Title: Association between antipsychotic use in pregnancy and the risk of gestational diabetes: population-based cohort studies from the United Kingdom and Hong Kong and an updated meta-analysis.

Short running title: Antenatal antipsychotics use and gestational diabetes

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Manuscript word counts: 3937/4000

Abstract (248/250 words)

Aims: To investigate whether exposure to antipsychotic medications during pregnancy is associated with gestational diabetes mellitus (GDM) in United Kingdom (UK) and Hong Kong (HK) population cohorts.

Methods: Two population-based cohort studies were conducted using data from the UK The Health Improvement Network (THIN) and HK Clinical Data Analysis and Reporting System (CDARS). Nondiabetic women who received any type of antipsychotic medicine before their first pregnancy were included in our cohorts. The exposed group comprised women who continued using antipsychotics from the start of pregnancy to delivery (***continuers***), while the comparison group included women who were prescribed antipsychotics before the start of pregnancy but stopped during pregnancy (***discontinuers***). GDM was identified using GDM diagnosis and/or clinicians reported GDM. Odds ratios (ORs) with a 95% confidence interval (CI) were calculated to assess the association between antipsychotic use during pregnancy and GDM. Propensity Score fine-stratification weighting was used to adjust for potential confounding factors.

Results: 3,114 women with registered first pregnancies (2,351 in THIN and 763 in CDARS) were included. 5.49% (2.55% in THIN and 14.55% in CDARS) were diagnosed with GDM. The adjusted OR of GDM in ***continuers*** was 0.73 (95% CI: 0.43-1.25) in THIN and 1.16 (95% CI: 0.78-1.73) in CDARS compared with ***discontinuers***.

Conclusions: Our results do not suggest an increased risk of GDM in women who continued using antipsychotics during pregnancy compared to women who stopped. Based on these results, women should not stop their regular antipsychotics prescriptions in pregnancy due to the fear of GDM.

Key words: Pregnancy, Antipsychotics, Gestational diabetes

1. Introduction (583)

Gestational diabetes mellitus (GDM) is a common pregnancy complication, defined as hyperglycemia, impaired glucose tolerance and impaired fasting glycemia, first diagnosed at any time during pregnancy (WHO, 2013, NICE, 2015a). The global prevalence of GDM is estimated to be 1.6% to 34.9%, with differences between ethnicities and geographic regions (Behboudi-Gandevani et al., 2019). The prevalence is two- to three-fold greater in Asian populations compared to Caucasian populations (Farrar et al., 2016). Women with older age, higher body mass index (BMI) or family history of diabetes are more likely to develop GDM during pregnancy (NICE, 2015a, Cypryk et al., 2008), and therefore have a higher possibility of preterm delivery, fetal macrosomia or type 2 diabetes after pregnancy (Association, 2004, Wendland et al., 2012).

To reduce symptoms and to prevent relapse, women with severe mental illness (SMI, such as schizophrenia) are commonly exposed to antipsychotics, both first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs), at childbearing age (Barbui et al., 2013, Khalifeh et al., 2015). The prescribing of antipsychotics both before and during pregnancy has increased over the last ten years (Lao et al., 2017, Reutfors et al., 2020). Lao et al. (2017) reported a 1.5-fold increase in pregnant women who were prescribed antipsychotics from 2004 to 2014 in Hong Kong (HK), from 0.18% to 0.27% (Lao et al., 2017). Additionally, Petersen et al. (2014) reported that 0.19% of women in the United Kingdom (UK) were prescribed antipsychotics during pregnancy

between 1995 to 2012, with an overall increase in use since 2007 (Petersen et al., 2014). In non-pregnant patients with SMI, treatment with antipsychotics is associated with metabolic side effects, such as weight gain and hyperglycemia (Jibson, 2014, Jibson, 2016), but the evidence in pregnancy is limited. A recent meta-analysis including six western population-based cohort studies found a 24% increased risk of GDM in mothers with gestational use of antipsychotics compared to women without gestational antipsychotics exposure (Wang et al., 2019b). However, there are outstanding knowledge gaps that previous studies failed to address: 1) no study investigated this association in Asian populations; 2) there is insufficient evidence to demonstrate the effect on GDM of FGAs vs SGAs, despite their different pharmacological effects (Dazzan et al., 2005); 3) no study specifically identified the differences between time of exposure (i.e. different trimesters); 4) lastly, whilst previous studies minimized bias by using methods such as high-dimensional propensity score matching, most studies compared women with gestational antipsychotic exposure to unexposed women, without mental health considerations, (Boden et al., 2012, Panchaud et al., 2017, Petersen et al., 2016, Vigod et al., 2015, Reis and Kallen, 2008) which may lead to indication bias (Wang et al., 2019a). For instance, women who are not prescribed antipsychotics during pregnancy, in particular those without psychiatric disorders, are more likely to have a healthier lifestyle which can affect the risk of GDM (Tryggvadottir et al., 2016) .

