszel random effects model and odds ratio (OR) as the effect measure with 95% confidence intervals (CIs). Risk of bias was assessed using Cochrane’s 2022 Risk Of Bias In Non-randomized Studies of Exposure tool.

Results

After screening 2671 articles, a total of 20 studies encompassing 611,569 patients were included. The pooled rate of sPTB in a subsequent pregnancy after second-stage CD was 6.93% (n=18 studies) and 2.64% after OVD (n=10 studies). A total of seven studies encompassing 75,460 patients compared the primary outcome of sPTB following second-stage CD versus OVD with an OR of 2.01 (95% CI 1.57-2.58) in favor of OVD. However, most studies did not include important confounding factors, did not address exposure misclassification due to failed OVD, and considered OVD homogenously with no distinction between forceps and vacuum.

Conclusions

While the evidence synthesis suggests that the risk of sPTB is higher in those with a previous second-stage CD compared with OVD , the risk of bias in these studies means these findings should be interpreted with caution.

Parental body mass index and offspring cardiovascular risk factors in adulthood: an intergenerational Mendelian randomization study

Tom Bond , *Laxmi Bhatta, Gunn-Helen Moen, Geng Wang, Nicole Warrington, Deborah Lawlor, Bjørn Olav Åsvold, Ben Brumpton, David Evans*

Abstract text
Background

Greater pre-pregnancy maternal and paternal body mass index (BMI) are associated with a poorer adult cardiovascular risk factor profile in their offspring, but it is unclear whether this is due to causal effects via developmental mechanisms.

Methods

We conducted a two-sample intergenerational Mendelian randomization (MR) study, to estimate the causal effects of maternal and paternal BMI on offspring adulthood BMI, waist-hip ratio (WHR), blood pressure (BP), lipids, glucose, glycated haemoglobin (HbA1c) and C-reactive protein (CRP), as well as offspring birth weight (BW; a positive control outcome for which we would expect to find a causal effect). Genetic instrumental variables (up to 485 independent SNPs) for parental BMI were obtained from the most recent GIANT consortium genome wide association study (GWAS). After harmonisation, summary outcome associations were extracted from GWAS we undertook of offspring outcomes with parental genotype, adjusting for offspring genotype, in UK Biobank, ALSPAC and HUNT (n = up to 564,765). We conducted sensitivity analyses which were robust to different patterns of horizontal pleiotropy.

Results

MR provided little evidence for a causal effect of maternal BMI on offspring outcomes except for BW (for which there was robust evidence for a causal effect). The differences (95% CI) in mean outcome SD per higher maternal BMI SD were -0.02 (-0.06, 0.02), 0.01 (-0.03, 0.05), 0.00 (-0.03, 0.03), -0.02 (-0.05, 0.02), 0.01 (-0.02, 0.05), -0.01 (-0.05, 0.03), 0.03 (-0.01, 0.07), 0.01 (-0.03, 0.06), -0.00 (-0.04, 0.04), 0.03 (-0.00, 0.07) and -0.03 (-0.07, 0.01) for BMI, WHR, systolic BP, diastolic BP, glucose, HbA1c, cholesterol, HDL-C, LDL-C, triglycerides, and CRP respectively. Results were similar for paternal BMI, and sensitivity analyses were consistent.

Conclusion

Our data suggest that neither maternal nor paternal BMI causally influence offspring cardiovascular risk factors in adulthood.

Paternal use of metformin and risk of major congenital malformations

Paz Lopez-Doriga Ruiz , ***Jacqueline M. Cohen***, *Lars J. Kjerpeseth, Kari Furu, Elisabeth Qvigstad*

Abstract text
Studies from Denmark have reported an association between paternal metformin use during spermatogenesis and risk of major congenital malformations (MCM), specifically genital malformations. We aimed to assess whether pre-conceptional use of metformin increases the risk of MCM in children of men with type 2 diabetes. We carried out a cohort study based on Norwegian health registers including live births from 2010-2020. We defined paternal diabetes as pre-conceptional use of glucose-lowering drugs (dispensed in the 180 days before pregnancy) or at least 2 diabetes diagnoses. We excluded children of fathers with pre-conceptional insulin use, assumed to be mostly type 1 diabetes, and of mothers with diabetes. MCM were identified from diagnoses in the medical birth and patient registers in the first year. We compared MCM in children of fathers with pre-conceptional metformin use with children of fathers registered with diabetes and no pre-conceptional use of metformin or other glucose-lowering drugs (GLD). In a secondary analysis, we compared the main reference group (no GLD) with children of fathers without diabetes. Adjusted risk ratios (aRRs) were estimated using log-binomial regression with inverse-probability of treatment weights based on the propensity score. 527,698 children met the inclusion criteria. We compared 587 (0.1%) children of fathers with pre-conceptional metformin use (n=27 MCM, 4.6%, 0 genital MCM) with 4424 (0.8%) children of fathers with diabetes and no GLD use (n=174 MCM, 3.9%; 24 genital MCM), aRR 1.3 (95% CI 0.8-2.2). Comparing diabetes and no GLD with 522,620 children of fathers with no diabetes (n=17,165 MCM, 3.3%; n=1735 genital MCM) the aRRs for any MCM and genital MCM were aRR 1.3 (95%CI 1.1-1.5) and 1.9 (95%CI 1.2-3.1), respectively. There was no difference in the risk of MCM between children of men with diabetes with and without metformin use preconceptionally, but an increased risk of malformations in the group with type 2 diabetes.

Perilous Medicine in Tigray: A Systematic Review

Hailay Gesesew , *Hafte Kebede, Kenfe Berhe, Nelsensius Fauk, Paul Ward*

Abstract text

Background: The war in Tigray, North Ethiopia which started in November 2020, has destroyed decades of the region's healthcare success. We synthesized the available evidence on 'perilous medicine' in Tigray to understand the data source, subjects and content covered, and gaps exist.

Methods: We employed a systematic review and performed a systematic search of MEDLINE, PubMed, CINHAL, Web of Science and Scopus of English written documents published from 4 November 2020 to 18-19 October 2022. We independently performed title, abstract and full-text screening; and applied using content synthesis. The PROSPERO registration number is CRD42022364964.

Results: Our systematic review search yielded 8,039 documents, and included 41 documents for synthesis. The areas were: (i) *attacks on infrastructure, health or aid workers, patients, ambulances or aid trucks* identified in 29 documents—the documents reported targeted attacks of health infrastructure and personnel; (ii) *interruption of health or social services* in 31 documents—the documents reported medical and humanitarian siege; (iii) *outcomes and direct or indirect impacts* in 33 documents—the documents reported increased magnitude of illnesses, and catastrophic humanitarian crises including the use of food, medicine and rape as tools of war; and (iv) *responses, rebuilding strategies, and recommendations* in 21 documents—the documents reported improvisation of services, and calling to seize fire, accountability and allow humanitarian.

Conclusions: Despite promising studies on conflict and health in Tigray, the documents lack quality of designs and sources, and depth and diversity of subjects and contents covered; calling further primary studies on a prioritized future agenda.

Physical activity, fitness, and cardiac autonomic function among adults born post-term

Päivi Oksanen , *Marjaana Tikanmäki, Mikko Tulppo, Maisa Niemelä, Raija Korpelainen, Eero Kajantie*

Abstract text

Background and objective: Recent studies have suggested that adults born post-term (≥42 completed weeks of gestation) have increased cardiometabolic risk factors, such as obesity and impaired glucose metabolism. We aimed to investigate the associations of post-term birth with midlife physical activity, muscular fitness, cardiorespiratory fitness, heart rate recovery, heart rate variability, and baroreflex sensitivity, which have been shown to be important determinants of cardiac autonomic function and health.

Study Design: We studied 4099 members of the Northern Finland Birth Cohort 1966 born at term (39–41 completed weeks of gestation, $n = 3130$) or post-term (≥42 completed weeks of gestation, $n = 969$), assessed at around 46 years of age. We measured daily physical activity by accelerometry for two weeks, muscular fitness by hand grip test, and cardiorespiratory fitness by peak heart rate during submaximal four-minute step test. Heart rate recovery was determined during the first 30 and 60 seconds after the step test. The outcomes were compared between adults born post-term and term controls using a multiple linear regression.

Results: When results were adjusted for sex, age, and maternal- and pregnancy-related covariates, adults born post-term undertook 3.5 min less (95% CI 1.0–6.0) daily moderate-to-vigorous physical activity, and had reduced cardiorespiratory fitness based on 2.3 bpm higher (95% CI 1.1–3.4) peak heart rate and 0.8 bpm slower (95% CI 0.2−1.3) heart rate recovery 30 seconds after the step test.

Conclusions: Adults born post-term undertake less moderate-to-vigorous physical activity and have reduced cardiorespiratory fitness compared with those born at term and may have altered cardiac parasympathetic regulation in middle age. While mechanisms remain uncertain, our findings reinforce previous suggestions that post-term should be included as perinatal risk factors of adult cardiometabolic disease.

Pregnancy characteristics and risk of a motor vehicle crash

Jennifer Hutcheon , *Sam Harper*

Abstract text

BACKGROUND: The WHO definition of maternal mortality excludes deaths due to motor vehicle crashes, on the grounds that these deaths are unrelated to pregnancy. Yet, some common consequences of pregnancy- such as increased fatigue- are also risk factors for motor vehicle crashes, providing some rationale for investigating whether exposures experienced during pregnancy may aggravate the risk of a motor vehicle crash. We examined the extent to which pregnancy-specific characteristics were associated with increased risk of a major motor vehicle crash.

METHOD: We conducted a population-based cohort study linking delivery records from a perinatal registry with automobile insurance claims records from British Columbia, Canada, 2010-2018. We used Poisson regression to estimate rate ratios (RR) for the association between demographic factors (maternal age, smoking status, rural residence, neighbourhood income quintile), factors linked with increased fatigue (multiple pregnancy, closely-spaced births, anemia), and severe nausea/vomiting (anti-emetic prescription [Diclectin], admission for hyperemesis) and risk of a major motor vehicle crash during pregnancy (a crash with a fatality, personal injury, or property damage>CDN$1000 [≈ €680]).

RESULTS: Among 322,596 pregnancies, there were 1,402 major motor vehicle crashes (4.3 per 1000). Although many demographic characteristics such as smoking status, rural residence, and lower neighbourhood income quintile were linked with an increased risk of motor vehicle crashes (RR=1.4 [95% CI: 1.1 to 1.7], 1.3 [1.1 to 1.5], and 1.3 [1.1 to 1.5], respectively), we found little evidence of associations between pregnancy-specific risk factors and motor vehicle crashes (e.g., anemia RR=1.1 [0.9 to 1.3], multiple birth RR= 1.0 [0.7 to 1.5], Diclectin prescription RR=0.6 [0.3 to 1.1]).

CONCLUSIONS: We found little evidence that pregnancy-related risk factors were associated with increased risk of a major motor vehicle crash.

Selected references

DISCLAIMER: All inferences, opinions, and conclusions drawn in this abstract are those of the authors, and do not reflect the opinions or policies of the Data Innovation Program or the Province of British Columbia.

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Pregnancy history at age 40 as a marker of cardiovascular risk

Liv Grimstvedt Kvalvik , *Rolv Skjærven, Gerhard Sulo, Aditi Singh, Quaker E. Harmon, Allen J. Wilcox*

Abstract text

Background: Individual pregnancy complications (such as preeclampsia, small birth weight and preterm delivery) have been linked to increased maternal risk of cardiovascular disease. We assessed how well a woman's total pregnancy history at age 40 predicts her risk of dying from atherosclerotic cardiovascular disease (ASCVD).

Methods: In this population-based, prospective study we used data from The Medical Birth Registry of Norway, the National Cause of Death Registry, the National Education Database and the Population Registry, Statistics Norway in the period 1967-2020. We identified 854 442 women born after 1944 or registered with a pregnancy in 1967 or later, and surviving to age 40. Our main outcome was the hazard ratio of ASCVD mortality up to age 69 for 40-year-old women, as predicted by exposure categories of combined parity (0, 1, 2, 3, or 4 recorded pregnancies) and number of complicated pregnancies (preterm delivery <35 gestational weeks, preeclampsia, placental abruption, perinatal death (stillbirth or death within first 7 days) and term or near-term birth weight <2700grams). Women with three pregnancies and no complications had lowest ASCVD risk and served as the reference group. Estimates were adjusted for women's birth year.

