J Nephropharmacol. 2024; 13(1): e10632.

https://jnephropharmacology.com DOI: 10.34172/npj.2023.10632

Journal of Nephropharmacology

The adverse effects of gestational diabetes mellitus on maternal and neonatal kidneys

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 29 June 2023
Accepted: 10 August 2023
ePublished: 23 September 2023

ABSTRACT

Gestational diabetes mellitus (GDM) is a complication of pregnancy defined as any level of early or first detection of glucose intolerance in pregnancy. It is a prevalent metabolic disorder associated with several maternal and neonatal complications. On the other hand, chronic kidney disease is a leading cause of premature morbidity and mortality worldwide, and diabetic nephropathy accounts for approximately half of all cases of end-stage renal disease. Due to these two conditions' high prevalence and significance, any possible association would be a public health concern requiring further investigation. To this end, the current study aimed to review the adverse effects of GDM on maternal and neonatal kidneys.

Keywords: Diabetes, Pregnancy, Infant

Implication for health policy/practice/research/medical education:
Gestational diabetes mellitus is a complication that is the most prevalent metabolic disorder during pregnancy. Evaluating its effects on renal function can effectively prevent renal impairment over the long term.

Please cite this paper as: Hassanzadeh Rad A, Nazeri N. The adverse effects of gestational diabetes mellitus on maternal and neonatal kidneys. J Nephropharmacol. 2024;13(1):e10632. DOI: 10.34172/npj.2023.10632.

Review

Introduction

Gestational diabetes mellitus (GDM) is a complication of pregnancy defined as any level of early or first detection of glucose intolerance in pregnancy (1). GDM currently affects up to 25.5% of pregnancies worldwide and is the most prevalent metabolic disorder during pregnancy (2,3). GDM is characterized by decreased insulin and insulin resistance, with placental hormones increasing insulin resistance during pregnancy to improve glucose supply to the fetus (4). The pancreatic beta cells, on the other hand, compensate for the increased demand for glucose to establish a normoglycemic state. In contrast, women who develop GDM are less sensitive to insulin, and their pancreatic beta cells do not secrete enough insulin to sustain euglycemia, leading to glucose intolerance (5).

Although GDM resolves after delivery, it can have both short- and long-term effects on the mother's and offspring's health. Mothers may encounter type 2 diabetes mellitus (DM), long-term obesity, hypertension, cardiovascular and metabolic disorders, dyslipidemia, higher risk of breast cancer, and postnatal depression (1,2,6). In addition, offspring may be significant for gestational age or exposed to fetal birth trauma, neonatal hypoglycemia, fetal hypoxia, delayed lung growth, and childhood obesity (7). GDM shares many risk factors and genetic susceptibility as type 2 DM. Despite the association between GDM and cardiovascular disease and type 2 DM, limited data exists concerning the effects of GDM on future kidney function. Furthermore, diabetic nephropathy is a common cause of end-stage renal disease (8). Consequently, evaluating the effects of GDM on renal function can be an effective means of preventing renal impairment over the long term.

Data acquisition

This narrative review examined the effects of GDM on maternal and offspring renal function. For relevant articles, we searched databases, including PubMed, Web of Science, and Scopus. We conducted specific keywords, including gestational DM, GDM maternal complication, GDM fetal complication, and pregnancy hyperglycemia complication, as the search terms and analyzed previous publications. The studies included were required to investigate renal complications of GDM in either the mother or fetus. Furthermore, the references included in

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these publications were analyzed to identify additional pertinent articles. Only English-language publications were considered, including population-based studies, systematic reviews, and clinical trials.

Results

GDM and microalbuminuria

Chronic kidney disease (CKD) is diagnosed when elevated albumin levels in the urine (albuminuria) persist for at least three months or when the glomerular filtration rate decreases. Albuminuria has a strong correlation with the progression of renal impairment. Recent recommendations emphasized regular albuminuria screening in diabetic patients (9). Similarly, the relationship between GDM and microalbuminuria has been particularly interesting.