The aim of our study was to assess whether women taking antipsychotics in pregnancy are at a possible increased risk of GDM. We conducted two separate cohort studies in

UK and HK to evaluate this association and to discuss the difference in findings between these two different populations. In both study cohorts, we compared the risk of GDM in a group of women exposed to antipsychotics before and during pregnancy (***continuers***) to women exposed to antipsychotics before pregnancy only (***discontinuers***). Prespecified subgroup analyses were conducted for users of FGAs and SGAs and for different periods (trimester) of exposure. Additionally, we updated the results of previous meta-analysis.

2. Methods (1274)

We used data from the UK The Health Improvement Network (THIN) database and HK Clinical Data Analysis and Reporting System (CDARS) database. The study protocols and analysis plans were approved by the Scientific Review Committee for THIN database (Reference Number: 7THIN002, January 2017) and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for CDARS database research (Reference Number: UW20-051).

2.1 Data source and study design

The THIN and CDARS databases consist of anonymized electronic health records from UK primary care and HK hospitals (Wong et al., 2016, Blak et al., 2011). THIN covers medical records of patients registered at 744 participating practices, comprising over 13 million patients meeting accepted data quality criteria and representing over 6% of the UK population (Horsfall et al., 2013, Blak et al., 2011). CDARS is managed by HK

Hospital Authority (HA) and currently contains 43 hospitals and institutions, 49 specialist outpatient clinics, and 73 general out-patient clinics which is accessible to all HK residents (over 7.5 million) (Hong Kong Hospital Authority, 2019, Wong et al., 2016). Data validation in both databases has demonstrated high coding accuracy with many high-quality, population-based studies published from the two databases (Lau et al., 2017, Man et al., 2017, Davé et al., 2010). We conducted two retrospective population-based cohort studies separately using data extracted from the THIN and CDARS database.

2.2 Study population

The study population consisted of the entire pregnancy population of THIN and CDARS aged between 15 and 50 years old from 1 January 1990 to 9 January 2017 in THIN and 1 January 2001 to 31 December 2015 in CDARS. Women with a history of GDM are more likely to develop GDM in pregnancy (Nilofer et al., 2012), our study cohorts therefore comprised primiparous pregnancies resulting in a live or stillbirth. Pregnancies ending in a miscarriage or abortion were excluded. To avoid potential bias, we also excluded women with a diagnosis of pre-existing diabetes (including both Type 1 and Type 2) before pregnancy; and those who had been prescribed any teratogenic medications (listed in Appendix 1) during pregnancy.

2.3 Pregnancy period and follow-up time

Pregnancy period definition is shown in Figure 1. In THIN, follow-up started 90 days prior to the theoretical start date of pregnancy (i.e. last menstrual period [LMP], start of pregnancy). Pregnancy start and end dates were derived from maternity-related information in the THIN health files. If the date of the LMP was not recorded, but a woman had a record of the gestational age of her fetus/duration pregnancy (i.e. 12 weeks), the theoretical start date of pregnancy was calculated by subtracting the pregnancy duration from the calendar date of the recording. In CDARS, follow-up started from the LMP (start of pregnancy), which was calculated by date of delivery minus gestational age at delivery. The pregnancy period was defined as the period between the start of pregnancy and the date of delivery. We defined all the time before the start of pregnancy as pre-pregnancy period. A 90-day grace period was chosen in THIN to allow for a period of time during which women were still exposed to antipsychotic, but no longer receiving new prescriptions. In CDARS, prescriptions are recorded by exact start and end date and a 90-day grace period was not deemed necessary. To identify the potential effects on the timing of exposure on the outcome, we further divided the pregnancy period into trimesters: first trimester (0-90 days after the LMP), second trimester (91-180 days after the LMP) and third trimester (181 days after the LMP to delivery). Women who were pregnant for 24 weeks or more were included. Follow-up ended at the earliest of the following: diagnosis of GDM, end of pregnancy, dates before end of pregnancy (death, patient left the practice [THIN]), or end dates of cohort (9 January 2017 [THIN], 31 December 2015 [CDARS]).

