Prenatal prescription corticosteroids and offspring diabetes: A national cohort study

Naomi H Greene,1* Lars H Pedersen,2,3 Simin Liu1,4 and Jorn Olsen1,3

1UCLA School of Public Health, Department of Epidemiology, Los Angeles, CA, USA, 2Department of Obstetrics and Gynecology, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark, 3Department of Public Health, Epidemiology Section, Aarhus University, Aarhus, Denmark and 4UCLA School of Medicine, Department of Obstetrics and Gynecology, Los Angeles, CA, USA

*Corresponding author. Department of Epidemiology, UCLA School of Public Health, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772, USA. E-mail: ngreene@ucla.edu

Accepted 29 November 2012

Background Foetal exposure to excess glucocorticoids has been associated with altered development of multiple foetal systems that may persist after birth and lead to an increased risk of diseases. The purpose of this study is to investigate the role of prenatal prescription corticosteroids for the development of diabetes among offspring.

Methods We conducted a national birth cohort study of children from singleton pregnancies born in Denmark between 1 January 1997 and 31 December 2004 with follow-up through 31 December 2008. Four Danish nationwide administrative registries were linked to identify specific exposures, outcomes and covariates of interest among 505,386 children from singleton pregnancies born alive to 360,484 women. We calculated hazard ratios (HRs) comparing diabetes incidence (separately for type 1 and type 2 diabetes/elevated blood glucose) in children exposed vs unexposed to prescription corticosteroids prenatally.

Results Prenatal exposure to prescription corticosteroids was associated with a small increase in offspring type 1 diabetes incidence rate [HR = 1.20, 95% confidence limits (CL) = 0.94, 1.53] and with a 51% increase in type 2 diabetes/elevated blood glucose hazard ratio when comparing children exposed prenatally to prescription corticosteroids with those unexposed (HR = 1.51, 95% CL = 0.69, 3.31). The data were consistent with a monotonic increase in overall diabetes hazard ratios with increasing strength of the corticosteroid.

Conclusions There may be a relation between prenatal prescription corticosteroid use and childhood diabetes but further studies with more extensive assessment of foetal exposures are warranted. If prenatal prescription corticosteroids contribute to the development of offspring diabetes, the public health implications could be substantial.

Keywords Prenatal, corticosteroids, childhood diabetes

Introduction Foetal exposure to excessive glucocorticoids has been associated with disturbances of insulin-glucose homeostasis,1 the hypothalamic-pituitary axis (HPA),1,2 and the immune system3 resulting in both central and peripheral alterations that are thought to persist after birth and may lead to an increased risk of chronic diseases such as diabetes mellitus.4 In animal studies,
rats prenatally exposed to synthetic glucocorticoids demonstrate altered responses to glucose load, insulin insensitivity and an enhanced sensitivity to glucocorticoid activity in the liver and adipose tissue (reviewed) and ‘blunted’ HPA activity in offspring. Further, the relationship with altered glucose metabolism/insulin insensitivity is independent of intrauterine growth restriction in sheep.

Diabetes is a problem of increasing magnitude among children around the world. In Danish children, the incidence of type 1 diabetes is estimated to be rising at an annual rate of 1.2% with the most rapid increases seen in the youngest age groups and higher overall annual incidence increases reported for Europe. Changes in type 2 diabetes incidence among European children are less known however the proportion of newly diagnosed diabetes cases that are of type 2 is increasing (about 25% of newly diagnosed diabetes cases in American youth in 2002–03 were type 2). In those aged 12 years and older, as much as 40% of prevalent diabetes is undiagnosed in the USA and, as many young patients with diabetes have no symptoms in childhood the proportion of undiagnosed diabetes among the young is likely to be even higher.