In a cohort study, Go et al evaluated the prevalence of microalbuminuria in 289 African American women with a history of GDM over a median follow-up period of 11 years. The findings revealed that these women had extremely high rates of microalbuminuria and suggested screening to detect the earliest stages of renal disease in this population (10). In a study involving 195 women with GDM, Shah et al assessed the risk of microvascular complications (including microalbuminuria). Despite their short-term exposure to overt hyperglycemia, third-trimester women had an increased risk of microalbuminuria (11).

Similarly, Bombak et al evaluated 37,716 female participants in a self-reported cohort study from 2000 to 2009. They demonstrated that women with GDM, even without overt diabetes, had a higher incidence of microalbuminuria and CKD stages 1-2 than women without diabetes. In addition, these women were more likely to have microalbuminuria if they were younger, African-American, obese, or hypertensive (12). In later research, Simone et al evaluated the effect of gestational dysglycemia and current glucose intolerance on microalbuminuria three years after delivery using a prospective cohort study involving 320 pregnant women. Contrary to previous research, the present glucose intolerance, but not previous gestational dysglycemia, was an independent predictor of microalbuminuria after adjustment for risk factors. They highlighted the significance of the current pre-diabetic state and suggested that the confounding effect of concomitant prediabetes affected the results of previous studies on participants (13).

Rawal et al discovered that women with a previous history of GDM were more likely to have a higher estimated glomerular filtration rate (eGFR), which could demonstrate early stages of hyperfiltration and renal damage, in a prospective study with 9 to 16 years of follow-up after pregnancy from 2014 to 2016. Even after adjusting for potential confounders such as diabetes family history, pre-pregnancy hypertension, and body mass index (BMI), the results remained consistent. However, there was no significant correlation between GDM and the urinary albumin-to-creatinine ratio (UACR) as an indicator of overt renal damage (14).

Based on the studies mentioned above, a connection between GDM and microalbuminuria appears to exist. However, the correlation is only significant if glucose intolerance is also present, and there is insufficient evidence to consider GDM as a risk factor for long-term microalbuminuria.

GDM and chronic kidney disease

In a recent Swedish cohort study, Peter Barrett et al investigated the independent association between GDM and maternal CKD. Their analysis revealed that women with GDM are more likely to develop CKD or end-stage kidney disease (ESKD). However, this association was insignificant among GDM patients who did not develop type 2 diabetes (except for glomerular CKD, which was higher in women with GDM alone). In addition, the results demonstrated that women with GDM and large for gestational age (LGA) exhibited an increased risk of CKD and ESKD (15).

Beharier et al conducted a retrospective population-based study on 9542 women with at least one previous GDM pregnancy, with a mean follow-up duration of 11.2 years, and found that these women had significantly more diagnosed renal disease than the control group. The most frequently diagnosed subtypes were hypertensive renal disease with or without renal failure, chronic renal failure, and end-stage renal disease. In addition, a linear correlation existed between the number of GDM pregnancies and the future risk of renal morbidity. The results implied an independent association between GDM and future renal morbidity after adjustment for parity and maternal age confounders (8).

GDM and kidney stones

Mao et al recently demonstrated in a self-reported study of 12,033 women with a history of GDM and renal stone that GDM independently increased the risk of nephrolithiasis. They evidenced that GDM may increase the risk of certain long-term complications, including metabolic syndrome and type 2 DM, both of which are risk factors for kidney stones. Nevertheless, after controlling for these covariates, the correlation remained significant. The authors noted that the study's cross-sectional design made it impossible to determine a cause-and-effect relationship between variables (16).

Similarly, Clennon et al retrospectively evaluated 5,734 pregnant women with urolithiasis in a cohort study. The findings revealed a significant association between urolithiasis and several variables, including GDM (17). The observations were also consistent with that of Tangren et al, albeit with reverse causality. They compared the pregnancy outcomes of 166 women with nephrolithiasis to

those of 166 women in the control group. They found that women with a history of kidney stones had an increased risk of developing GDM (18).

