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Metabolic disorders during pregnancy and postpartum cardiometabolic risk

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ABSTRACT

Hormonal changes during pregnancy can trigger gestational diabetes (GDM), which is constantly increasing. Its main characteristic is pronounced insulin resistance, but it appears to be a multifactorial process involving several metabolic factors; taken together, the latter lead to silent or clinically evident cardiovascular (CV) events. Insulin resistance and central adiposity are of crucial importance in the development of metabolic syndrome and they appear to correlate with CV risk factors, including hypertension and atherogenic dyslipidaemia. Hypertensive disease of pregnancy (HDP) is more likely to be an accompanying co-morbidity in pregnancies complicated with GDM. There is still inconsistent evidence as to whether or not co-existent GDM and HDP have a synergistic effects on post-partum risk of cardio-metabolic disease; however, this synergism is becoming more accepted since both these conditions may promote endothelial inflammation and early atherosclerosis. Regardless of the presence or absence of the synergism between GDM and HDP, these conditions need to be dealt early enough, in order to reduce CV morbidity and to improve health outcomes for both women and their offspring.

Introduction

There are several pregnancy indices of hormonal changes (such as oestrogens, progesterone, corticotropin-releasing hormone, cortisol, human placental growth hormone and human placental lactogen) that are implicated in the development of gestational diabetes cases (GDM) (1). Epidemiological evidence has consistently shown that among mothers with prior history of GDM, 30-84% of them had GDM recurrence in subsequent pregnancies (2), 20-40% developed metabolic syndrome (MetS) within 2-20 years (3,4), and 17-63% developed type 2 diabetes mellitus (T2DM) and obesity within 5-16 years (5-7). Longitudinal studies have shown that women with prior GDM and obesity were at higher risk to develop MetS compared with those without such metabolic history (8), and these women with prior GDM and obesity had relatively higher values of anthropometric parameters (such as body mass index [BMI] and waist circumference), blood pressure, glucose, homeostatic model assessment [HOMA], insulin, C-peptide and fibrinogen, together with lower HDL-C levels (9).

Insulin resistance and central adiposity are of crucial importance in the development of MetS, and they appear to correlate with cardiovascular (CV) risk factors, including hypertension, atherogenic dyslipidaemia, and glucose intolerance. The underlying mechanism of GDM is mainly pronounced insulin resistance (1). However, other factors, such as race, ethnicity, environmental and genetic factors (10), appear to contribute to the development of silent or clinical CV events. Interestingly, hypertensive disease of pregnancy (HDP) is very likely to be an accompanying co-morbidity in pregnancies complicated with GDM (11-13). Indeed, both these gestational complications share common risk factors such as maternal age, parity and pre-pregnancy BMI. Arguably, they may also share underlying mechanisms predisposing to subsequent recurrence of pregnancy complications and postpartum cardio-metabolic disorders (14-18).

However, it may be also true that HDP and GDM are the result of inherent susceptibility to CVD. Mothers who were obese or had a personal history of chronic hypertension or diabetes before pregnancy are more likely to develop HDP or GDM (19-21), and family history of CV risk is closely related to future CVD (22,23).

Is there a synergistic effect of GDM and HDP on post-partum cardio-metabolic risk?

It has been reported that there is a significant link between pregnancy complications (GDM and HDP) and CVD later in life (18,24), since HDP and GDM may promote endothelial inflammation and early atherosclerosis independently of underlying conditions (25-30). HDP and GDM also negatively impact on inflammatory biomarkers, including higher levels of plasminogen activator inhibitor-1, adiponectin, C-reactive protein, leptin, and tumour necrosis factors-alpha (1,14). Importantly, these inflammatory biomarkers play an important role beyond their role in diabetes, insulin resistance, visceral obesity, CVD and hypertension (32,33). Moreover, GDM and HDP are linked with elevated low-density lipoprotein (LDL) cholesterol and small dense LDL particles, which are implicated in CVD (31,34).

Even though GDM and HDP may co-exist in pregnancies of the same mothers and are associated with CV risk, some controversy remains as to whether or not co-existent GDM and HDP have a synergistic effect to the risk of postpartum cardio-metabolic disease (13). GDM or HDP is associated with a 15-fold higher risk in postpartum diabetes, with a 6-fold greater risk of postpartum hypertension, and a 40% risk increase for CVD mortality in the mothers (35). Meta-analyses have demonstrated that GDM is associated with a 7-fold higher risk of type 2 diabetes in affected mothers, and HDP is associated with a double risk of postpartum diabetes (5,26). It has also been shown that a prior GDM can enhance the risk of having not only T2DM but also CVD, independently (36).

The study of Li et al. (37) interestingly shows that GMD and HDP contribute independently and not synergistically to the postpartum cardiometabolic risk, and this was somewhat unexpected, given the accumulating evidence (35-37) that suggest that these conditions interplay in increasing the risk of diabetes, hypertension and CVD later in the mothers' lives as well as in their offspring (10,26,38). There are some potential limitations in the study of Li et al. that need to be briefly discussed (37). First, the small cohort of subjects and the relative brief follow-up period. In addition, GDM cases may be somewhat misclassified because the diabetes diagnosis required fasting and/or the 2 hour glucose testing after a 75 g oral glucose intake. Further, the data on GDM and HDP history were based on self-reports only. Finally, as already highlighted by the authors, since some mothers with an episode of GDM and/or HDP did not or were not able to conceive subsequently, these findings could have underestimated their risks.

It is well known in literature that women with GMD and HDP are more prone to MetS (39-41) and they appear to transmit an increased risk to the offspring through vertical transmission (8). Thus, it seems that women with GMD and HDP create an adverse metabolic memory (42).

Conclusion

Women who have had GDM and/or HDP are now recognised to carry a high risk of CVD and, regardless of the presence or absence of the synergism between GDM and HDP, they need to be followed very carefully. Indeed, the American Heart Association recommends long-term surveillance and management of CV risk factors in women with these pregnancy-related complications (43,44). Of note, many women with GDM have later in life an undiagnosed T2DM (45) and, therefore, increased awareness of GDM and HDP is needed.

In addition, postpartum screening tools and biomarkers of subsequent risk are very helpful in long-term follow-up.

Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This editorial was written independently. The authors have given talks, attended conferences and participated in advisory boards and trials sponsored by various pharmaceutical companies.

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