Results: Among women reaching age 40, risk of ASCVD before age 69 increased with greater number of complicated pregnancies in a strong dose-response fashion, reaching 23-fold risk (95% confidence interval 10-51) for women with four complicated pregnancies. Based on pregnancy history alone, 19% of women at age 40 (including nulliparous women) had ASCVD mortality risk in the range of 2.5 to 5-fold.

Conclusions: Pregnancy history at age 40 is highly predictive of ASCVD mortality over the next 30 years. Pregnancy history at age 40 could be useful as a routine clinical screen to identify at-risk women young enough to benefit from intervention, and perhaps even before clinical markers of CVD risk have fully emerged.

Prenatal exposure to food chemicals and allergic or respiratory diseases up to 5 years

Manel Ghozal , *Manik Kadawathagedara, Rosalie Delvert, Amandine Divaret-Chauveau, Chantal Raherison, Marie Aline Charles, Karine Adel-Patient, Blandine Lauzon-Guillain*

Abstract text

Introduction

The aim of this study was to assess associations between prenatal exposure to food chemicals and development of allergic or respiratory diseases in childhood.

Methods

Analyses were based on 11,638 children from the ELFE study. Prenatal exposure to food chemicals was assessed by combining maternal food intake during pregnancy and concentration levels of 219 chemicals in food products. Eight mixtures of food chemicals were also identified. Allergic and respiratory diseases (eczema, food allergy, wheezing, asthma and allergic rhinitis) were reported by parents during phone interviews between 2 months and 5.5 years. First, the associations between exposure to each food chemical and the risk of ever allergic or respiratory diseases up to 5.5 years were analyzed using separate logistic regression models adjusted on maternal characteristics (including education, smoking and diet quality), child's characteristics and family history of allergies. A correction for multiple testing was applied. Second, the 8 mixtures were considered together in a regression model.

Results

In the single-exposure approach, higher prenatal exposure to several food chemicals was associated with higher risk of eczema (dioxins, furans, PAHs, trace elements, mycotoxins, PCBs and pesticides) or food allergy (trace elements and pesticides), while some chemicals were associated to a decreased risk of food allergy (mycotoxins, pesticide carbaryl, PFAAs), up to 5.5 years. A mixture composed mainly of trace elements, furans and PAHs was associated with higher risk of eczema (odds ratio (OR) [95% confidence interval (CI)] = 1.16 [1.07 ; 1.27]) and a mixture composed mainly of pesticides was associated with higher risk of wheezing (OR[95%CI]= 1.05 [1.01 ; 1.10]).

Conclusion

In this large birth-cohort, we report associations between perinatal exposure to some chemicals, alone or as mixture, and increased risk of self-reported allergic symptoms. More studies are needed to confirm these results.

Preterm birth and chronic obstructive pulmonary disease in early- and mid-adulthood: A nationwide register study from Finland and Norway

Anna Pulakka , *Kari Risnes, Johanna Metsälä, Suvi Alenius, Katriina Heikkilä, Sara Marie Nilsen, Pieta Näsänen-Gilmore, Peija Haaramo, Mika Gissler, Signe Opdahl, Eero Kajantie*

Abstract text

Background: Preterm birth affects lungs in several ways, but not many studies have a follow-up until middle age. Our aim was to investigate the association between the full range of gestational ages (GA), and chronic obstructive pulmonary disease (COPD) in early and mid-adulthood.[1]

Methods: We used nationwide register data on individuals born 1987-1998 in Finland and 1967-1999 in Norway. GA was derived from the Medical Birth Registers and categorised as extremely preterm (23 to 27 weeks), very preterm (28 to 31 weeks), moderately preterm (32 to 33 weeks), late preterm (34 to 36 weeks), early term (37 to 38 weeks), full-term (39 to 41 weeks, reference) and post-term (≥42 weeks). We linked the data with hospital inpatient and outpatient care episodes from the Hospital Discharge Registers. COPD was defined as having a care episode with diagnostic code J41-J44 using the 10th revision of International Statistical Classification of Diseases codes at age 18-29 in Finland (during 2005-2016) or age 18-50 in Norway (during 2008-2017). We adjusted the models for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's hypertensive disorders during pregnancy, mother's asthma, and mother's and father's education.

Results: We included 706 717 individuals from Finland (4.8% preterm) and 1 669 528 from Norway (5.0% preterm). The risk for COPD was higher in Norway in all groups born preterm, and decreased in a dose-response manner with increasing GA. The highest risk was for those born extremely preterm: odds ratio (OR) 9.58, 95% confidence interval (CI) 5.50-16.69. In Finland, there were no COPD cases in the extremely or very preterm groups, but the risk of COPD was markedly increased for the moderately preterm group (OR 3.95, 95% CI 1.38-11.32).

Conclusion: Preterm birth is a risk factor for COPD in adulthood. Our results call for diagnostic vigilance when adults born very preterm present with respiratory symptoms.

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Preterm birth and other adverse birth outcomes by unaffordable housing in Canada: a population-based cohort study

Azar Mehrabadi , *Gabriel Shapiro, Seungmi Yang*

Abstract text

Background

Socioeconomic risk factors are known drivers of adverse birth outcomes. Unaffordable housing is a key target for policy interventions. We estimated the burden of housing unaffordability among those giving birth and compared preterm birth and other adverse birth outcomes by housing unaffordability status.

Methods

This population-based retrospective cohort study used 2014-2016 birth registration data linked with the 2016 long-form census and included singleton births among home owners and renters. Unaffordable housing was defined as the proportion of pre-tax income spent on shelter, using a 30% cut-off and a discrete unaffordability measure. The primary outcome was preterm birth (gestational age <37 weeks). Secondary outcomes were stillbirth and infant death. Log-binomial regression estimated the association of housing unaffordability with outcomes adjusting for other risk factors.

Results

Among 162 700 livebirths and stillbirths (2,740 renters and 109,660 owners), 33% of renters and 17% owners experienced unaffordable housing. There was no association of housing unaffordability with preterm birth among owners (6.4 % vs 6.1%; adjusted risk ratio [aRR], 0.98; 95% CI, 0.92-1.05) or renters (7.9 % vs 7.3%; adjusted risk ratio [aRR], 1.07; 95% CI, 1.00-1.15). Similarly there was no association of housing unaffordability with other birth outcomes. Preterm birth was more common renters versus owners. The associations were similar by income strata and using a discrete measure of unaffordability.

Interpretation

This nationally representative cohort study in Canada found a high burden of housing unaffordability among renters, with no association between unaffordable housing and preterm birth or other outcomes. Unaffordable housing is itself a key negative indicator of child and family well-being. Effective policy interventions can help eliminate the burden of unaffordable housing

Preterm birth and the risk of multimorbidity in adolescence: A multi-register study

Katriina Heikkilä , *Johanna Metsälä, Anna Pulakka, Sara Marie Nilsen, Mika Kivimäki, Kari Risnes, Eero Kajantie*

Abstract text

Background Multimorbidity affects people of all ages but its risk factors in the early part of the lifecourse are unclear. We examined preterm birth (<37 weeks) and gestational age (the degree of prematurity) as risk factors for diverse health outcomes and multimorbidity (≥2 diseases) in adolescence (age 10-18 years).

Methods We used population-wide data from Finland (1,187,610 adolescents born in 1987-2006) and Norway (555,431 adolescents born in 1998-2007). Gestational age at birth was ascertained from medical birth registers and categorised as 23-27 weeks (extremely preterm), 28-31 weeks (very preterm), 32-33 weeks (moderately preterm), 34-36 weeks (late preterm), 37-38 weeks (early term), 39-41 weeks (full-term, reference category) and 42-44 weeks (post-term). Individuals were followed up from age 10 up to age 18 by record linkage to nationwide registers. We used Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for multiple health outcomes during adolescence.

Findings Mean follow-up was 6 years (SD: 3 years). Preterm birth was associated with increased risks of 20 hospital-treated malignant, cardiovascular, endocrinological, neuropsychiatric, respiratory, genitourinary and congenital health outcomes, after correcting for multiple testing and ignoring small effects (HRs <1·2). Multivariable-adjusted HRs comparing preterm to full-term born adolescents were 1·46 (95% CI: 1·42 to 1·49) for one disease, 2·90 (95% CI: 2·19 to 2·39) for 2 diseases and 4·22 (95% CI: 3·66 to 4·87) for ≥4 diseases the Finnish data. Results in the Norwegian data showed a similar pattern. We observed a consistent dose-response relationship between an earlier gestational age and an increased risk of multimorbidity in both datasets.

Interpretation Preterm birth is associated with increased risks of diverse multimorbidity patterns at age 10-18 years. Adolescents with a preterm-born background could benefit from diagnostic vigilance directed at multimorbidity.

Prevalence and associated factors of antibiotic exposure during pregnancy in a large French population-based study during the 2010-2019 period

Anh Tran , *Mahmoud Zureik, Jeanne Sibiude, Jérôme Drouin, **Sara Miranda**, Alain Weill, Rosemary Dray-Spira, Xavier Duval, Sarah Tubiana*

Abstract text

Background: Although bacterial infections are frequent during pregnancy, the prescription of antibiotics to pregnant women represents a challenge for physicians driven by the benefit-risk balance.

Objectives: To assess the extent of prenatal antibiotic exposure and its associated factors.

Methods: This study included pregnancies in the Mother-Child EPI-MERES Register 2010-2019 (built from the French National Healthcare Data System) regardless of outcome. Antibiotic exposure was defined as having at least one antibiotic prescription filled during pregnancy. The prevalence of pregnancies exposed to antibiotics was estimated. Univariable Poisson regression with generalized estimating equation was used to compare the number of antibiotic prescriptions filled during pregnancy and after pregnancy with period one year before pregnancy. Multivariable Poisson regression was used to investigate factors associated with prenatal antibiotic exposure.

Results: Among 9,769,764 pregnancies, 3,501,294 (35.8%) were exposed to antibiotics and amoxicillin was the most common. The prevalence of antibiotic exposure during pregnancy decreased substantially from 38.0% in 2010 to 32.1% in 2019. Compared with a similar period one year before pregnancy, the number of filled antibiotic prescriptions was lower during pregnancy [Incidence rate ratio (IRR) 0.903, 95% confidence interval (CI) 0.902-0.905] and during period one year after pregnancy [IRR 0.880, 95%CI 0.879-0.881]. Region of residence, deprivation index, smoking-related conditions, and chronic diseases (especially chronic respiratory diseases) were associated with prenatal antibiotic exposure.

Conclusions: Antibiotic prescriptions were filled less frequently during pregnancy than the preceding year. This could be due to a more relevant benefit-risk assessment. Pregnant women living with social deprivation, those with smoking-related conditions, and those with chronic diseases were more likely to fill antibiotic prescriptions.

Recurrence of congenital heart defects in siblings: a multinational comparison

Natasha Nassar

Abstract text

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Character with spaces count (n=1995)

Abstract

Background: The recurrence risk of congenital heart disease (CHD) increases with a known family history of this condition, but few studies have investigated the risk of CHD recurrence among siblings. This study aims to examine the recurrence risk of CHD in siblings within a population-based cohort and combine results in a systematic review and meta-analysis.

Method: All singleton liveborn infants born in 2001-2019 New South Wales (NSW), and 2008-2020 in Victoria, Australia, with a recorded diagnosis of CHD (ICD10-AM codes: Q20-Q26.9) up to one year of age were identified using linked birth and hospital admission records. Sibling pairs were identified using the unique project number of each mother. The recurrence risk ratio (RRR) was calculated using log-binomial models with CHD in the older sibling as exposure and CHD in the younger sibling as outcome, adjusting for year of birth, maternal age, and maternal diabetes. A systematic review was then conducted using MEDLINE and Web of Science databases with relevant data extracted and meta-analysis conducted using random-effects model.

