Pregnancy complications and subsequent risk of preterm birth

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Study question What specific conditions and outcomes of a first pregnancy at term predict preterm birth in a subsequent pregnancy?

Methods In this population based prospective study, data from the medical birth registry in Norway were used to link pregnancies for 302 192 Norwegian women who had a second pregnancy in 1999-2015. The primary outcome was preterm delivery (<37 gestational weeks) in second births that followed a term birth with any of the pregnancy complications of pre-eclampsia, placental abruption, stillbirth, neonatal death, and small for gestational age.

Study answer and limitations The absolute risks for preterm delivery in a second pregnancy were 3.1% with none of the five term complications (8202/265 043), 6.1% after pre-eclampsia (688/11 225), 7.3% after placental abruption (41/562), 13.1% after stillbirth (72/551), 10.0% after neonatal death (22/219), and 6.7% after small for gestational age (463/6939). The unadjusted relative risk for preterm birth after term pre-eclampsia was 2.0 (95% confidence interval 1.8 to 2.1), after term placental abruption was 2.3 (1.7 to 3.1), after term stillbirth was 4.2 (3.4 to 5.2), after term neonatal death was 3.2 (2.2 to 4.8), and after term small for gestational age was 2.2 (2.0 to 2.4). On average, the risk of preterm birth was increased 2.0-fold (1.9-fold to 2.1-fold) with one complication in the first pregnancy and 3.5-fold (2.9-fold to 4.2-fold) with two or more complications. Norwegian birth registry data are unbiased for pregnancy history, but inevitably include some misclassification.

What this study adds Pre-eclampsia, placental abruption, stillbirth, neonatal death, or small for gestational age experienced in a first term pregnancy are associated with a substantially increased risk of subsequent preterm delivery.

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<table>
<thead>
<tr>
<th>Outcome in term 1st pregnancy</th>
<th>Crude relative risk (95% CI)</th>
<th>Adjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1.96 (1.82 to 2.12)</td>
<td>1.97 (1.82 to 2.12)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>2.34 (1.74 to 3.14)</td>
<td>2.25 (1.68 to 3.02)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>4.22 (3.40 to 5.24)</td>
<td>4.21 (3.39 to 5.22)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>3.25 (2.18 to 4.83)</td>
<td>3.18 (2.15 to 4.70)</td>
</tr>
<tr>
<td>SGA</td>
<td>2.16 (1.97 to 2.36)</td>
<td>2.04 (1.86 to 2.24)</td>
</tr>
</tbody>
</table>

Unadjusted (filled diamonds) and adjusted (open diamonds) relative risks for preterm birth in second pregnancy by complications in first pregnancy at term, Norway, 1999-2015. Reference is term birth in first pregnancy without any of the five complications. Analyses are adjusted for maternal age, year of birth for first child, and maternal education. SGA=small for gestational age.
SGLT2 inhibitors and kidney outcomes in the real world

ORIGINAL RESEARCH Scandinavian cohort study

Use of sodium-glucose cotransporter 2 inhibitors and risk of serious renal events

Pasternak B, Wintzell V, Melbye M, et al

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Study question What is the association between use of sodium-glucose cotransporter 2 (SGLT2) inhibitors and risk of serious renal events in data from routine clinical practice?

Methods This cohort study of nationwide register data from Sweden, Denmark, and Norway, 2013-18, included 29 887 new users of SGLT2 inhibitors and 29 887 new users of an active comparator, dipeptidyl peptidase-4 inhibitors, matched one to one on the basis of a propensity score with 57 variables. Mean follow-up time was 1.7 (SD 1.0) years.

The main outcome was serious renal events, a composite of renal replacement therapy, hospital admission for renal events, or death from renal causes.

Study answer and limitations The mean age of the study population was 61.3 (SD 10.5) years; 11 108 (19%) of patients had cardiovascular disease and 1974 (3%) had chronic kidney disease. Use of SGLT2 inhibitors, compared with use of dipeptidyl peptidase-4 inhibitors, was associated with a 58% lower risk of the primary outcome (2.6 events per 1000 person years versus 6.2 events per 1000 person years; hazard ratio 0.42 (95% confidence interval 0.34 to 0.53); absolute difference –3.6 (–4.4 to –2.8) events per 1000 person years). This was an observational study, and the possibility of unmeasured confounding cannot be ruled out.

What this study adds Complementing the results of randomised trials, these data suggest that SGLT2 inhibitors might lower the risk of serious renal events in routine clinical practice.

COMMENTARY Observational data from clinical practice favour these drugs over DPP4 inhibitors

Chronic kidney disease affects 700 million individuals worldwide and contributes to one in 20 deaths annually.1 Globally, the age standardised mortality rate attributable to chronic kidney disease has remained virtually unchanged over the past decade, in contrast with most other non-communicable chronic diseases for which these rates have fallen.2 3 This seemingly intractable problem is driven largely by diabetes.1 It is thus not surprising that sodium-glucose cotransporter 2 (SGLT2) inhibitors have garnered considerable attention following recent clinical trials showing consistent benefits of these glucose lowering drugs on major adverse kidney outcomes.4 5 6

Taken together, current evidence strongly suggests a role for SGLT2 inhibitors in people with or at risk of chronic kidney disease. Yet the key trials left important questions unanswered for clinicians and patients. All were placebo controlled and had highly selected participants, making the results hard to translate to real world use.