Prescription corticosteroids are used to treat a wide variety of disorders (many autoimmune diseases and asthma) during pregnancy. Corticosteroid medications are prescribed to between 1% and 7% of pregnant women, depending on the preparation and underlying indication. Even so, almost without exception these medications have been classified as Category C pharmaceuticals by the United States Food and Drug Administration, underscoring the suspected risk or lack of knowledge. Importantly, the long-term consequences for the prenatally exposed child remain uncertain, among which an increased susceptibility for diabetes mellitus should be considered. We therefore investigated the association between prenatal exposure to prescription corticosteroids and offspring diabetes mellitus in a large national cohort study.

Research design and methods
The study incorporated data from four Danish nationwide administrative registries: the National Medical Birth Registry (hereafter Birth Registry), the Register of Medicinal Product Statistics (hereafter Prescriptions Database), the Fertility Database and the National Hospital Discharge Register (hereafter Hospital Registry), linking the extracted information on pregnant women’s redemption of prescription corticosteroids [Anatomic Therapeutic Classification (ATC) groups H02A and H02B(systemic), R03B (inhaled), and R01A,D07A, D07B, D07C, D07X, S01B, S01C, S02B, S02C (topical)]. We constructed a dichotomous variable to describe prenatal exposure and classified the exposure into three separate groups according to the route of administration (systemic, inhaled or topical) to model increasing strengths of corticosteroid exposure.

Children were considered exposed if the mother redeemed one or more corticosteroid prescriptions from start of gestation to birth. The start of gestation was calculated by subtracting the gestational age at birth in days from the child’s date of birth. When gestational age at birth was not available for a specific child or when it was greater than 315 days (< 0.1%), we subtracted the mean gestational age at birth (280 days) of the population from his or her date of birth.

The Fertility Database contains annually updated information on occupation, income, education, social benefits and housing circumstances on all men aged 12–64 and women aged 12–49 years. We linked children to their parents in the Fertility Database and extracted parental combined income in the year of the child’s birth. If income was not available for the child’s year of birth, we used income from the year following the birth.

The Hospital Registry records data on all hospital admissions and, since 1995, also includes information on outpatient and emergency room events coded according to the International Classification of Diseases (ICD-10) codes. We took hospital discharge codes for type 1 (E10) and type 2 (E11) diabetes. As some children with type 2 diabetes are undiagnosed, we included children with elevated blood glucose levels (ICD-10 code R73) in the group with type 2 diabetes to capture at least a proportion of the undiagnosed. We supplemented our outcome status assignment using child redemptions of insulin and/or antidiabetic drugs from the Prescriptions Database.

Children in the cohort were followed from birth until they received a hospital discharge code of type 1 diabetes or type 2 diabetes/elevated blood glucose, or redeemed a prescription for insulin/antidiabetic drugs, or died or emigrated or when follow-up ended (31 December 2008). Follow-up ended at
diabetes diagnosis or end of the study period for 685 children who emigrated and 2301 children that died.

Guided by the literature on the potential aetiologies of childhood diabetes, we constructed a model using directed acyclic graphs (available on request)\(^2\) to identify potential sources of existing bias and to avoid introducing bias through inappropriate adjustment (i.e., controlling for potential intermediates).

Women hospitalized between 24 and 34 weeks of gestation for preterm labour/threatened preterm delivery may be given at least one course of systemic glucocorticoid\(^2\) and the conditions underlying preterm delivery (or the threat of it) may be associated with diabetes other than through steroid exposure. We therefore included a dichotomous indicator for any hospital admission for the following ICD-10 codes between 24 and 34 weeks of gestation: O42 for premature rupture of membranes, O60 for preterm labour, O14 and O15 for pre-eclampsia and eclampsia, O43–O45 for various placental disorders that may cause early delivery, O47 for threatened preterm labour and O34 for shortened cervix.