Result: A total of 704,057 sibling pairs in NSW and 354,412 sibling pairs in Victoria were included. Among sibling pairs, the prevalence of CHD in the younger sibling was 220 and 248 per 10,000 for NSW and Victoria, respectively. The adjusted RRR was 2.63 (95%CI 2.19-3.13) in NSW and 3.48 (95%CI 2.65-4.58) in Victoria. RRR of severe CHD was 4.19 (95%CI 2.37-7.41) in NSW and 2.31 (95%CI 0.58-9.20) in Victoria. Four population-based studies were included in the meta-analysis, including the current study and studies from Denmark and Norway. The pooled RRR in siblings of any CHD was 3.09 (95%CI 2.73-3.49; I^2=84%) and severe CHD was 5.04 (95%CI 3.36-7.55; I^2= 30%).

Conclusion: The overall risk of having a sibling with CHD increased 3-fold, and 5-fold for severe CHD, when the older sibling was affected. Findings provide important information for pregnancy counseling and aids risk prediction.

Risk of adverse pregnancy outcomes in twin-and singleton-born women: an inter-generational cohort study

Prativa Basnet , *Rolv Skjaerven, Quaker Harmon, Kari Klungsøyr, Linn Marie Sørbye, Nils-Halvdan Morken, Liv Grimstvedt Kvalvik*

Abstract text

Introduction: Human fetuses inherit genetic characteristics from their mothers, and their intrauterine environment may also impact later reproductive health. Singleton-born women exposed to preeclampsia in utero are at increased risk of preeclampsia in their own pregnancies. However, little is known about the inter-generational risk of adverse pregnancy outcomes among twin-born women, who have a higher risk of intrauterine exposure to adverse outcomes such as preeclampsia. Thus, our aim was to compare the risk of as preeclampsia, preterm delivery and perinatal loss between twin-born and singleton-born women. We also evaluated whether in utero preeclampsia exposure in these women modified the risk.

Methods: Population-based cohort study of 9568 twin- and 510 084 singleton-born women from the Medical Birth Registry of Norway. Women's twin versus singleton birth was the exposure, further stratified by their in utero exposure to preeclampsia. Outcomes were preeclampsia, preterm delivery and perinatal loss in the next generation. Generalized linear models with log link binomial distribution estimated adjusted (age, birth year and education) relative risks (aRRs) of adverse pregnancy outcomes with 95% confidence intervals (CIs).

Results: There were not increased risks for adverse pregnancy outcomes in twin-born compared with singleton-born women: preeclampsia aRR 1.01 (95% CI 0.94-1.09), preterm delivery 0.99 (95% CI 0.93-1.04) and perinatal loss 0.98 (95% CI 0.83-1.16). When stratified by in utero exposure to preeclampsia, twin-born women had a lower risk of adverse outcomes; preeclampsia aRR 0.75 (95% CI 0.61-0.92), preterm delivery 0.78 (95% CI 0.64-0.97) and perinatal loss 0.49 (95% CI 0.22-1.11), compared to singleton-born women exposed to preeclampsia.

Conclusion: Although a larger proportion of twin-born than singleton-born women are exposed in utero to preeclampsia and preterm delivery, there was no increased risk of these adverse outcomes in their own pregnancies.

Risk of major malformations associated with topical retinoid use in pregnancy – results from Nordic population-based cohorts

Erle Refsum , ***Kari Furu***, *Carolyn E Cesta, Felix Wittström, Helga Zoega, Vidar Hjellvik, Jacqueline M Cohen*

Abstract text
Background: Isotretinoin is a systemic retinoid used to treat severe acne and recognized as a potent teratogen. Topical retinoids are used to treat milder forms of acne and are contraindicated during pregnancy as a precaution, despite limited safety data.

Objectives: To describe the prevalence of prescription topical retinoid use in the first trimester of pregnancy and estimate associated risk of major congenital malformations (MCMs).

Methods: We conducted a population-based cohort study using national health register data. We included all registered births with a gestational age of at least 22 weeks in Iceland, Norway, and Sweden from 2003 to 2020. The main exposure was first trimester use of topical retinoids, defined as having filled a prescription from the date of last menstrual period (LMP) +14 days to LMP+97 days. In sensitivity analyses, we defined exposure as use during the period most sensitive to teratogenic effects, LMP+35 to LMP+70. We compared first trimester use of topical retinoids to unexposed pregnancies and to topical azelaic acid or clindamycin (active comparators). The main outcome was any nongenetic MCM. We estimated risk ratios (aRR) and 95% confidence intervals (CIs) with log-binomial regression, adjusted for country, maternal age, and birth year.

Results: Of 2,461,016 births included in the cohort, 70.6 per 100,000 were exposed to topical retinoids in the first trimester. In pregnancies exposed to topical retinoids, 3.8% resulted in an MCM (65 of 1,725), compared to 3.1% of unexposed (76,201 of 2,434,270), aRR 1.2 (95% CI 0.95-1.52), and 2.9% of pregnancies exposed to azelaic acid or clindamycin (176 of 5,902), aRR 1.2 (95% CI 0.93-1.63). Sensitivity analysis showed results closer towards the null.

Conclusion: We found no excess risk of MCM associated with use of topical retinoids in the first trimester. Limiting to pregnancies resulting in a birth could underestimate both the prevalence and MCM risk.

Risk of obstetric anal sphincter injury (OASIS) in the second birth after perineal wound complications in the first birth

Agnes Rygaard , *Maria Jonsson, Anna-Karin Wikström, Sophia Brismar Wendel, Susanne Hesselman*

Abstract text
Introduction: Perineal wound complications, including infection, hematoma and wound dehiscence, occur in 0.1-4% of all birth-related perineal tears. Prior OASIS is the main risk factor for recurrent OASIS. The aim of this study was to investigate if perineal wound complications alone or in conjunction with prior OASIS are associated with an increased risk.

Material and methods: A nationwide cohort study of 411 317 women with a first and second singleton, term birth 2001-2019 in Sweden. Data on ICD-10 diagnostic codes and surgical procedures were retrieved from the Medical Birth Register and the Patient Register. Wound complication at first birth was defined as ICD-10 codes including wound infection, dehiscence or hematoma. OASIS at first and second birth was defined by check-box in medical charts, ICD-10 diagnostic and procedure codes. Association between wound complication at first birth and OASIS at second birth was investigated by logistic regression. Estimates were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CIs), women with neither OASIS, nor perineal wound complication at first birth as reference. Adjustment was made for dystocia, operative vaginal birth and birth weight.

Results: Of 411 317 women, 2 600 (0.6%) had a perineal wound complication at first birth. 5318 (1.3%) women had an OASIS at second birth. Women with no wound complication but OASIS at first birth had aOR of 6.64 (6.22-7.08 95% CI) of recurrent OASIS. Women with wound complication but no prior OASIS had aOR of 2.61 (2.03-3.40 95% CI) of OASIS at second birth, women with wound complication and OASIS at first birth, aOR 10.20 (6.69-15.54 95% CI).

Conclusion: Perineal wound complication at first birth is associated with increased risk of OASIS at second birth. The combination of wound complication and prior OASIS increases the odds more than 10-fold and should be taken account at antenatal counselling.

Key words: obstetrics, perineal wound complication, OASIS

Risk of preterm birth associated with ADHD medication use in early pregnancy

Chaitra Srinivas , *Øystein Karlstad, Hein Stigum, Kari Furu, Carolyn E Cesta, Johan Reutfors, Jennifer Hutcheon, Jacqueline M Cohen*

Abstract text

Background

Evidence on attention-deficit/hyperactivity disorder (ADHD) medication safety in pregnancy is limited.

Objective

We aimed to determine if ADHD medication use in early pregnancy is associated with risk of preterm birth.

Methods

In a cohort study using register data from Norway (2009-2020) and Sweden (2006-2019) we included singleton births ≥22 weeks gestation. ADHD was defined as having a specialist care diagnosis (ICD-10 F90) any time before delivery or a prescription fill for ADHD medication (amphetamine, dexamphetamine, methylphenidate, atomoxetine, lisdexamfetamine, or guanfacine) from a year before the last menstrual period (LMP) until delivery. We defined early-pregnancy ADHD medication use as ≥1 prescription fills from conception (LMP+14 days) to <22 weeks (LMP+153 days). Unexposed pregnancies had no ADHD medication fills from 3 months before conception to <22 weeks. Preterm birth was defined as birth at <259 days. We described the risk of preterm birth in women with ADHD versus no ADHD, regardless of treatment use, and estimated risk ratios (RRs) for preterm birth associated with ADHD medication use among women with ADHD, using inverse probability of treatment weighted log-binomial regression.

Results

We included 689 921 births from Norway, and 1 451 438 from Sweden. Women with ADHD (n=28 137) had an increased risk of preterm birth (7.4%) compared to those without (5.4%), regardless of medication use in pregnancy (crude RR 1.4, 95% CI 1.3-1.4). Among women with ADHD, risk of preterm birth was higher among exposed (n=4270, 8.4%) than unexposed (n=20 055, 7.1%; crude RR 1.2, 95% CI 1.1-1.3). However, the association attenuated to the null on adjusting for confounders (adjusted RR 1.0, 95% CI 1.0-1.1).

Conclusions

In conclusion, there is higher risk of preterm birth among women with ADHD, however, ADHD medication use in early pregnancy was not associated with increased risk of preterm birth.

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Severe maternal morbidity surveillance: temporal trends and regional variations in Sweden, 1999-2019.

Eleni Tsamantioti , *Anna Sandström, Giulia Muraca, K.S. Joseph, Katarina Remaeus, Neda Razaz*

Abstract text
Objective: To quantify temporal trends and regional variations in severe maternal morbidity (SMM) in Sweden with a view to informing clinical practice and population health initiatives.

Methods: We carried out a population-based cohort study using data on all live birth and stillbirth deliveries in Sweden from January 1999 to December 2019**.** SMM types and subtypes were identified based on a standard list (modified for Swedish data), using diagnosis and procedure codes among all deliveries >=22 weeks' gestation (including complications within 42 days after delivery)**.** Contrasts between regions were quantified using rate ratios (RRs) and 95% confidence intervals (CIs). Temporal changes of SMM types and subtypes were also described.
Results: Between 1999 and 2019, there were 59,789 SMM cases among 2,212,576 deliveries, corresponding to 270.2 (95% CI 268.1-272.4) per 10,000 deliveries. SMM rates increased from 1999 to 2006 and then decreased. Severe preeclampsia,eclampsia and HELLP syndrome (103.8 per 10,000 deliveries), severe hemorrhage (133.7 per 10,000 deliveries) and sepsis (10.4 per 10,000 deliveries) were the most common SMM types. Severe haemorrhage rates increased from 94.9 in 1999 to 169.3 per 10,000 deliveries in 2006 and then declined to 111.2 per 10,000 deliveries in 2019. Embolism, disseminated intravascular coagulation and shock, acute renal failure, cardiac complications, sepsis, and assisted ventilation rates increased, whereas surgical complications, severe uterine rupture and anesthesia complications declined. Rates of composite SMM in 1999-2019 were higher in Västra Götalands, Värmland, Kronoberg, Uppsala, and Norrbotten, compared with the rest of Sweden, whereas rates were lower in Örebro, Sörmland, Gotland and Jönköping regions.
Conclusion: The observed spatio-temporal variations in composite SMM and SMM types provide substantive insights and suggest regional priorities for clinical and public health intervention for improving maternal health.

Sex Chromosome Aneuploidies: The effect of number of X chromosomes on serum screening markers

Misgav Rottenstreich

Abstract text

Objective: To evaluate the association between the type of sex chromosome aneuploidies (SCAs) in terms of the number of X chromosomes and abnormalities of maternal serum screening.

Method: This retrospective cross-sectional study included all singleton pregnancies terminated from 1998 through 2015, due to SCAs in a single institute. We compared

the pregnancy characteristics, prenatal genetic screening results, and indications for invasive testing in two subgroups: SCAs with a single X (X0 and 47, XYY) – [X1] group and those with more than one X chromosome (47, XXY; 47, XXX) - [X+] group.