2.4 Exposure and comparator cohorts

Prescriptions of any antipsychotic listed in Chapter 4.2.1 of the British National Formulary (BNF) were extracted from the prescribing and dispensing records (Appendix 1). To minimize drug misclassification, we restricted women who received at least two prescriptions in THIN (normally 28 days for one prescription) and at least 56 days coverage time of prescriptions in CDARS as our study population. We defined women who received any antipsychotic before and during pregnancy (***continuers***) as exposure cohort, while the comparator cohort comprised women who did not receive any antipsychotic during pregnancy, but did before pregnancy (***discontinuers***). Additionally, we specifically identified the risk of GDM in users of two different drug classes (i.e. exclusive FGAs and exclusive SGAs) and the most commonly prescribed antipsychotics in each database (mutually exclusive).

2.5 Outcome definition

GDM was defined as the earliest recording during pregnancy of the following: 1) a first recorded diagnosis of GDM (diseases are coded using Read Code in THIN and the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] in CDARS) or 2) a clinician reported GDM in CDARS or 3) a recorded fasting plasma glucose level of 5.6 mmol/liter or above or a 2-hour plasma glucose level of 7.8 mmol/liter or above in THIN (NICE, 2015b, HKCOG, 2016).

2.6 Covariates

The following variables were considered as covariates in both databases: maternal age and calendar year at the start of pregnancy, maternal underlying medical conditions (epilepsy, hypertension and SMI [e.g. schizophrenia, bipolar disorder and depression]), time from the first prescription of any antipsychotics to start date of study, and use of other psychotropic drugs (antidepressants, BNF Chapter 4.3 and lithium, BNF Chapter 4.2.3). Additionally, the following variables were used in THIN only: BMI, smoking status, alcohol consumption status and family history of diabetes, and CDARS only: household income status.

2.7 Statistical analysis

Analyses were conducted separately in THIN and CDARS. Odds ratios (ORs) with a 95% confidence interval (CI) were calculated to assess the association between antipsychotic use during pregnancy and GDM using Propensity Score (PS) fine-stratification weighting. PS, defined as the probability of exposure treatment conditional on observed baseline information, can be used to account for a large number of confounders efficiently in pharmacoepidemiology studies (Desai et al., 2017, Rosenbaum and Rubin, 1983). In this study, we used PS fine-stratification weighting as this particular method performs better at low exposure prevalence (Desai et al., 2017). Subgroup analyses were 1) to assess the comparative safety of FGAs and SGAs during pregnancy; 2) to evaluate the risk of GDM in users of the most commonly prescribed individual antipsychotics in each database, and 3) to stratify users of antipsychotics by trimester of exposure. Moreover, adjusted logistic regression analyses without PS were

conducted to identify the contribution of each individual confounding variable in a sensitivity analysis. Multiple imputation was used to replace missing BMI, smoking status, and alcohol consumption status (Leyrat et al., 2019). A *P-value* < 0.05 was considered statistically significant. STATA 15 and SAS 9.4 were used for conducting statistical analyses.

2.8 Secondary analyses

We conducted a post hoc meta-analysis to synthesize the results of THIN and CDARS and added the current study to the most recent meta-analysis evaluating the association between antipsychotics use in pregnancy and GDM (Wang et al., 2019b). In particular, we did a meta-analysis to synthesize the results of relavent studies identifying the difference between ***continuers*** and ***discontinuers***. Estimates (risk ratio [RR]) were pooled using the random-effect model with the corresponding 95% CI for each outcome (DerSimonian and Laird, 1986). Heterogeneity was evaluated using I^2, where a value of 0% is considered as unobserved heterogeneity and larger values indicating increasing heterogeneity (Higgins et al., 2003). A *p-value* < 0.1 was considered statistically significant for heterogeneity which indicates a high degree of variance among the included studies.