We estimated hazard ratios (HRs) comparing children exposed vs unexposed to prenatal prescription corticosteroids using a Cox proportional hazards model. Time on study was defined by the time in months from birth until a diagnosis of diabetes, death, emigration or end of follow-up, as described above. Adjustment was made for the child’s sex, maternal age at birth of the child (<20 years, 20–24, 25–29, 30–34, 35–39, ≥40 years), maternal smoking during pregnancy (ever/never), marital status (had a partner vs no partner), income and calendar time (year of child’s birth). In addition, we combined information from the Hospital Registry and the Prescriptions Database to construct a child-specific parental diabetes history. Proportionality of the hazards was evaluated by examining product terms between time and each covariate in the model. Statistical analyses were carried out using SAS (version 9.2, SAS, Cary, NC).

Additional analyses were conducted to test the sensitivity of our main results to some of the model assumptions. Our proxy for foetal exposure to prescription corticosteroids was the redemption of any corticosteroid prescribed to pregnant women. Compliance in use of prescribed drugs is known to be less than perfect and some of the redeemed drugs were probably never taken. We therefore repeated the main analyses defining exposure as having redeemed >1 prescription within the defined exposure window under the assumption that >1 redemption increased the likelihood the drug was used. To account for potential genetic or environmental factors as well as maternal behaviour change between pregnancies, all of the above analyses were repeated for only the firstborn child (between 1997 and 2004) of each of the 360 484 women. Finally, we carried out our main analyses restricted to children born at term (≥259 days of gestation).

As the information we extracted from the Danish administrative registries had already been collected and was made anonymous to investigators, the UCLA Office for the Protection of Human Research Subjects determined that our study did not require IRB Approval or Exemption. The study was approved by the Danish Data Inspectorate and by Statistics Denmark.

## Results

Of the 505 386 children from live-born singleton pregnancies by 360 484 mothers during the study period, 232 056 (46%) were the only child, 226 526 (45%) had one sibling and 41 922 (8%) had two siblings, leaving about 1% who had between 3 and 6 siblings. In this birth cohort, 37 018 (7%) women were aged 35 years or older at their birth vs 17% of the unexposed). Exposure groups were well balanced in terms of median income, parental diabetes history, smoking status, delivery of a small-for-gestational age or preterm infant. The difference in preterm birth was more marked when considering corticosteroids by delivery mechanism in that 12% of those exposed to systemic prescription corticosteroids were born preterm or very preterm as opposed to 6% in those exposed to inhaled corticosteroids and 5% in those exposed to topical corticosteroids as well as in those unexposed to any steroids (results not shown).

During 4 020 245 person-years of follow-up (1997–2008), we identified 785 type 1 diabetes cases, 30 type 2 diabetes cases and 36 children with elevated blood glucose levels (851 incident cases with an overall incidence rate of 21.2/100 000 person-years). The adjusted type 1 diabetes hazard ratio for prenatal exposure to any type of prescription corticosteroid preparation was 1.20 (95% hazard limits of 0.94, 1.53) and, for type 2 diabetes /elevated blood glucose, the adjusted hazard ratio was 1.51 (95% limits of 0.69, 1.31).

These associations persisted in multiple sensitivity analyses (Table 3). When defining exposure as more than 1 prescription redemption (Model 1), there was more than double the hazard ratio when comparing exposed and unexposed children with respect to both diabetes types (type 1 diabetes: HR = 2.17, 95% limits 0.69, 8.69; type 2 diabetes/elevated blood glucose: HR = 2.89, 95% limits 0.91, 9.24). When including only the firstborn child (Model 2), the point estimate for type 1 diabetes increased slightly whereas the point estimate for type 2 diabetes/elevated blood glucose dropped slightly; however, the 95% limits...
remained essentially unchanged. When restricting to only those children born at term (Model 3), the point estimates moved slightly but the 95% limits were nearly unchanged.