Results: There were 196 pregnancies with SCAs that underwent termination: 80 women in the [X1] group (60 women -X0 and 20 women -47, XYY) who were compare to 116 women in the [X+] group (74 women- 47, XXY; 42 women- 47, XXX). While the [X1] group had higher nuchal translucency result, all second trimester screening test (alpha-fetoprotein, free β-subunit Human chorionic gonadotropin, unconjugated estriol) were significantly higher in the [X+] group.

Overall invasive prenatal testing was performed following an abnormal screening test significantly more often in the [X^{+}] group compared to the [X1] group (68.1% vs 35.0%, $p<0.001$).

Conclusion: A difference in screening results between SCA karyotypes may be associated with X chromosomal dosage.

Short-term variation of the fetal heart rate as a marker of intraamniotic infection in pregnancies with preterm prelabor rupture of membranes

Brynhildur Tinna Birgisdottir , *Ingela Hulthén Varli, Sissel Saltvedt, Farhad Abtahi, Ulrika Åden, Malin Holzmann*

Abstract text
Introduction: Intraamniotic infection and subsequent early onset neonatal sepsis (EONS) are among the main complications associated with preterm prelabor rupture of membranes (PPROM). Currently used diagnostic tools have been shown to have poor diagnostic performance for intraamniotic infection and poor predictive performance for EONS. This study aimed to investigate the association between intraamniotic infection and short-term variation (STV) of the fetal heart rate in pregnancies with PPROM.

Material and methods: Observational cohort study of 647 pregnancies with PPROM, delivering between 24 + 0 and 33 + 6 gestational weeks during 2012 to 2019 in five labor units in Stockholm and Gotland County, Sweden. Electronic medical records were examined to obtain background and exposure data. Since histological acute chorioamnionitis can be observed in the absence of positive microbiology and biochemical markers for inflammation, we used the diagnosis of EONS as a proxy for the exposure intraamniotic infection. Cardiotocography traces were analyzed by a computerized algorithm for STV of the fetal heart rate, which was the main outcome measure.

Results: Twenty-five neonates developed EONS after birth. Neonates who developed EONS had significantly lower STV values in the last cardiotocography trace before birth than neonates who did not develop EONS (5.65 vs 6.66 ms; unadjusted difference: −1.01, p = 0.042). After adjustment for smoking and diabetes, this difference remained significant. EONS with a positive blood culture (n = 11) showed an even larger absolute difference in STV (−1.60; p = 0.031), with a relative decrease of 21.4%.

Conclusions: In pregnancies with PPROM, fetuses who develop EONS after birth have slightly lower STV of the fetal heart rate than fetuses who do not develop EONS. STV might be useful as adjunct surveillance in pregnancies with PPROM.

Skin-to-skin contact, cognition and behavior at 5 years among children born extremely and very preterm: the EPIPAGE-2 cohort study

Ayoub Mitha , *Laetitia Marchand, Jean-Christophe Rozé, Pierre Kuhn, Monique Kaminski, Véronique Pierrat*

Abstract text

Importance: Early skin-to-skin contact (SSC) is beneficial for the physiological stability of preterm-born infants, breastfeeding and support bonding between infant and the parents. However, long-term effects of SSC on neurodevelopmental outcome for extremely and very preterm infants are still debated.

Objective: To evaluate associations between early SSC, cognition and behavior at 5 years among children born extremely (24-27 completed gestational weeks) and very preterm (28-31 weeks).

Methods: Using the French population-based EPIPAGE-2 cohort, exposition to SSC during the first week of life was evaluated by a propensity score analysis based on individual and unit characteristics with inverse probability of treatment weighting approach. Outcomes were full-scale-intelligence-quotient (Wechsler Preschool and Primary Scale of Intelligence, 4th edition) and behavioral difficulties (strengths and difficulties questionnaire) among 2,561 infants born between 24 and 31 completed gestational weeks and survivors at 5 years. Distributions of the scores in contemporary term-born children were used as reference.

Results: Among participants, 1,581 (61.7%) were exposed to early SSC with large variability between neonatal units (range 15%-75%). At 5 years, early SSC was associated with increased proportions of children with full-scale-intelligence-quotient $\geq$ - 1 standard deviation (adjusted odd ratio 1.27, 95% confidence interval (1.01;1.59)), and with trend for higher full-scale-intelligence-quotient (mean difference +1.6, 95% confidence interval (-0.3;3.5)). Strengths and Difficulties Questionnaire scores were not different between groups exposed/not exposed to early SSC.

Conclusion and relevance: Early SSC among very preterm infants was associated with higher full-scale-intelligence-quotient at 5 years. Variability of practices among units deserves attention. Further evaluation of the dose-effect is needed.

Stillbirth in Iceland 1996-2021; incidence and etiology

Ragnheidur Ingibjorg Bjarnadottir , *Thora Steffensen, Karin Pettersson, Nikos Papadogianniakis, Alexander Smarason, Johanna Gunnarsdottir*

Abstract text

Objectives: Iceland has a low stillbirth rate (SBR) which fluctuates greatly due to its small population of 390.000. This study aims to explore the changes in the SBR over a quarter of a century and understand the main causes of stillbirth (SB).

Methods: Data was collected from medical records of mothers who delivered stillborn infants (n=385) from 22+0 weeks of gestation in Iceland 1996-2021. The placental pathology was reviewed and classified according to the Amsterdam consensus. The Stockholm classification of stillbirth (SB) was used to determine the cause of death. The result were compared between two periods (1996-2008 and 2009-2021).

Results: Comparing former and latter periods, the total SBR decreased significantly from 4.11 to 2.88/1000 infants, p=0.005. However there was no decrease in the SBR at term, 1.19 vs. 1.15 /1000 term infants, p=0.89. Intrapartum SB was rare (n=5). The most common primary causes of death were umbilical cord complications (n=99, 25.7%) and placental insufficiency (n=96, 24.9%), followed by infection (n=48, 12.5%), placental abruption (n=43, 11.2%) and unexplained (n=43, 11.2%). Comparison between 1996-2008 (n=225) and 2009-2021 (n=160) showed a reduction in infections (14.2 vs. 5.6%) and abruption (12.9 vs 8.7%) as primary cause of death in the latter period. Cord complications were unchanged (23.6 vs 28.8%). However, there was an increase in placental insufficiency (16.0 vs 37.5%) in the latter period.

Conclusion: Although the overall SBR has decreased, the SBR at term has not. This, along with the increase in placental insufficiency calls for further research.

Temporal trends in maternal pre-existing chronic conditions during pregnancy in Sweden and Canada, 1999-2019

Louise Lundborg , *Cande V. Ananth, KS Joseph, Sven Cnattingius, Neda Razaz*

Abstract text

Background: There has been a substantial increase in several chronic health conditions at all ages, including in the child-bearing population, and such conditions contribute significantly to severe maternal morbidity and maternal mortality.**Objectives:** To examine temporal trends in the rate of pre-existing chronic conditions in pregnancy.**Design:**Population-based cross-sectional analysis study.**Setting and participants:** 1 944 029 births in Sweden between 1999-2019 and 825 203 births in BC, Canada between 2000-2019.**Main outcome measures:** Prevalence of 20 chronic conditions associated with obstetric morbidity, namely; depression, anxiety, bipolar, schizophrenia/psychotic, eating disorder, MS, SLE, epilepsy, migraine, rheumatoid arthritiscerebrovascular, chronic hypertension, ischemic heart disease, chronic heart disease, diabetes, thyroid disorder, asthma, chronic kidney disease, celiac disease, inflammatory bowel disease. Prevalence rates and rate ratios with 95% CIs of chronic conditions in relation to age, period, and birth cohort were derived through age-period-cohort models.**Results**: The overall prevalence of having any of the investigated chronic conditions in Sweden was 11.19 % and BC, Canada 36.85 %. The prevalence of ≥1 chronic condition during pregnancy increased substantially in Sweden from <3% in 1999 to almost 18% (N=13 364) in 2019. In BC, Canada, in 2019, 34.1% (n = 14 732) of the women had a pre-existing chronic condition during pregnancy, although the temporal trend was stable during the study period.

Conclusion: In Sweden, the temporal burden of pre-existing chronic conditions during pregnancy increased substantially in the last 20 years, and an overall high stabile burden of maternal chronic conditions during pregnancy was observed in BC.The high prevalence of chronic conditions in the childbearing population calls for an increase in pre-conceptional services, and more coordinated multi-speciality care in pregnancy.

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The ALSPAC G2 cohort: An update and opportunity for new research

Louise Jones , ***Kate Northstone***, *Deborah Lawlor*

Abstract text

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal birth cohort study based in Bristol, UK. More than 14,000 women were originally enrolled – they were eligible to take part in the study if they were pregnant with a delivery date falling between 1st April 1991 and 31st December 1992 and resident in the local Bristol area. These women, their partners and children have been followed ever since.

As the original child cohort (known as G1) have moved into adulthood, they have started having their own children. A previous published study used data collected up to 2018 on 810 G2 infants/children from 548 families[1]. Those data showed that compared to their mothers generation, contemporary pregnant women were younger, more likely to have symptoms of antenatal depression, less likely to smoke, and had a higher mean BMI, and total cholesterol. Their children were more likely to be delivered by C-section, have a higher mean birth weight and were more likely to be breast fed.

We have now recruited more than double the number of G2 offpsring and data continues to be collected via questionnaires, face to face visits and linkage to health records. We will present an update of numbers and on the cross generational differences on larger numbers and for some early childhood outcomes.

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The association between epigenetic age acceleration and fecundability

Lise Andrea Arge , *Yunsung Lee, Siri Eldevik Håberg, Maria Christine Magnus*

Abstract text

Background: Fecundability decreases with age, particularly among women. Whether accelerated biological aging might also be associated with fecundability has not been studied. The objective of this study was therefore to evaluate the association between epigenetic age acceleration and fecundability among men and women.

Methods: We studied 1815 men and women with planned, naturally conceived pregnancies and available blood samples participating in the Norwegian Mother, Father and Child Cohort Study. DNA methylation levels among participants were measured with the Illumina Methylation EPIC Array, and epigenetic age was estimated using six different established epigenetic clocks. We obtained residuals of a linear regression of chronological against biological age, and used proportional probability regression to estimate fecundability ratios (FRs) and 95% confidence intervals (CIs) by residual groups. We also generated flexible spline models for each of the six clocks.

Results: Women with the highest epigenetic age acceleration (residual z scores >1.5) had decreased fecundability estimated by both the DunedinPACE (FR 0.80, CI 0.65-0.99) and Lu (FR 0.80, CI 0.65-0.97) clocks, as compared to women with non-accelerated aging (residual z scores -0.5-0.5). A statistically significant relationship between epigenetic age and fecundability was not found among men, with FRs of 1.17 (CI 0.99-1.38) and 0.99 (CI 0.83-1.18) for DunedinPACE and Lu respectively. We will further explore adjustment for body mass index, education and smoking.

Conclusion: Accelerated epigenetic aging was associated decreased fecundability among women but not men. The underlying explanations for this observation need to be further explored.

The association between SARS-CoV-2 and de novo hypertension during pregnancy – a population-based cohort study in Sweden and Norway

Anne K. Örtqvist , *Maria C. Magnus, Elisabeth Dahlqvist, Jonas Söderling, Kari Johansson, Anna Sandström, Siri E. Håberg, Olof Stephansson*

Abstract text

Background The suggested association between SARS-CoV-2 and de novo hypertension during pregnancy (HDP) may be due to bias. We aimed to further investigate this association, taking temporality and confounding into account.

Methods The study included all pregnant women with a singleton birth after 22 gestational weeks in the Swedish Pregnancy Register and the Medical Birth Register in Norway between March 2020 and May 2022 (N=312,456). De novo HDP was defined as a composite outcome of a diagnosis of gestational hypertension, preeclampsia, 'hemolysis, elevated liver enzymes, low platelets' syndrome and/or eclampsia from gestational week 20 up until 1 week after delivery. Dates of all PCR-verified SARS-CoV-2 tests and dates of diagnoses of HDP were collected from national health and surveillance registers. The association between SARS-CoV-2 and HDP was investigated using a stratified Cox proportional hazard model, with SARS-CoV-2 as time-varying variable. Thus, those with SARS-CoV-2 after onset of HDP were censored. The model was adjusted for background characteristics and stratified by date of conception, taking variation in baseline risks of SARS-CoV-2 and testing capacity during the study period into account.