Cumulative evidence In this issue, Pasternak and colleagues report how they sought to answer some of these questions in a cohort study using pooled national registry data from Scandinavia.7 They used propensity scores to match new users of SGLT2 inhibitors or dipeptidyl peptidase-4 (DPP4) inhibitors between 2013 and 2018. The primary outcome was: first occurrence of renal replacement therapy, hospital admission for renal events, or death from renal causes. In the primary analysis, SGLT2 inhibitor initiation, compared with DPP4 inhibitor initiation, was associated with a 58% lower risk of the primary outcome over a mean follow-up of 1.4 (SGLT2 inhibitors) to 2.0 (DPP4 inhibitors) years. This difference was primarily driven by lower rates of renal replacement therapy and hospital admission with SGLT2 inhibitor use.

Subgroup analyses found consistent benefits for people who initiated SGLT2 inhibitors across sex, age groups, and individual drugs, but greater risk reduction in those with cardiovascular disease and those with chronic kidney disease.

The results from this well designed study are qualitatively consistent with previous clinical trials and smaller observational studies, and add new evidence that SGLT2 inhibitors seem preferable to DPP4 inhibitors in people at risk of developing or worsening diabetes related kidney disease. The protective effect of SGLT2 inhibitors seems to occur independent of improved hyperglycaemic control and probably independent of other effects shared by DPP4 inhibitors (such as reduced...
The protective effect of SGLT2 inhibitors seems to occur independent of improved hyperglycaemic control

blood pressure or weight loss).

**Patient population**
Although SGLT2 inhibitors appeared particularly beneficial in people with cardiovascular disease or chronic kidney disease, it is perhaps more informative that these drugs were associated with a lower risk of development and progression of diabetic kidney disease in people without these overt comorbidities, who have largely been excluded from clinical trials. Most participants in the study did not have diagnoses of cardiovascular disease, and only around 3% had diagnosed chronic kidney disease.

Despite this study’s strengths, the results should be interpreted with some caution. Sensitivity analyses supplemented with clinical data suggested a modest degree of unmeasured confounding in the primary analysis.

Additional unmeasured confounding is possible; any such confounder would, however, need to be associated with both treatment and outcome by a risk ratio of 1.8-fold (based on data from Sweden) or 2.0-fold (Denmark) for the confidence intervals to include null results.9

Overall, the findings by Pasternak and colleagues add to the impressive track record for SGLT2 inhibitors.

Additional pragmatic comparative effectiveness trials in real world settings and more diverse populations could add further support for broader access to these drugs, not only in high income countries but also in lower income countries where the burden of kidney disease is disproportionately high.1

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Find the full version with references at http://dx.doi.org/10.1136/bmj.m1584
Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association

Li Y, Teng D, Shi X, et al
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Study question There is interest in whether recent healthcare reforms and programmes for non-communicable diseases in China have been associated with change in diabetes. What is the prevalence of diabetes using the 2018 American Diabetes Association (ADA) diagnostic criteria in mainland China in 2017?

Methods A population based, cross sectional study was carried out using a multistage, stratified sampling method to select a nationally representative sample of 75 880 people aged 18 and older in the general population from 2015 to 2017. Participants recorded their demographic characteristics, lifestyle, and history of disease on a questionnaire. Anthropometric and clinical assessments were made of serum concentrations of fasting plasma glucose (one measurement), two hour plasma glucose, and glycated haemoglobin (HbA1c). The 2018 ADA and World Health Organization diagnostic criteria were used to estimate the prevalence of diabetes among adults living in China, and the prevalence by sex, regions, and ethnic groups.

Study answer and limitations The weighted prevalence of total diabetes (n=9772), self-reported diabetes (n=4464), newly diagnosed diabetes (n=5308), and prediabetes (n=27 230) diagnosed by the ADA criteria was 12.8% (95% confidence interval 12.0% to 13.6%), 6.0% (5.4% to 6.7%), 6.8% (6.1% to 7.4%), and 35.2% (33.5% to 37.0%), respectively, among adults living in China. The weighted prevalence of total diabetes was higher among adults aged 50 and older and among men. The prevalence of total diabetes in 31 provinces ranged from 6.2% in Guizhou to 19.9% in Inner Mongolia. Among five investigated ethnicities, Han ethnicity had the highest prevalence of diabetes (12.8%) and Hui ethnicity had the lowest (6.3%). The weighted prevalence of total diabetes (n=8385) using WHO criteria was 11.2% (10.5% to 11.9%). Limitations include lack of repeat testing in people with abnormal glucose values over time and the non-inclusion of non-residents, such as internal migrant workers, in the study due to the study design.

What this study adds The overall prevalence of diabetes in mainland China in 2017 was 12.8% using the ADA diagnostic criteria and 11.2% using WHO criteria, but the second value could be higher than in previous national surveys (2007, 2010, 2013) using the same WHO diagnostic criteria. These findings indicate that diabetes is an important health problem in China.

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