Table 1 Selected characteristics of mothers and children from Danish singleton live births (1996–2004) (n = 505,386), 1997–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed to prenatal prescription corticosteroids</th>
<th>Unexposed to prenatal prescription corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>358 (1%)</td>
<td>11,550 (3%)</td>
</tr>
<tr>
<td>20–24</td>
<td>4,068 (11%)</td>
<td>52,025 (11%)</td>
</tr>
<tr>
<td>25–29</td>
<td>12,465 (34%)</td>
<td>157,105 (34%)</td>
</tr>
<tr>
<td>30–34</td>
<td>13,264 (36%)</td>
<td>166,963 (36%)</td>
</tr>
<tr>
<td>35–39</td>
<td>5,841 (16%)</td>
<td>69,160 (15%)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>10,22 (3%)</td>
<td>11,565 (3%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.1 (4.8)</td>
<td>30.0 (4.8)</td>
</tr>
<tr>
<td>Income (US$)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>Median (IQR) $45,660 ($22,470)</td>
<td>$45,990 ($23,233)</td>
</tr>
<tr>
<td>Marital status&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Had partner 19,988 (54%)</td>
<td>24,741 (55%)</td>
</tr>
<tr>
<td>No partner</td>
<td>16,992 (46%)</td>
<td>20,357 (45%)</td>
</tr>
<tr>
<td>Child’s sex&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Male 18,902 (51%)</td>
<td>240,239 (51%)</td>
</tr>
<tr>
<td></td>
<td>Female 18,116 (49%)</td>
<td>227,876 (49%)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>Yes 733 (2%)</td>
<td>7683 (2%)</td>
</tr>
<tr>
<td></td>
<td>No 36,285 (98%)</td>
<td>460,685 (98%)</td>
</tr>
<tr>
<td>Smoking&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Former/current smoker 9,285 (25%)</td>
<td>114,001 (25%)</td>
</tr>
<tr>
<td>Did not smoke</td>
<td>27,589 (75%)</td>
<td>351,487 (76%)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>&lt;10th percentile 446 (1%)</td>
<td>5474 (1%)</td>
</tr>
<tr>
<td></td>
<td>≥10th percentile 36,396 (99%)</td>
<td>459,718 (99%)</td>
</tr>
<tr>
<td>Preterm birth&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Very preterm 616 (2%)</td>
<td>7568 (2%)</td>
</tr>
<tr>
<td></td>
<td>Preterm 1295 (4%)</td>
<td>15,101 (3%)</td>
</tr>
<tr>
<td></td>
<td>Term 34,781 (95%)</td>
<td>441,913 (95%)</td>
</tr>
<tr>
<td>Threat of preterm labour&lt;sup&gt;h&lt;/sup&gt;</td>
<td>821 (2%)</td>
<td>9230 (2%)</td>
</tr>
<tr>
<td>Diabetes in child</td>
<td>T1 DM 71 (&lt;1%)</td>
<td>714 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>T2 DM/AGTT&lt;sup&gt;ib&lt;/sup&gt; 7 (&lt;1%)</td>
<td>59 (&lt;1%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentages may not add to 100% due to rounding.

<sup>b</sup>Missing in 1.1%.

<sup>c</sup>Missing in 3.1%.

<sup>d</sup>Converted at USD/DKK = 0.16935.

<sup>e</sup>Missing in 0.1%.

<sup>f</sup>Dichotomous variable missing in 0.5%.

<sup>g</sup>Very preterm: <241 days, Preterm: 241–258 days, Term: ≥259 days

<sup>h</sup>Admitted to hospital for threat of preterm labour between 24–34 weeks gestation

Under the assumption that the strongest corticosteroid dose would be delivered by systemic prescription corticosteroids, followed by inhaled preparations, with topical corticosteroids being considered the weakest
dose, we performed a trend analysis in increasing diabetes rates (both diabetes types combined due to small numbers in cells when considering types 1 and 2 separately) with increasing strength of dose. Figure 1 illustrates the relationship graphically, when including the unexposed in the analysis and the \( P \)-value for trend was 0.03. When excluding the unexposed group from the trend analysis, now including only children born to mothers with conditions necessitating corticosteroid treatment, the increase in the point estimate for a one-step increase in steroid strength (i.e. the increase in the hazard rate going from inhaled vs topical corticosteroids to systemic vs topical corticosteroids) doubled; however, the \( P \)-value for the trend was 0.14.