Results SARS-CoV-2 was not associated with an increased risk of HDP (adjusted Hazard Ratio 0.99, 95% Confidence Interval 0.93-1.04). Further, results were similar when examining SARS-CoV-2 by trimester and for different calendar time periods corresponding to dominating virus variants.

Conclusions Using nationwide registry data from Sweden and Norway, we did not find any evidence of an association between SARS-CoV-2 infection during pregnancy and subsequent development of HDP. In this study, timing of infection and onset of HDP was accounted for, which has been lacking in previous studies. Nevertheless, as SARS-CoV-2 in pregnancy is related to other adverse outcomes in pregnancy, vaccination of pregnant women is still highly recommended.

The association between uterine incision extensions and subsequent preterm birth

Giulia M. Muraca , *Abirami Kirubarajan, Misgav Rottenstreich*

Abstract text
Objective

We aimed to quantify the association between uterine incision extensions and preterm birth (PTB) in a subsequent delivery.

Methods

We performed a retrospective cohort study using electronic perinatal data collected in 4 university-affiliated obstetrical centers in Israel, representing approximately 25% of all deliveries in the state of Israel. The study included patients with a primary cesarean delivery (CD) of a term, singleton live birth and a subsequent singleton birth in the same catchment (2006-2021). The primary outcome was subsequent PTB <37 weeks; secondary outcomes included subsequent PTB <34, <32 and <28 weeks. We assessed crude and adjusted associations between uterine incision extensions and subsequent PTB in multivariable regression models using odds ratios (ORs) and 95% confidence intervals (CIs). Adjusted models included several factors such as length of labour, indication for CD, chorioamnionitis, and smoking during pregnancy.

Results

A total 4,827 patients met the study inclusion criteria. The overall rate of uterine incision extension was 6.0% and the total rate of PTB in the subsequent pregnancy was 4.9%. Patients with a uterine extension were more likely to have a longer duration of active labour, chorioamnionitis, failed vacuum delivery attempt, second stage CD, and persistent occiput posterior position of the fetal head in the primary CD and higher rates of smoking in the subsequent pregnancy. We found a higher, but statistically insignificant rate of subsequent PTB <37 weeks among patients with vs without uterine incision extensions (adjusted OR 1.49, 95% CI 0.89-2.50). However, a significantly higher rate of PTB <34 weeks was found among patients with vs without extensions (adjusted OR 2.49, 95% CI 1.04-5.96).

Conclusion

Patients with a uterine incision extension have a 2.5-fold higher rate of PTB <34 weeks compared with patients who do not sustain this injury. This association was not observed for PTB <37 weeks.

THE ASSOCIATION OF UMBILICAL CORD LENGTH PERCENTILE TO CEREBRAL PALSY IN THE CHILD, A NATIONWIDE STUDY

Cathrine Ebbing , *Svein Rasmussen, Jørg Kessler, Dag Moster*

Abstract text

Introduction: Cerebral palsy (CP) is a group of movement disorders usually diagnosed in childhood. A substantial proportion is thought to be caused by antenatal events. More boys than girls are diagnosed with CP. As sex-differences are also present in umbilical cord length it is conceivable that long term consequences of cord length exert a sex specific pattern. Here we study the association of cord length percentiles with CP and if associations differ between boys and girls. Materials and Methods: We performed a national cohort study by linking The Medical Birth Registry of Norway with other national registries. All live born singletons from 1999 through 2017 (n=1 087 486) were followed up through 2019. Diagnoses of CP were provided by the Norwegian National Insurance Scheme and the Norwegian Patient Registry. We used logistic regression to calculate Odds Ratios (OR) with 95% Confidence Intervals (CI). Stratified analyses were carried out based on sex. Exposures were extreme cord lengths; short (<5th cord length percentile) or long >95th percentile, using ≥5th percentile or ≤95th centile respectively, as reference. Demographic and possible confounding variables were included in the model according to their potential influence on the risk estimates. Results: We identified 2443 cases with CP (59.8% boys). A short cord carried increased risk; adjusted (a) OR 1.3 (95%CI 1.1-1.6) among both boys and girls (boys aOR 1.3 (95%CI 1.0-1.7), and girls aOR 1.4, (95%CI 1.0-1.8)). A long cord showed a similar association; aOR 1.3, 95%CI 1.0-1.5, but this association was only evident among boys (aOR 1.4 (95%CI 1.1-1.7)), and not girls (aOR 1.1 (95%CI 0.9-1.5)). Adjusting for maternal age and parity did not affect the results. Conclusions: We demonstrate an association of extreme umbilical cord lengths with later CP. The association of a long cord to CP was only evident in boys. Umbilical cord properties may lie in the causal path leading to CP and exhibit sex-specific effects.

The epidemiology and clinical workload of children requiring neonatal care and paediatric intensive care in the first two years

Sarah Seaton , *Cheryl Battersby, Peter Davis, Alan Fenton, Josie Anderson, Tim van Hasselt, Elizabeth Draper*

Abstract text

Background: Approximately one in seven babies in the United Kingdom require specialist neonatal care. Admissions to neonatal care have been increasing and following discharge any further intensive care needs are provided in paediatric intensive care units (PICU). To date no one has explored the needs of children who were admitted to neonatal care and PICU before the age of two years on a population level.

Methods: We linked neonatal admissions of children born in 2013-2018 (National Neonatal Research Database) with paediatric intensive care admissions (Paediatric Intensive Care Audit Network) from 2013-2020 in England and Wales. We present observed characteristics and workload using totals and percentages to describe the cohort for the first time.

Results: A total of 389,268 babies were admitted to neonatal care from 2013-2018. In total 18,551 (4.8%) were admitted to PICU at least once before two years of age. Children who were in neonatal care accounted for over half of PICU admissions and 60% of PICU care days out of all children admitted to PICU before two years of age and born in 2013-2018. The most common reasons for the first PICU admission were cardiac (n=7220; 72.3% born at term) and respiratory (n=5435; 65.5% born preterm) conditions.

Conclusion: Whilst only a small percentage of children admitted to neonatal care have ongoing healthcare needs in PICU, they account for a large proportion of the workload provided to children before the age of two years. This group of children with ongoing healthcare needs in early life require further study.

The epidemiology of pain in very preterm infants – a nationwide, population-based cohort study

Hillary Graham , *Mikael Norman, Stellan Håkansson, Kari Johansson, Martina Persson, Ylva Blomqvist, Neda Razaz*

Abstract text

Introduction: A detailed understanding of neonatal pain burden, validated scale assessments, and pharmacological treatment patterns in very preterm infants is lacking.[1-2] The aim was to explore and visualize the daily pain and treatment in Sweden.

Methods: all infants delivered at 22–31 weeks of gestation with at least one neonatal unit admission reported daily to SNQ (n = 2 935) and discharged to home between January 2020 and December 2022 were defined as the study population. Infants who died during neonatal care and infants with malformations were included in this descriptive cohort study. Proportions with pain, pain assessment scales, or pharmacologically treated were calculated for each gestational week and postnatal day (0-83 days) up to hospital discharge or 34 weeks postmenstrual age.

Results: From 2,935 very preterm infants admitted with a total 137,905 days of neonatal care, 1,884 (64%) infants were reported to have experienced pain at any time during their hospital stay. At postnatal day 0, 13, and discharge, proportions for 22 weeks (Pain: 51%, 51.6%, 27.3%; Treatment: 0%,3.2%, 4.5%) compared to 31 weeks (Pain: 31.7%, 6%, 5.5%; Treatment:10.7%, 1.5%, 0.8%) indicate earlier gestational ages have higher proportions of pain and decreased proportions of pharmacological pain treatment. Proportion with pain decreased by -4.3% to -1.7% (variability related to postnatal days for regression) for each week higher in gestational age starting at postnatal day 13 ($r = -0.90$ to -0.79, $p \leq 0.05$). The proportion of infants assessed via a validated pain scale decreased linearly by -6.5 to -1.2% for each week higher in gestational age ($r = -0.98$ to -0.74, $p \leq 0.02$).

Conclusion: Neonatal pain patterns and treatment in very preterm infants follow non-linear gestational age specific postnatal trajectories, with higher proportion of pain and lower pain treatment rate with decreasing gestational age. Validated pain scales report consistent linear postnatal trajectories.

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The epigenetic landscape of gestational age

Kristine Løkås Haftorn , *Jon Bohlin, Siri Eldevik Håberg, Astanand Jugessur*

Abstract text

Gestational age at delivery may serve as an indicator of newborn maturity, with the length of pregnancy being closely linked to maternal characteristics and exposures, perinatal outcomes, and long-term health of the offspring. Accurate estimation of gestational age can be important for ensuring proper perinatal care. Furthermore, gaining insights into the mechanisms underlying developmental maturation during gestation is essential for advancing our understanding of the triggers of delivery and the mechanisms contributing to preterm birth.

Recent research has shed light on the association between gestational age and DNA methylation, a key epigenetic modification involved in embryonic development and cell type differentiation. The development of DNA methylation-based models, commonly referred to as epigenetic clocks, has enabled accurate prediction of gestational age. While thousands of DNA methylation sites (CpGs) have been associated with gestational age, only a handful are necessary for precise prediction, accounting for a significant portion of the variance related to gestational age. Notably, some of these CpGs exhibit a nonlinear relationship with gestational age, highlighting the importance of considering nonlinearity to ensure accurate gestational age prediction, particularly in preterm newborns.

Part of the association between gestational age and DNA methylation appears to be driven by nucleated red blood cells, potentially representing a signature of red blood cell development. Moreover, several of the gestational age associated CpGs are located in or near genes and regulatory regions relevant to cell type development, immune responses, metabolism, and developmental processes. Further investigation into the relationship between DNA methylation and gestational age is warranted to enhance our understanding of the epigenetic regulation of fetal growth and development.

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The estimated effect of first trimester season and vitamin D on pubertal timing in children: a cohort study and an instrumental variable analysis

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Abstract text

Background

Season of birth has been associated with age at menarche. Maternal vitamin D levels in pregnancy may explain this effect. We investigated whether season of first trimester and maternal vitamin D levels in first trimester were associated with pubertal timing in girls and boys.

Methods

We conducted a follow-up study of 15 819 children born 2000–2003 from the Puberty Cohort, nested in the Danish National Birth Cohort (DNBC). Mean differences in attaining numerous pubertal markers, including a combined estimate for the average age at attaining all pubertal markers, were estimated for low (November–April) relative to high (May–October) sunshine exposure season in first trimester using multivariable interval-censored regression models. Moreover, we conducted a two-sample instrumental variable analysis using season at gestational week 8 as an instrument for maternal first trimester 25-hydroxyvitamin D_3 ($25(OH)D_3$) plasma levels obtained from a non-overlapping subset (n = 827) in the DNBC.

Results

For the combined estimate, girls and boys of mothers who had their first trimester during November–April had earlier pubertal timing than girls and boys of mothers whose first trimester occurred during May–October: -1.0 months (95% confidence interval (CI): -1.7 to -0.3) and -0.7 months (95% CI: -1.4 to -0.1), respectively. In the instrumental variable analysis, girls and boys also had earlier pubertal timing: respectively, -1.3 months (95% CI: -2.1 to -0.4) and -1.0 months (95% CI: -1.8 to -0.2) per SD (22 nmol/L) decrease in maternal $25(OH)D_3$ plasma levels.

Conclusion

First pregnancy trimester during November–April and lower maternal $25(OH)D_3$ in first trimester were associated with earlier pubertal timing in girls and boys. Future studies should aim to elucidate if intervening on low maternal vitamin D levels during seasons with low exposure to sunshine would be beneficial with regard to pubertal timing in the children.

The Finnish Gestational Diabetes (FinnGeDi) study: Missing sibling – a role of first-pregnancy gestational diabetes?

Elina Keikkala , *Jenni Pukkila, Sanna Mustaniemi, Hilkka Nikkinen, Jenni Kinnunen, Eero Kajantie, Marja Vääräsmäki*

Abstract text

Background: Women who have had a severe pregnancy disorder are less likely to have subsequent children than women with a normal pregnancy. The effect of gestational diabetes is not known.