3. Results (669)

3.1 Primary analysis

Study flow chart and a summary of characteristics of both study cohorts can be seen in Figure 2 and Table 1, respectively. Overall, 3,114 first pregnancies (2,351 in the UK and 763 in HK) were included in our analyses. The mean maternal age at delivery was 29.47 years old (Standard Deviation [SD]: 6.61 years) in UK patients and 30.44 years (SD: 5.76 years) in HK patients. In both populations, ***continuers*** were more often diagnosed with underlying medical conditions compared to ***discontinuers***. Also, ***continuers*** were more likely to have a BMI of over 30 kg/m^2 (21.83% vs 15.85%) and more likely to be prescribed antidepressants (THIN: 53.88% vs 30.82%; CDARS: 30.73% vs 15.00%, respectively) and lithium (THIN: 2.33% vs 0.57%; CDARS: 2.60% vs 0, respectively). Most of included women (58.41 %) had their first prescription more than two years before pregnancy and were registered as current smoker (50.74%) and/or drinker (57.64%).

In total, 171 women (5.49%; 2.55% in THIN and 14.55% in CDARS) were diagnosed with GDM in both databases, 91 of 171 women diagnosed with GDM (53.22%) had received continued treatment with antipsychotics into pregnancy (Table 2). Specifically, for ***continuers***, the incidence of GDM was 16.78% (n=71) in CDARS and 2.58% (n=20) in THIN. The crude OR of antipsychotic use during pregnancy and GDM was 1.02 (95% CI: 0.60-1.76) in THIN and 1.51 (95% CI: 0.99-2.30) in CDARS when ***continuers*** were compared with ***discontinuers***. Adjusted ORs (aORs) of THIN (0.73, 95% CI: 0.43-1.25) and CDARS (1.16, 95% CI: 0.78-1.73) showed no evidence of an association between continued use of antipsychotic medication during pregnancy and the onset of GDM.

The contribution of each individual confounding variable is shown in Appendix 5, a higher risk of GDM can be found in mothers aged 30 or older.

Using UK data, 324 women continued the use of FGAs only during pregnancy of whom less than five (<1.54%) developed GDM (Table 2). 193 women in the HK database continued FGAs of whom 39 (20.21%) had a diagnosis of GDM. 349 mothers in THIN were continually prescribed SGAs in pregnancy of whom 14 (4.01%) were diagnosed with GDM, while 149 women received SGAs only of whom 22 (14.77%) developed GDM in CDARS. There was no evidence that either FGAs or SGAs were associated with an increased risk of GDM (THIN: FGAs: aOR: 0.57, 95% CI: 0.20-1.65, SGAs: aOR: 0.98, 95% CI: 0.51-1.88; CDARS: FGAs: aOR: 1.15, 95% CI: 0.71-1.86, SGAs: aOR: 1.04, 95% CI: 0.58-1.85).

The most commonly used antipsychotic agents in THIN were quetiapine (n=571), chlorpromazine (n=450) and olanzapine (n=450), while haloperidol (n=443), risperidone (n=353) and trifluoperazine (n=317) were the most common in CDARS. Numbers of GDM in each specific drug exposure were very limited and no statistically significant association was found in either THIN or CDARS (Appendix 2 and 3).

There was no evidence of an association between antipsychotic exposure and GDM by stratifying trimesters in both populations (Table 2).

3.2 Secondary analysis

Overall, when our results were combined in a meta-analysis, there was no statistically significant association between prenatal continued exposure to antipsychotics and the risk of GDM (aOR: 0.95, 95% CI: 0.61-1.49, I^2=46.2%, p=0.173) (Figure 3). Additionally, there was no evidence for an increased or a decreased risk of GDM in women who had continued treatment with FGAs or SGAs only during pregnancy (FGAs: aOR: 0.95, 95% CI: 0.52-1.75, I^2=28.9%, p=0.236; SGAs: aOR: 1.01, 95% CI: 0.66-1.56, I^2=0.0%, p=0.894). There was no evidence of a change in risk of GDM and prenatal exposure to haloperidol, quetiapine, chlorpromazine, or olanzapine (Appendix 4). Adjusted results showed no statistically significant association between prenatal antipsychotic exposure in any trimester and the risk of GDM (Appendix 6).