**Discussion**

In this Danish cohort of children from singleton pregnancies born 1997–2004 and followed through 2008, we observed a relation between prenatal prescription...
corticosteroid use and childhood diabetes, but these estimates come with uncertainties and could be chance findings. Yet, the associations were stronger for systemic preparations compared with those delivered through inhalation or topically, as might be expected if the associations represent causal relations. In sensitivity analyses with a more restrictive exposure definition (>1 prescription corticosteroid redemption), or in only the firstborn child, or in only those children born at term, the associations persisted albeit with less precision.

The trend illustrated in Figure 1 is central to the interpretation. The most commonly used corticosteroids in the systemic, inhaled and topical groups were prednisolone, budesonide/fluticasone and hydrocortisone butyrate, respectively. Oral prednisolone has between 70% and 100% bioavailability in the maternal circulation (‘high’, Figure 1).24 Depending on the inhalation device, budesonide has high lung deposition properties but perhaps 40–60% may be swallowed instead, allowing about 36% systemic bioavailability of unmetabolized steroid (‘medium’, Figure 1).25,26 The amount of corticosteroid applied topically that reaches the maternal and foetal circulations depends on many factors including dose, surface area treated, number of applications, duration of treatment and the condition of the treated skin.27 We found no specific studies that addressed the quantification of systemic absorption of topical corticosteroids during pregnancy (‘low’, Figure 1). These differences in pharmacokinetics may be used to investigate a potential dose–response pattern or the existence of a potential threshold below which steroids have no effects on the pregnancy.

Owing to a natural barrier in the placenta at the site of maternal–foetal exchange (the type 2 isoform of 11-beta hydroxysteroid dehydrogenase (11βHSD2) which causes active steroid to be converted to an inactive state28), the developing foetus typically has lower levels of circulating glucocorticoids than the mother. However, this protection is not fully in place very early in pregnancy. It is furthermore thought to dissipate later in pregnancy. As the enzymes become saturated, some of the glucocorticoids may cross through in their active form, reaching the foetal circulation intact.29 In addition, some prescription corticosteroids remain wholly or partially unmetabolized by 11βHSD2 and therefore the steroid hormone may pass through to the foetus in its active form. Of the corticosteroids in the present study, a small proportion of systemic prednisolone may pass to the placenta unmetabolized,30 and inhaled budesonide and fluticasone may cross the placenta completely unmetabolized.31 We were unable to find studies that specifically investigated the ability of topically applied hydrocortisone butyrate to cross the human placenta, but hydrocortisone crosses the human placenta to a minor extent, with the majority metabolized by the 11βHSD2.32

Potential sources of confounding must be considered when interpreting these findings. First, maternal stress may exacerbate underlying conditions necessitating corticosteroid usage and also affect risk of offspring diabetes because of high maternal endogenous glucocorticoid levels entering the foetal circulation. A woman’s pre-pregnancy body mass index may represent genetic and environmental influences on offspring diabetes risk and be associated with prenatal prescription corticosteroid usage through its relationship with the underlying conditions or the severity of the condition during pregnancy. We were not able to adjust for these potential confounders due to lack of

---

**Figure 1** Diabetes rate comparing each level of exposure to that in the unexposed. Y-axis is on the natural log scale and data labels are presented on the anti-log scale.
availability of such data in the administrative registries and failure to account for these could have inflated our observed association estimates.

Second, prescription redemption during pregnancy served as our proxy for prenatal exposure to prescription corticosteroids but it may also be a marker for the presence of the underlying disease, constituting a potential source of ‘confounding by indication’ if the underlying disease is a risk factor for diabetes in children.