Aim: To study probability of a new delivery of women who have experienced gestational diabetes in their first pregnancy.

Methods: All singleton primiparous women who gave birth in Finland in 2009 (n=25 696) after exclusion of pre-pregnancy diabetes (n=193) were included. Gestational diabetes was diagnosed in 2521 (9.8%) women according to the comprehensive screening following the national guidelines. First and possible subsequent deliveries within 10 years follow-up and potential confounders were identified from the Medical Birth Register and the Care Register for Health Care. Relative risk was calculated and the multivariate logistic regression was used to analyze the effect of gestational diabetes to the probability of subsequent delivery.

Results: Relative risk to have a subsequent delivery after gestational diabetes was 0.89 (95% confidence interval, CI, 0.86-0.91) as 67.3% of women with and 75.7% of women without a history of gestational diabetes had at least one subsequent delivery. When adjusting with potential first-pregnancy confounders (maternal age, pre-pregnancy body-mass-index, socioeconomic / cohabiting status, infertility treatment, gravidity > 1, any hypertensive disorder, caesarean section, preterm delivery, maternal hospitalization > 7 days at postpartum, small- or large-for-gestational age and adverse neonatal outcome) OR was 0.89 (0.80 – 0.99). When further adjusted with maternal type 1 or type 2 diabetes after the first delivery OR was 0.86 (0.77 – 0.96) or with maternal mental disorder before the first delivery OR was 0.90 (0.80 – 1.00). Sensitivity analyses performed for women < 40 years old did not change the results.

Conclusion: Women who have had gestational diabetes are less likely to have subsequent children than women with a normoglycemic pregnancy.

The Genetics of Extreme Birthweight and its Relationship with Cardiometabolic Disease

Gunn-Helen Moen , *David M Evans*

Abstract text

Background and aim: The Barker Hypothesis posits that the relationship between birthweight and diabetes is due to environmentally induced intrauterine growth restriction and developmental compensations later in life that increases risk of disease. In contrast, previous genome-wide association studies (GWAS) have suggested that fetal genetic factors explain most of this observational association. However, these GWAS have only focused on birthweight within the normal range and have typically excluded individuals with birthweight <2.5kg or >4.5kg.

Material and methods: We performed GWAS analysis of low (<2.5kg) and high (>4.5kg) birthweight in the UK Biobank using REGENIE (N_{low} = 20,947; N_{high} = 12,715; $N_{controls}$ = 207,506) as well as GWAS of continuous birthweight (both including (N = 241,168) and excluding (N=207,506) birthweights <2.5kg or >4.5kg) using BOLT-LMM. We ran bivariate LD score regression analysis to estimate the genetic correlation between extremes of birthweight and cardiometabolic traits.

Results: Bivariate LD score regression suggested that high birthweight has a similar genetic aetiology to birthweight within the normal range (rG = 0.91, $p=1.02x10^{-77}$), whereas a separate set of genes may also be important for low birthweight (rG = -0.73, $p=8.12x10^{-70}$). Of the glucose related traits, low birthweight had the strongest correlation with type 2 diabetes (rG=0.28, $p=3.47x10^{-15}$), whereas high birthweight correlated strongest with fasting insulin (rG=0.21, $p=8.95x10^{-6}$). The inclusion of individuals with extremes of birthweight in the GWAS of continuous birthweight increased the number of genome-wide significant loci from 86 to 145.

Conclusion: Our analyses suggest that high birthweight has similar underlying genetics as birthweight within the normal range, however there may be some separate genetic influences on low birthweight specifically.

The relationship between cesarean delivery and fertility: a population-based cohort study

Yeneabeba Tilahun Sima , *Maria Christine Magnus, Liv Grimstvedt Kvalvik, Nils-Halvdan Morken, Kari Klungsøyr, Rolv Skjærven, Linn Marie Sørbye*

Abstract text

Background

Previous studies have found that women with caesarean delivery (CD) have fewer number of pregnancies. The potential role of CD on reduced fertility is not known.

Objective

To assess the bidirectional relationship between CD and fertility.

Design

Prospective, population-based cohort study.

Setting

Data from the Norwegian Mother, Father, and Child Cohort study linked with the Medical Birth Registry of Norway.

Participants

We evaluated aspects of fertility among 42,379 women with more than one birth by mode of delivery in a previous birth. Further, we assessed the reverse association between fertility and risk of CD among 74,025 women.

Main outcome measures

We examined the fecundability ratio (per cycle probability of pregnancy) and relative risk (RR) of having longer time to pregnancy (≥ 12 months) by previous mode of delivery (vaginal delivery or CD). For the reverse association we estimated the RR of CD by the number of cycles women needed to conceive (in women without prior CD), using multivariable regression.

Results

Women with previous CD had lower fecundability ratio (0.90, 95% confidence interval 0.88 to 0.93) and longer time to pregnancy (RR 1.21, 1.10 to 1.33), compared to women with prior vaginal delivery. When assessing the reverse association between number of cycles and CD, we found that women who didn't conceive within 12 or more cycles had higher risk of CD (RR 1.55, 1.46 to 1.64) compared to women who conceived within the first two cycles. Associations remained after controlling for sociodemographic and clinical risk factors and were observed across parity groups.

Conclusion

Among women with more than one child, those who had CD had subsequent lower fecundability ratio and longer time to pregnancy compared to those who had vaginal delivery. However, women who needed longer time to conceive were also prone to be delivered by CD. We therefore found evidence of a bidirectional relationship between CD and fertility.

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Time-varying effects are common in genetic control of gestational duration

Julius Juodakis

Abstract text

Time-varying effects are common in genetic control of gestational duration

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Abstract

Preterm birth is a major burden to neonatal health worldwide, determined in part by genetics. Recently, studies discovered several genes associated with this trait or its continuous equivalent – gestational duration. However, their effect timing, and thus clinical importance, is still unclear. Here, we use genotyping data of 31,000 births from the Norwegian Mother, Father and Child cohort (MoBa) to investigate different models of the genetic pregnancy “clock”. We conduct genome-wide association studies using gestational duration or preterm birth, replicating known maternal associations and finding one new foetal variant. We illustrate how the interpretation of these results is complicated by the loss of power when dichotomizing. Using flexible survival models, we resolve this complexity and find that many of the known loci have time-varying effects, often stronger early in pregnancy. The overall polygenic control of birth timing appears to be shared in the term and preterm, but not very preterm periods, and exploratory results suggest involvement of the major histocompatibility complex genes in the latter. These findings show that the known gestational duration loci are clinically relevant, and should help design further experimental studies.

Timing of elective cerclage removal and perinatal outcomes: A retrospective multicenter study

Tzuria Peled , *Hen Y. Sela, Ari Weiss, Sorina Grisaru-Granovsky,* ***Misgav Rottenstreich***

Abstract text

Objective:

Cervical cerclage is a well-known surgical procedure performed in pregnancies of women with cervical insufficiency aiming to reduce pre-term birth (PTB). We aimed to investigate the preferred timing of elective cerclage removal in women with cervical cerclage who reached 36 weeks of gestation.

Study design:

A multicenter retrospective cohort study of all women with singleton pregnancies who underwent cervical cerclage and reached 36 weeks and zero days of gestation and were eligible for vaginal delivery. Perinatal outcomes of women with elective cerclage removal at 37 weeks were compared to those with removal at 36 weeks of gestation. The primary outcome was a composite adverse maternal outcome. Univariate analyses were followed by multivariate logistic regression (adjusted Odds Ratio (aORs); [95% Confidence Interval]).

Results:

A total of 322 women met inclusion criteria, of whom 145 (45%) underwent cerclage removal at 36 weeks and 177 (55%) at 37 weeks of gestation. We found no difference between the groups in the rates of maternal or neonatal complications, including excessive maternal bleeding (>1000 ml), cervical trauma, and intrapartum cesarean. Multivariate analyses revealed that cerclage removal at 37 weeks was not associated with composite adverse maternal outcome [aOR 0.86 (0.43- 1.70), P=0.67]. However, 6.9% of the women who underwent cerclage removal at 36 weeks had preterm delivery before 37 weeks.

Conclusion:

In women with cervical cerclage who reach 36 weeks and are eligible for vaginal delivery, removal of cerclage at 37 weeks of gestation is not associated with increased maternal morbidity compared to removal at 36 weeks and may reduce the risk for late preterm delivery.

Tissue-specific epigenetic differences in adults born preterm with very low birth weight compared with their same-sex siblings

Helena Hauta-alus , *Justiina Ronkainen, Juho Kuula, Darina Czamara, Anni Heiskala, Samuel Sandboge, Johan Björkqvist, Nina Kaseva, Katri Räikkönen, Kirsi Pietiläinen, Sylvain Sebert, Elisabeth Binder, Eero Kajantie*

Abstract text
Preterm birth and very low birth weight (VLBW; ≤1500 g) increase the long-term risks for poor health and chronic diseases, however, the mechanisms remain unknown. One suggested pathway is epigenetic modifications such as DNA methylation (DNAm), but few studies have assessed other tissues than blood. We examined whether DNAm in blood or fat differs between VLBW adults and their siblings.

The current analysis is based on the Adults Born Preterm Sibling Study and included 78 adults born preterm (<37 gestational week) with VLBW (<1500g) with 76 same-sex sibling-controls born at mean gestational age 40 weeks with mean birth weight of 3361g, all born between years 1976-1996. Epigenome-wide DNAm at cytosine-guanine dinucleotide (CpG) sites were examined from blood and fat tissue by Illumina EPIC 850K at mean age of 29 years. Mixed model was conducted adjusting for age, sex, batch, estimated cell composition and maternal smoking.

None of the DNAm differences in blood attained epigenome-wide significance. In fat tissue 440 CpG sites were differentially methylated with false discovery rate [FDR] p<0.05 and 86 CpG sites with epigenome-wide significance of $p<9.4 \times 10^{-8}$ between VLBW and their sibling-controls after adjustments. Top sites were annotated to genes related to fat metabolism (e.g. *FADS2*, cg00264176: coefficient (standard error [SE]) 0.08 (0.01), FDR $p=9.1 \times 10^{-15}$; *ACSL3*, cg14157824: 0.05 (0.01), $p=6.1 \times 10^{-11}$) and neural development (e.g. *KIF26A*, cg08277679: 0.05 (0.01), $p=1.7 \times 10^{-12}$; *QPRT*, cg05127221: 0.06 (0.01), $p=4.9 \times 10^{-11}$) among other functions.

Our results suggest tissue-specific DNAm differences in VLBW adults compared with their siblings with pronounced associations in fat tissue rather than blood. The differentially methylated CpG sites observed were related to genes that have central roles in fatty acid and cholesterol metabolism, cell growth and nervous system development indicating possible pathways for adverse metabolic disturbances of VLBW adults.

To intervene or to wait? Pelvic floor dysfunction after a prolonged second stage of labor in primiparous women

Sandra Bergendahl , *Anna Sandström, Hongwei Zhao, Jonathan Snowden, Sophia Brismar Wendel*

Abstract text

Objective

To investigate the effect of vacuum extraction (VE) or cesarean section (CS) as compared to expectant management on pelvic floor dysfunction (PFD) one to two years postpartum in primiparous women with a prolonged second stage of labor.

Methods

A population-based questionnaire and cohort study in Stockholm Region, Sweden, including 1302 primiparous women with a second stage of labor ≥3 h, who gave birth between Dec 1st, 2017 and Nov 30th, 2018. Maternal, neonatal and childbirth characteristics and outcomes were retrieved from computerized medical records. The one-year follow-up questionnaire from the national Perineal Laceration Register, covering symptoms of urinary and anal incontinence, and pelvic organ prolapse, was sent 12-24 months after childbirth. Exposure was VE or CS intervention between 3-4 h or 4-5 h of second stage, compared to expectant management. Primary outcome was a composite outcome of PFD. The risk of PFD was calculated using Poisson regression with robust variance estimation, presented as crude and adjusted relative risks (aRR) with 95% confidence intervals (CI). The possible mediating effect of obstetric anal sphincter injury (OASIS) on PFD was further investigated.