Effects of GDM on fetus

It is known that in-utero exposure to hyperglycemia has been linked to an increased risk of glucose intolerance, cardiovascular morbidity, and obesity in offspring (19). These complications have varying effects on renal function. However, there are few studies on the direct effects of GDM on the kidneys of fetuses.

Renal development and function

The developmental origins of health and disease are now well-established, and it is known that certain in-utero events can have lasting effects on the fetus (20). Reduced nephron number is considered a vulnerability factor and accelerates the onset of CKD (21). Khalil et al investigated the renal function of 21 offspring of mothers with type 1 DM at baseline and during amino acid infusion. They observed that their renal reserve was lower than the control group. This suggested global hyperfiltration or an established glomerular disorder. In addition, they reported that birth weight may influence renal function in adults whose mothers had diabetes during pregnancy. Uncontrolled type 1 DM can induce fetal renal malformations (22).

Aisa et al evaluated the renal development and function of 139 GDM neonates aged 30 to 40 days in a retrospective observational study. They demonstrated that neonates with GDM had significantly smaller total renal and cortical volumes. Furthermore, some urinary biomarkers that are indicators of renal impairment were elevated in these newborns. However, there was no difference between the control group and the neonates of compliant GDM mothers, indicating that strict glucose control may promote normal renal development in newborns. Intriguingly, the results demonstrated that a healthy maternal weight gain could prevent the renal complications of GDM (23). Similarly, Cappuccino et al measured renal cortex volume and microalbuminuria in 29 children of mothers with a history of GDM and found a direct correlation between reduced nephrogenesis, proteinuria, and GDM (24).

Compared to previous studies, the presence of proteinuria in these children may indicate that early tubulointerstitial changes in neonates may lead to the development of proteinuria in early childhood (27). Prior evidence suggests the median fetal kidney volume is more significant in hyperglycemic pregnancies, contrary to the studies' findings (25). Consequently, this issue requires further investigation.

Renal malformations

Previous research has linked maternal diabetes to renal malformations, such as agenesis and dysgenesis of the kidneys (26). Nevertheless, inconsistent associations have been found between gestational diabetes and congenital disabilities (27). A case-control study found that only maternal obesity was associated with an increased risk of congenital disabilities in infants born to mothers with GDM. The authors hypothesized that pre-gestational status was a factor in these patients' increased risk (28). Shnorhavorian et al examined the relationship between maternal risk factors and congenital urinary tract anomalies using a case-control study involving 4673 participants. GDM was associated with a 42% increase in the risk of kidney anomalies (including renal agenesis/dysgenesis and cystic kidney disease, among others) and a 25% increase in congenital urinary tract anomalies. However, the risk ratio was not significant (29). A later Taiwanese population-based study confirmed the link between GDM and congenital urinary tract anomalies. Anomalies of the genitourinary system in mothers with GDM, mothers with any DM, and mothers without DM were 0.19%, 0.20%, and 0.07%, respectively (30).

Conclusion

GDM remains the most prevalent metabolic disorder during pregnancy and a global health concern. In this review, we compiled the available evidence regarding the long-term renal complications of GDM in women and fetuses. Accordingly, numerous studies have demonstrated the effects of hyperglycemia on maternal and fetal kidneys, but it is essential to note that evaluated studies are heterogeneous, and numerous confounders exist. Therefore, it is difficult to determine whether GDM without previous hyperglycemia is independently associated with renal impairment. In either case, a multidisciplinary approach to managing GDM and early evaluation of neonates aids in preventing the disease's numerous adverse effects, including renal damage.

Authors' contribution

Conceptualization: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Data curation: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Formal analysis: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Investigation: Afagh Hassanzadeh Rad, Niloufar Nazeri.
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Validation: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Visualization: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Writing-original draft: Afagh Hassanzadeh Rad, Niloufar Nazeri.
Writing-review and editing: Afagh Hassanzadeh Rad, Niloufar Nazeri.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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