Third, if exposure to prescription corticosteroids during pregnancy or the disease being treated were associated with a general sense of heightened health concern, then children born to exposed women may have been more closely screened and more likely to be diagnosed with diabetes/prediabetes, potentially resulting in inflated associations. This may have been especially true for the more serious underlying conditions. However, relatively few studies have examined foetal programming by maternal disorders, though recently maternal stress during pregnancy has been investigated in relationship to long-term outcomes in children.33,34 We found no evidence in the literature linking specific conditions requiring perinatal prescription corticosteroids to offspring diabetes.

A unique strength in our study was the ability to use comprehensive nationwide registry data with nearly 100% follow-up. Information in the Drugs Database is entered by the pharmacists whenever a prescription is redeemed, providing some safeguard for the validity of exposure assessment (i.e. eliminated recall bias and produced an accurate record of prescription name, preparation and timing of redemption). We also have almost complete information on all live births from the Birth Registry (i.e. entered by trained midwives). Via linkage to the Fertility Database, we were able to extract accurate information regarding income as the data are taken directly from tax files.

The association between prenatal corticosteroids and diabetes mellitus observed in this cohort is in agreement with findings from controlled animal experiments and observational human studies relating various exposures characterized by elevated maternal glucocorticoid levels (e.g. maternal undernutrition and famine, maternal stress, and synthetic glucocorticoids) to increased risk of chronic diseases in the offspring including diabetes.1–4,35,36 The theoretical foundation for the above-cited studies as well as our current investigation is the Thrifty Phenotype hypothesis as first presented by Hales and Barker.4,37

Further investigations comparing our findings with those where the underlying conditions are treated with non-steroidal medications may be useful. However, such comparisons are problematic for several reasons including lack of available data on use of over-the-counter medications (such as might be used as alternatives to steroids for allergies, psoriasis, rheumatoid arthritis and lupus) and non-equivalence of affected groups (short-acting β2 agonist albuterol is recommended for use in those with only intermittent episodes of asthma, and the recommendation for using the longer-acting β2 agonists is usually in combination with inhaled corticosteroids).

There may be critical windows outside which steroids may not exert the types of effects that could lead to diabetes in the offspring. We were limited in our ability to examine the timing of exposure by the rarity of the exposure and outcome across trimesters. However, the analysis suggested that third trimester exposures, whether adjusted or unadjusted for exposures in the other two trimesters as well as hospitalization for threat of preterm delivery, may be driving the overall positive associations seen in the main analyses (HR for all diabetes = 1.45, 95% hazard limits = 0.97, 2.15; see Supplementary Table S1, available as Supplementary data at IJE online).

Leaving women untreated for conditions requiring steroids during pregnancy may carry a greater risk for their offspring than being treated even if the associations we present are causal. Nonetheless, there is a paucity of research into the long-term effects in offspring of prenatal exposure to glucocorticoids and a potential association between prescription corticosteroids and offspring diabetes may influence prescription patterns. This could be the case for corticosteroids used to mature the foetal lungs in, for example, intrauterine growth restriction, where the optimal dosage and number of repeat injections are still to be determined. Further studies with more extensive assessment of foetal exposures are warranted to examine whether prenatal prescription corticosteroid exposure plays a role in the development of diabetes in the offspring.

**Supplementary Data**

**Supplementary Data** are available at IJE online.

**Funding**

L.H.P. is supported by a Sapera Aude DFF-Postdoctoral grant from the Danish Council for Independent Research.

**Acknowledgements**

N.G. (University of California, Los Angeles) researched data, wrote the manuscript, contributed to the discussion and reviewed/edited the manuscript. L.H.P. (Aarhus University, Aarhus, Denmark) researched data, contributed to the discussion and reviewed/edited the manuscript. S.L. (University of California, Los Angeles) contributed to the discussion and reviewed/edited the manuscript. J.O. (University of California, Los Angeles, Aarhus University, Aarhus
References