Results

In total, 35.1% of women reported PFD, ranging from 12.5% in women with CS at 3-4 h and 45.9% in women with VE at 3-4 h. Compared to expectant management, the aRR for PFD was increased in VE at 3-4 h (1.33, 95% CI 1.06-1.65) and 4-5 h (1.34, 95% CI 1.05-1.70), but unaffected in CS. The increased risk after VE was not mediated by OASIS.

Conclusion

Symptoms of PFD was common after a first delivery with a prolonged second stage. PFD was increased after VE but unaffected by CS compared to expectant management. If a spontaneous vaginal delivery seems possible, allowing an extended duration of the prolonged second stage does not increase the risk of PFD.

Trends in caesarean section rates in Europe from 2015-2019 using Robson's Ten-Group Classification System: A Euro-Peristat study

Melissa Amyx , ***Marianne PHILIBERT***, *Sophie Alexander, Serena Donati, Mélanie Durox, Alex Farr, Maria Fernandez Elorriaga, Günther Heller, Theopisti Kyprianou, Ewa Mierzejewska, Alexander Smarason, Vlad Tica, Ivan Verdenik, Irisa Zile-Velika, Jennifer Zeitlin*

Abstract text

Objectives: To assess changes in caesarean section (CS) in Europe from 2015-2019 and utilize the Robson Ten Group Classification System to evaluate the contribution of different obstetric populations to overall CS rates and trends

Design: Observational study utilizing routine birth registry data from Euro-Peristat network (all live and still births ≥22 weeks gestational age, from 2015 to 2019) in 28 European countries

Methods: Using a federated model, individual-level data from routine sources in each country were formatted to common data model and transformed into anonymous, aggregate data. Comparison of yearly CS rates, Robson group-specific relative size, CS rate, relative and absolute contribution to overall CS rate.

Results: Among the 28 European countries, CS rates (2015: 16.0-55.9%; 2019: 16.0-52.2%) and trends varied (-3.7-+4.7%; 9 countries decreasing, 7 stables [≤±0.2], 12 increasing). Using the Robson Classification (17 countries), in most countries, labour induction increased (Groups 2a, 4a), while multiple pregnancies (Group 8) decreased. In countries with decreasing overall CS rates, CS tended to decrease in most Robson groups, while in countries with increasing overall CS rates, CS tended to increase in most Robson groups. In countries with the greatest increase in CS rates (>1%), absolute contributions of Groups 1 (nulliparous term cephalic singletons, spontaneous labour), 2a and 4a, 2b and 4b (prelabour CS), and 10 (preterm cephalic singletons) to overall CS tended to increase.

Conclusions: Analysis of the Robson Classification shows varying CS trends and rates across Europe. Comparisons between European countries, particularly those with divergent trends, could provide insight into strategies to reduce CS without indication.

Trends in diabetes in pregnancy in Iceland during 1997-2020

Jamie Ontiveros , *Jóhanna Gunnarsdóttir, Jóhanna Jakobsdóttir, Fredrik Ahlsson, Kristjana Einarsdóttir*

Abstract text
Introduction

The prevalence of diabetes in pregnancy has been increasing globally and has been associated with rising levels of obesity, advanced maternal age, and changes to screening and diagnostic guidelines. The aim of this study was to provide an overall analysis of the trends in diabetes in pregnancy among singleton pregnancies in Iceland according to diabetes type.

Methods

This population-based cohort study used registry-based data from the Icelandic Medical Birth Register to capture the prevalence of type-1, type-2, and gestational diabetes among singleton pregnancies in Iceland from 1997-2020. We used Poisson regression analysis to estimate prevalence ratios (PR) with 95% confidence intervals (CI) for each diabetes type by 4-year time periods, adjusted for confounders.

Results

Our preliminary analysis indicated increasing trends for all three types of diabetes in pregnancy during the study period, with a marked increase seen in gestational diabetes in 2017-2020 (PR=22.90, CI=18.76–27.94) when compared to 1997-2000. Maternal age per year was significantly associated with gestational diabetes and type-2 diabetes, (PR=1.08, CI=1.07–1.08) and (PR=1.09, CI=1.06–1.13) respectively. Further analysis of the effect of maternal age and BMI on the increasing trends in diabetes in pregnancy will be presented at the conference.

Conclusion

The preliminary study indicated increasing trends in diabetes in pregnancy in Iceland for each diabetes type, with a marked increase in gestational diabetes. A more detailed analysis of the factors associated with the increasing trends will be presented at the conference.

Trial of labor outcomes after knotless barbed vs. conventional suture for closure of the uterine incision at cesarean Delivery

Michal Novoselsky Persky , ***Misgav Rottenstreich***

Abstract text

Objective: To evaluate the effect of knotless barbed suture use for closure of the uterine incision at cesarean delivery on maternal and neonatal outcomes at the subsequent trial of labor.

Methods: A multicenter retrospective cohort study of women with singleton pregnancies who underwent their first trial of labor after cesarean of delivery between 2005 and 2021. Trial of labor outcomes was compared between parturients who had had knotless barbed sutures vs. conventional sutures for uterine incision closure in their primary cesarean delivery. The primary outcome of this study was a trial of labor failure. Secondary outcomes included adverse maternal and neonatal outcomes.

Results: During the study period, 5,087 women underwent a trial of labor and met inclusion and exclusion criteria, of whom 174 (3.4%) had a prior use of knotless barbed sutures and 4913 (96.6%) had conventional sutures. In univariate analysis, there were no significant differences in the trial of labor failure, uterine scar rupture, or dehiscence rates. This was confirmed on multivariate analyses for the failure of the trial of labor. Comparable composite maternal and neonatal outcomes were found.

Conclusion**:** Knotless barbed suture use for closure of the uterine incision at cesarean delivery is associated with a comparable vaginal birth rate as well as maternal and neonatal outcomes in the subsequent trial of labor.

Unravelling the Proteomic Signature of Breastfeeding and Lactation

Linda Repetto , *Solène Cadiou, Maeregu Woldeyes Arisido, Claudia Giambartolomei, Emanuele Di Angelantonio, Luisa Zuccolo*

Abstract text

Rationale: Most infants are not breastfed according to WHO recommendations, despite the majority of women initiating breastfeeding at birth. Individual determinants of successful breastfeeding and lactation are ill-characterised and their mechanisms largely unclear. Proteomic signals have been widely implicated in many aspects of reproduction and fertility, but not explored in relation to breastfeeding. Uncovering which proteins are predictive of past lactation success could shed light on the molecular mechanisms of this complex phenotype.

Aim: To identify proteomic signatures indicative of breastfeeding and lactation success in a South Asian population-based cohort of women, through epidemiological and bioinformatic analyses.

Methods: We explore the phenotypic association between a comprehensive panel (SomaLogic) of 7,000 proteins measured in 5,000 women from a South Asian cohort and their breastfeeding history. We create multivariable linear models adjusted for technical, environmental and maternal confounders, and corrected for multiple testing. The association of identified breastfeeding-predictive proteins with a panel of socioeconomic and cardiometabolic variables is then tested in men and non-breastfeeding women from the same cohort as negative controls. Next, we further explore the biological roles and associated pathways of the identified proteins. Specifically, we explore the functions of the identified proteins via functional enrichment and by interrogating publicly available datasets on the association of those proteins with lactation-relevant genetic variants in oxytocin and prolactin encoding genes.

Conclusion: The insights gained from this study have the potential to enhance our understanding of biological mechanisms governing breastfeeding and lactation and their implications for maternal and infant health, ultimately guiding the development of strategies to improve breastfeeding success.

Use of oral misoprostol improve women satisfaction after prostaglandin-induced cervical ripening: A comparative study with standardized questionnaire

Mathilde Lepelletier , ***Aude Girault****, Marie Provenzano, Quentin Lojou, François Goffinet, Camille Le Ray*

Abstract text

Objective: Induction of labor is often associated with negative experience. No cervical ripening method has shown to be superior in terms of effectiveness. However, limited study explore women satisfaction. The aim of our study was to assess women satisfaction comparing intravaginal dinoprostone and oral misoprostol.

Method: A prospective study was conducted including all patients with a Bishop score ≤3. We compared two-month inclusion periods (period 1: intra vaginal dinoprostone slow release device / period 2: oral misoprostol). 165 patients were included, 81 in the dinoprostone group and 84 in the misoprostol group. Primary outcome was women satisfaction for induction of labor using the self-reported standardized and validated EXIT questionnaire (72 % fulfilled). Secondary outcomes included efficacy, safety, obstetrical and neonatal outcomes.

Results: Patients induced with misoprostol reported higher levels of satisfaction, especially less discomfort compared to those induced with dinoprostone (mean discomfort score 2.26 ± 0.98 versus 2.80 ± 0,85, p<0,01). Adverse effects were less often reported in the misoprostol group (20.2% versus 48.1%, p<0.01). Women delivered faster in the misoprostol group; 39.3% patients gave birth within 24 hours following cervical ripening versus 18.5%, p<0.01. There were no differences in mode of delivery obstetric and neonatal outcomes.

Conclusion: For women needing cervical ripening, oral misoprostol has demonstrated to be a non-invasive, effective, and safe method for labor induction, with higher levels of satisfaction consecutive to less discomfort in comparison with intra vaginal dinoprostone slow release device.

Use of specialized healtcare services across gestational ages for individuals aged 0 to 12 years: a population-based study

Sanna Beckstrøm , *Sara Marie Nilsen, Kari Risnes, Kristine Pape*

Abstract text
Background: The survival rate in recent decades for preterm born children is increasing together with decrease in major sequelae following improved quality of neonatal care. Still, being born preterm is associated with increased health impairment. This also applies to those born moderate to late preterm. This study will include public involvement and aims to advance prior knowledge by exploring health outcomes in childhood in updated data across the range of gestational ages.

Methods: Epidemiological data from three registers, the Medical Birth Registry of Norway, the Norwegian Patient Registry and Statistics Norway is used in our study. The population includes all live born individuals between 2008 and 2022. Outcomes of interest were identified with public involvement, including parents of preterm children, public health nurses and hospital professionals working with preterm children. Regression analysis will be used to compare healthcare use at different ages in childhood, across gestational ages. In addition, sibling comparison will be performed to account for unmeasured familial confounding.

Results: Preliminary discussions with public involvement have identified outcomes of interests as: healthcare use in transitional stages such as between kindergarten and school, regulation- and relational behavior, nutritional diseases, and common childhood diseases such as respiratory tract infections. Further analysis of outcomes will be performed in June-23.

Conclusion: Updated health related data across the range of gestational ages will be of importance to involved stakeholders. Recruiters from public involvement will aid results reaching the right forums.

Visual function in Norwegian children aged 5-13 years with prenatal exposure to opioid maintenance therapy (OMT): a case-control study

Kathinka Aslaksen , *Gro Horgen Vikesdal, Marit Torbergsen Voie, Jon Skranes, Olav Haugen*

Abstract text

Visual function in Norwegian children aged 5-13 years with prenatal exposure to opioid maintenance therapy (OMT): a case-control study

Introduction: Previous studies on visual outcomes in children prenatally exposed to opioid maintenance therapy (OMT) have reported increased frequency of strabismus and other oculomotor problems as well as poorer visual acuity. The aim of this study was to compare various aspects of long-term visual function in a large group of OMT-exposed children with a control group.

Methods: In a cross-sectional case-control study, 63 children aged 5-13 years with prenatal OMT-exposure were compared with 63 age-and gender matched, non-exposed controls regarding important visual parameters, such as visual acuity, orthoptic status, refractive state, colour vision, and visual field.

Results: The OMT-exposed children had significantly poorer visual acuity, both for the best eye, the worst eye and binocularly. Two children had mild visual impairment. Manifest strabismus was more frequent in the OMT-group, 30%, versus 4.8% in the control group. Manifest nystagmus was present in ten (16%) of the exposed children compared to one among the non-exposed children. The accommodative amplitude was decreased in the OMT-group compared to the controls.

The methadone-exposed children had poorer visual acuity, increased frequency of strabismus and a higher percentage of nystagmus, hypermetropia and astigmatism compared to the buprenorphine-exposed children.