We added our results to the previous meta-analysis using a random effects model. The pooled RR reduced from 1.24 (95% CI: 1.09-1.42) to 1.19 (95% CI: 1.02-1.37) for any antipsychotic prescriptions (Appendix 7). The I^2 was 22.4%. Additionally, the pooled RR of studies comparing ***continuers*** to ***discontinuers*** was 1.11 (95% CI: 0.91-1.35, I^2=21.6%, Appendix 8).

4. Discussion (1355)

In our two population-based cohort studies using electronic health records of women prescribed antipsychotic agents before their first pregnancy, our results suggest no evidence of a change in risk of GDM in women who were prescribed any type of antipsychotic agent during any time in pregnancy or in different trimesters. Although FGAs and SGAs have different mechanisms of action which may result in different

risks of GDM (Meltzer, 2013), no evidence of an increased risk among women who continued treatment with either FGAs or SGAs was found. Results of the updated meta-analysis support the association between prenatal antipsychotics during pregnancy and the risk of GDM. However, there is weak evidence to support this association when we particularly compared ***continuers*** to ***discontinuers***,

In general, women who were prescribed antipsychotic medication during pregnancy had a more severe psychiatric illness, greater medical and social comorbidities than ill non-medicated and healthy women. Whether in UK or HK, the majority of women who were prescribed antipsychotics pre-pregnancy stopped using antipsychotics at the beginning of pregnancy (Lao et al., 2017, Petersen et al., 2014). Among the ***continuers***, the majority of the women would continue antipsychotics treatment from the start of pregnancy to the third trimester in HK, but this was less common in the UK. Additionally, whether ***continuers*** or ***discontinuers***, proportions of women with GDM in HK (n=71, 14.55%) are much higher than those in UK (n=60, 2.55%). This may be partly explained by ethnicity and geographic region differences – the highest and lowest prevalence of GDM were reported in East-Asians and Caucasians, respectively (Farrar et al., 2016, Behboudi-Gandevani et al., 2019).

Only a few studies have investigated the association between prenatal exposure to antipsychotics and the risk of GDM (Wang et al., 2019b). Our results are partly in line with the only previous studies comparing ***continuers*** with ***discontinuers*** (Park et al., 2018, Petersen et al., 2016), Park et al. (2018) is also the study that carried most weight

in the recent meta-analysis (Wang et al., 2019b). Both Park et al. and the current study found no evidence of an increased risk of GDM among women who continued exposure to aripiprazole or risperidone. However, Park et al. (2018) reported that continued treatment with olanzapine (adjusted relative risk [aRR]: 1.61, 95% CI: 1.13-2.29) or quetiapine (aRR: 1.28, 95% CI: 1.01-1.62) was associated with a higher risk of GDM when compared with women who discontinued the treatment. Park et al. (2018) used similar statistical adjustment methods (PS weighting), but their sample only included women who were prescribed SGAs up to three months before the LMP. Additionally, our results in THIN are in the same direction as the results of the previous UK study using the THIN database with data until 2012 (Petersen et al., 2016). Whilst neither Petersen et al. nor the current study found an increased risk of GDM in users of antipsychotic agents during pregnancy, Petersen et al. found a lower aRR of GDM in 416 women who received antipsychotic treatment in pregnancy compared to 670 women who discontinued antipsychotic treatment before pregnancy (aRR: 0.43, 95% CI: 0.20-0.93) (Petersen et al., 2016).

Our results are also in line with another study that adjusted for potential confounding: Panchaud et al. (2017) compared pregnant women who took SGAs in pregnancy to psychiatrically ill women who were not exposed to SGAs in pregnancy and their results did not suggest an increased risk of GDM in exposed women (aOR: 0.79, 95% CI: 0.40-1.56) (Panchaud et al., 2017). Moreover, Boden et al. (2012) evaluated specific drugs (olanzapine and clozapine) and reported a statistically non-significant association between women with olanzapine and/or clozapine exposure in pregnancy compared

with women without any antipsychotics (aOR: 1.94, 95%: CI 0.97-3.91) (Boden et al., 2012). However, they did not use mutually exclusive comparison cohorts. Also, in a PS matched cohort study, Vigod et al. (2015) did not find an increased risk of GDM among women who were treated with any type of antipsychotics (aOR 1.10, 95% CI 0.77-1.57) (Vigod et al., 2015). Although Reis and Kallen observed an increased risk of GDM among women who self-reported any antipsychotic use in early pregnancy (aOR: 1.78, 95% CI: 1.04-3.01) using Swedish National registries, they did not fully address the effect of confounding by indication (Reis and Kallen, 2008).