Discussion: The findings in our study suggest a direct opioid-related adverse effect on the fetal developing visual system, causing a high risk of long-term abnormal visual outcomes. The in utero OMT-exposed children had a significantly higher prevalence of strabismus and nystagmus, as well as lower visual acuity and accommodation amplitude than the controls.

Buprenorphine exposure was clearly associated with more favorable results than methadone exposure on most visual outcome measures.

What do we register? The validity of prenatal AUDIT screening for alcohol disorders- a Swedish register study

Susanne Hesselman , *Joline Asp, Ulrika Pellas, Susanne Lager, Anna Wikman*

Abstract text
Background: Nordic countries have a long tradition of using population-based data for monitoring healthcare and research. The objective of this study was to assess the external validity of the Alcohol Use Disorders Identification Test (AUDIT), recorded at antenatal care, as an indicator for alcohol-addiction disorders.
Methods: Prenatal AUDIT screening points in the Swedish Pregnancy register of 739 735 pregnancies were linked to national health databases. The AUDIT score was dichotomized into <6 points (low-risk use) and ≥ 6 points (hazardous use). Alcohol disorders were defined by a diagnostic code or drugs dispensed for alcohol dependence in national health registers. The diagnostic accuracy of an AUDIT score of ≥6 points for alcohol-addiction disorders were calculated. Women with mismatched information in the register were characterized, and compared by multinominal logistic regression with odds ratio (OR) with 95 % CI to women with matched information.
Results: Alcohol disorder was recorded in 3.1%, and among 3.5% of pregnancies an AUDIT ≥6 points was registered. The diagnostic accuracy of the AUDIT ≥6 points for detection of an alcohol disorder the year prior to pregnancy was 95.7%, with a positive likelihood ratio of 8.03 (95% CI 7.5,8.6). The sensitivity was 33.0%. Being of younger age, nulliparous, with low education, and of Swedish origin increased the likelihood of being misclassified with the AUDIT. A medical history of neuropsychiatric disorders was associated with being false negative classified, OR 10.39 (95% CI 9.89,10.90).
Conclusions: The accuracy of AUDIT in screening for alcohol disorders in a low-risk use population was high, but only identified one third of women with alcohol related disorders when using a cut-off of six points.

Women’s pre-pregnancy care: Understanding how women interact with General Practice services prior to becoming pregnant using routine health data

Yangmei Li , *Jennifer Kurinczuk, Fiona Alderdice, Maria Quigley, Oliver Rivero-Arias, Julia Sanders, Sara Kenyon, Dimitrios Siassakos, Claire Carson*

Abstract text

Background

Optimising health prior to pregnancy benefits women at the time, throughout the pregnancy and the life course of mother and baby. In the UK pre-pregnancy care tends to be provided through primary care with the onus on women to seek services. We aimed to describe women’s engagement with General Practice (GP) services including pre-pregnancy care received and explore whether women with pre-existing risk factors receive targeted care.

Methods

Clinical Practice Research Datalink (CPRD) GOLD data were used to identify women aged 18-48yrs on 01/01/2017 registered for 12 months with an English GP with linked hospital data. Women’s demographic characteristics, lifestyle factors and pre-existing conditions were described. Diagnoses and prescriptions codes for health conditions and pre-pregnancy care were used to describe engagement with GP services. CPRD Pregnancy Register and hospital data were used to identify subsequent pregnancies and describe pre-pregnancy care in the year prior to conception. Women with known risk factors were assessed for evidence of targeted provision.

Results

Of >200,000 women included 20,884 became pregnant in 2017-2018. 6.6% had pre-pregnancy care in the year prior to pregnancy; 35.6% had general health promotion including advice on nutrition, smoking cessation, weight, alcohol and contraception. While women with pre-existing conditions generally received higher levels of general health promotion (43.3%~77.4% for various risk groups) than the overall population, the levels of pre-pregnancy care were similar (6.8%~11.8%).

Conclusions

Pre-pregnancy care is rarely recorded in primary care in England, reflecting low levels of consultations for pregnancy planning. Most women do not seek support from GP services until after conception. This represents a missed opportunity for promoting pre-pregnancy and subsequent health, particularly in those with recognised risk factors for poor pregnancy, perinatal and longer-term outcomes.

Oral

Cardiovascular disease risk factors and infertility: Multivariable and one-sample Mendelian randomization analyses in the Trøndelag Health Study

Karoline H. Skåra , *Álvaro Hernáez, Øyvind Næss, Abigail Fraser, Deborah A. Lawlor, Stephen Burgess, Ben Brumpton, Maria C. Magnus*

Abstract text
Several cardiovascular disease (CVD) risk factors are associated with increased risk of infertility, but the causal nature of the relationships remain unclear. To study these relationships, we used data from the Trøndelag Health Study (HUNT) in Norway, including three survey collections from 1995-1997 (HUNT2), 2006-2008 (HUNT3) and 2017-2019 (HUNT4). We included 26,816 women and 15,533 men participating in HUNT with infornation on their fertility status, genotype, and at least one CVD risk factor of interest measured within the age of 45 years. The CVD risk factors included body mass index (BMI), systolic and diastolic blood pressure, lipid profile, and smoking behaviours. Our outcome measure was self-reported infertility, defined as having tried to conceive for more than 12 months without getting pregnant or the use of assisted reproductive technology to get pregnant.

Infertility was reported by 17% of women and 16% of men. In multivariable analyses in women, we found positive associations between BMI, triglyceride levels, lifetime smoking index, smoking intensity and smoking initiation with infertility, and an inverse association between high-density lipoprotein cholesterol and infertility. Adjusted odd ratios (ORs) among women ranged from 1.09 (95% confidence interval [CI]: 1.04, 1.14) per standard deviation (SD) increase in triglyceride levels to 1.22 (CI: 1.14, 1.31) in daily smokers compared to non-daily smokers. In multivariable analyses in men, we found no robust associations between any CVD risk factors and infertility. In one-sample Mendelian randomization (MR) analyses, we only observed evidence of a relationship between smoking initiation and infertility among women (OR: 1.13; CI: 1.01, 1.25).

In conclusion, we observed relationships between several CVD risk factors with infertility in women, although only the relationship between smoking initiation and infertility was replicated in MR analyses. Larger MR studies are warranted to confirm our findings.

Fit and precision of growth references to identify births with negative outcome in Iceland

Áslaug Haraldsdóttir , *Linda Lindström, Alexander Kristinn Smárason, Hulda Hjartardóttir, Thor Aspelund, Jóhanna Gunnarsdóttir*

Abstract text

Objective

To find what proportion of Icelandic infants are classified as abnormally small or large at birth by different growth references and compare their precision in identifying stillbirths and Apgar score under 7 at 5 minutes.

Methods

In this population based cohort study of all singleton births between 2000 and 2020 in Iceland, three references for estimated fetal weight were used to calculate percentiles for birth weight by gestational age; the new Swedish, Hadlock's, and INTERGROWTH-21st fetal growth reference. The fit of the reference was assessed by calculating the proportion of the population on 5 centile intervals. Also, the proportion classified as small for gestational age (SGA, <10th percentile) and large for gestational age (LGA, >90th percentile) was calculated and stratified by maternal citizenship. Logistic regression will be used to calculate the association between SGA and stillbirth and low Apgar score. Number and rates of events, sensitivity, and false positive rate of the 10th percentile threshold will be calculated.

Results

Birth weight for gestational age percentiles were evenly distributed when the Swedish reference was used and ranged from 4.4% to 6.1% for each 5 centile interval, whereas the range was 1.8% to 8.8% for Hadlock's and 0.8% to 29.5% for INTERGROWTH-21st references. The proportion of the population classified as SGA by the new Swedish, Hadlock's and INTERGROWTH-21st references was 10.7%, 4.2%, and 1.7%, and as LGA was 11.0%, 15.7%, and 41.6%, respectively. Migrant women more often gave birth to infants classified as SGA (16.3%, 6.6%, and 2.6%, respectively) and less often as LGA (6.7%, 9.7%, and 29.9%, respectively). Calculations comparing the precision of the references are underway.

Conclusion

The Swedish growth reference classified appropriate proportion as SGA and LGA, but the other references did not. The performance of the references to detect stillbirths and low Apgar score will be presented in the fall.

Racial/ethnic Disparity in Severe Maternal Morbidity Following ART Conception

Jenna Victory , *Sid John, Jeffrey Bone, Li QIng Wang, Hamideh Bayrampour, K.S. Joseph, Sarka Lisonkova*

Abstract text

Background. Assisted reproductive technology (ART) that includes egg and sperm manipulation during conception is associated with adverse birth outcomes and racial/ethnic disparity in these outcomes is larger in women with ART. Racial/ethnic disparity in severe maternal morbidity (SMM) in women with ART is understudied.

Objective. To compare SMM in women with spontaneous vs ART conception in various racial/ethnic groups.

Methods. We included all singleton live births and stillbirths in the United States, 2016-2017; data were obtained from live birth and fetal death certificates. Rates of SMM (including eclampsia, uterine rupture and/or intrapartum hysterectomy, blood transfusion, and ICU admission) were contrasted between women with spontaneous vs ART conception, stratified by race/ethnicity group: non-Hispanic White (NW), non-Hispanic Black (NB), American Indian/Alaskan Native (AIAN), Asian/Pacific Islander (API), and Hispanic. We used logistic regression to adjust for potential confounders and to assess possible effect modification.

Results. Among 7,505,189 women, 53% were NW; 15% NB; 1% AIAN, 7% API; and 24% were Hispanic. ART was used by 48,584 (0.7%) women and the rate of SMM was 1.6% in ART vs 0.7% in the spontaneous conception group. Odds of SMM was significantly increased in women with ART (adjusted odds ratio [AOR] 2.1; 95% confidence interval [CI] 2.0-2.3). AORs for SMM and its components comparing ART to non-ART conceptions were broadly similar between race/ethnicity groups. The only exception was rupture/intrapartum hysterectomy, where ART had a stronger association in Hispanic (AOR 6.1, CI: 3.7-10.3) than in NW women (AOR 3.2; CI 2.5-3.9).

Conclusion. Women who use ART have 2-fold higher odds of SMM, and this increase is similar across all race/ethnicity groups. Hispanic women were found to have elevated ART-associated odds of uterine rupture and/or intrapartum hysterectomy compared to non-Hispanic White women, which warrants further investigation.

The association between change in estimated fetal weight centile at 20-weeks and birthweight centile with adverse pregnancy and perinatal outcomes

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Abstract text

BACKGROUND Adverse pregnancy outcomes have a devastating impact on women, families and society. One contributing factor to these poor outcomes is placental insufficiency resulting in reduced fetal growth velocity. The aim of this study was to explore whether change between estimated fetal weight centile at 20-weeks and birthweight centile is associated with adverse pregnancy outcomes.

METHODS: We used routinely collected data on up to 57,770 singleton pregnancies between 2011-2021 in North Bristol NHS Trust that had at least one ultrasound measure in the 2nd trimester and birthweight. We generated estimated fetal weight centiles for gestational age (mean 20.1 weeks (SD=1.8)) calculated from the Hadlock method and then compared them to their observed birthweight Hadlock centile. We developed a continuous variable of this difference between 20 weeks and birth centile in 10 centile units and compared both negative (reduction in weight centile) and positive (increase in weight centile) with no change (defined as +/- 10 centiles of their expected birthweight). Multivariable logistic regression was used to estimate the association between this centile difference and outcomes including emergency caesarean and stillbirth, controlling for their starting centile at ~20 weeks, maternal age, body mass index, and parity.

RESULTS: When compared with babies who were within +/- 10 centiles of their expected birthweight, odds ratios (OR) (95%CI) for emergency caesarean were 1.09 (1.07 to 1.11) per 10 centile reduction and 1.01 (0.99 to 1.02) per 10 centile increase. In comparison, for stillbirth, the OR for stillbirth was 1.67 (1.48 to 1.90) per 10 centile reduction and 0.82 (0.74 to 0.90) per 10 centile increase.

CONCLUSION: Our findings suggest that a drop or gain of 10-20 centiles between the 20-week scan and birth are related to adverse pregnancy outcomes. This work might begin to help inform guidance about the use of fetal growth scans and adverse pregnancy outcomes.

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