The potential consequences of an untreated mental disorder may contribute to a higher probability of relapse or exacerbate symptoms, therefore, antipsychotics should be prescribed where clinically necessary (Jones et al., 2014). Our study results may have a clinical implication that it is not necessary to stop or switch to other antipsychotics considering the potential harm of GDM. However, it is recommended to follow The National Institute for Health and Care Excellence (NICE) guidelines that regular screening for GDM (blood glucose and HbA1c) is necessary for pregnant women who are prescribed antipsychotics (NICE, 2014).

Our study has several strengths. This study is the first study using an Asian clinical database in addition to a UK population database. Both of which are representative of the general populations in the UK and HK (Wang et al., 2019a). Moreover, this study is the first study evaluating the association between antipsychotic exposure and GDM by stratifying by different drug classes and specific individual drugs (mutually

exclusive) and different timings of exposure which addressed previously published research gaps (Wang et al., 2019b). To identify the exposures, we used automated dispensing and prescribing records, which are free of recall bias. Additionally, although there isn't really a way to address confounding by indication, we restricted the cohorts as ***continuers*** and ***discontinuers*** to minimize the effect of confounding by indication. Furthermore, we updated the meta-analysis, the results of which indicate that the association between prenatal use of antipsychotics and risk of GDM may be partially explained by confounding by indication of antipsychotics. If there is a causal association, the size of the effect is probably smaller than that reported previously.

Nonetheless, our study is not without some limitations. Firstly, antipsychotics are often initially prescribed by specialist care providers rather than primary care providers in the UK, and this may have led to an underestimation of exposure duration or overall exposure episodes in the UK cohort. However, primary care physicians may maintain or continue prescriptions initially started by a specialist. All of the patients in our THIN cohort received a minimum of two primary care prescriptions for antipsychotic agents. CDARS includes public hospital and ambulatory clinic medical records so does not have this problem, and similarly presents non-significant results. Secondly, although we used two population-based databases, our overall sample size was relatively small. Thirdly, data in the THIN and CDARS databases are not collected for research purposes. Factors such as BMI, smoking status, alcohol consumption status, and family history of diabetes are not recorded in CDARS; ethnicity, family history of diabetes and household income are not quantified for all patients in THIN. Although patients were

well matched on many baseline characteristics using PS, it is possible that the observed comorbidities were insufficient to identify and account for patients experiencing a higher baseline risk of GDM. For instance, schizophrenia and psychotic disorders have been independently associated with metabolic and diabetic risk (Ventriglio et al., 2019) and whilst we considered these underlying diagnoses as confounding variables in our adjusted analyses, we did not take time since diagnosis into consideration. However, data in primary care (THIN) and secondary care (CDARS) can be considered complementary. Additionally, decisions to continue or discontinue medication during pregnancy may depend on other risk factors (e.g. BMI), thus, ***continuers*** and ***discontinuers*** may receive different metabolic monitoring and prenatal care during pregnancy, which is not free of bias. Lastly, as different diagnostic criteria for GDM have been used over time, non-differential misclassification of undiagnosed or wrongfully diagnosed GDM may have affected our results. The oral glucose tolerance test (OGTT) conducted at 24-28 weeks of gestation is considered as the 'gold standard' (Behboudi-Gandevani et al., 2019). The UK NICE guidelines published the current thresholds for the diagnosis of GDM in 2015 (NICE, 2015b). However, any bias resulting from nondifferential misclassification would be directed towards the null and is unlikely to have affected the interpretation of our results.

5. Conclusion (56)

Our results suggest no evidence of an increased risk of GDM in women who continue using antipsychotics during pregnancy compared to women who stop. Women should

not stop their regular antipsychotics prescriptions in pregnancy due to the fear of GDM and should discuss their individual cases with doctors. Routine screening for GDM is nevertheless indicated.

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