Effects of Risk Factors for Pregnancy Outcomes of Subsequent Pregnancy Associated with Gestational Diabetes Mellitus: A Retrospective Cohort Study in China.

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Research Article

Keywords: Random Forest algorithm, recurrent GDM, maternal and child outcomes

Posted Date: October 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-962585/v1>

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Abstract

Background

Since the implementation of the three-child policy in China, the number of high-risk pregnant women has increased, causing serious challenges to health care during pregnancy. In this article, we aimed to investigate the impact of several risk factors for maternal and neonatal outcomes in pregnancies complicated by gestational diabetes mellitus (GDM) and recurrent GDM to formulate a management strategy to minimize the effect of risk factors for gestational diabetes.

Results

Pre-pregnancy body mass index (BMI) and gestational weight gain affect maternal and child outcomes in the first and second onset of GDM. Pregnancy interval and fasting blood glucose in early pregnancy influence maternal and child outcomes of recurrent GDM. Maternal lipid levels during early pregnancy have a marked influence on neonatal outcomes in recurrent GDM.

Conclusions

On the basis of this result, weight management should be closely monitored before and during pregnancy. For planning of the second pregnancy with a previous history of GDM, a reasonable time between pregnancies is ideal. Moreover, in the next pregnancy, control of fasting blood glucose and lipid levels during the first trimester is necessary to improve both maternal and child outcomes.

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance or diabetes diagnosed at the outset or during pregnancy, usually during the second or third trimesters ¹. Women with a history of GDM are at increased risk of developing the condition in future pregnancies ². GDM is a high-risk factor in pregnancies and therefore accurate hierarchical management of pregnant women with GDM is of considerable importance. Research has shown that there is variable quality and conflicting evidence on the different risk factors for maternal and child outcomes. Pre-pregnancy body mass index (BMI), gestational weight gain (GWG), fasting blood glucose (FBG), triglyceride (TG), and high-density lipoprotein (HDL) in early pregnancy are risk factors for the development of GDM, while interpregnancy interval, macrosomia during the index pregnancy, and a history of preterm birth are risk factors for the recurrence of GDM.^{3–5} Pregnant women who develop GDM are prone to a number of maternal and neonatal complications, which include which include premature rupture of membranes (PROM), preeclampsia (PE), premature birth (PTB), high cesarean section rate, hypoglycemia, congenital malformations, macrosomia, respiratory disorders, etc. ^{6–8}

The significance of this study lies in the control of risk factors before the diagnosis of GDM or undiagnosed GDM, in order to reduce the incidence of pregnancy complications and prevent the

occurrence and development of adverse maternal and child outcomes.

Methods

Study population A total of 415 women hospitalized at the Fujian Provincial Maternity and Children's Hospital between May 2012 to September 2020 were included in this retrospective study. All the women had delivered two sequential, live, singleton infants and were diagnosed with GDM during pregnancy. The inclusion criteria were (1) a diagnosis of GDM during the two pregnancies and glucose intolerance that was relieved post-partum. The exclusion criteria were (1) pre-existing diabetes diagnosed before pregnancy. (2) Multiparity. (3) Incomplete clinical information in our hospital. (4) During the two pregnancies the women had different husbands. Figure 1 shows that a total of 12,849 primiparous women were diagnosed with GDM between May 2012 and September 2020 at Fujian Maternal and Child Health Hospital. Of these, we excluded 765 women for late miscarriages, stillbirths, and multiple pregnancies. A total of 1811 women had a second pregnancy and delivered in our hospital during the observation period, of which 896 women were diagnosed with recurrent GDM. During the observation period, 43 women were excluded due to pre-pregnancy diabetes. Additionally, we excluded 22 cases involving multiple pregnancy, 37 cases of late abortion or still death, and 19 cases due to three or more times of delivery. Furthermore, 379 cases lack of basic information or 75g OGTT outcome in our hospital. Finally, 415 women were eligible and included in further analysis.

Clinical measurements and definitions

The data recorded at baseline included gestational age (weeks), age, height and weight (pre-pregnancy and antepartum), abdominal circumference of the mother during early pregnancy, and medical history. Laboratory tests were also carried out which included FBG, HDL, TG levels in early pregnancy. Maternal and neonatal complications were also investigated. The maternal complications included cesarean section, postpartum hemorrhage, premature rupture of the membranes, hypothyroidism, hypertension, preeclampsia, fetal distress, and premature birth, while the neonatal complications included hypoglycemia, hyperglycemia, macrosomia, neonatal infection, hyperbilirubinemia, respiratory failure, congenital heart disease, and neonatal sepsis. Pre-pregnancy BMI was calculated by the weight and height before pregnancy. Gestational weight gain was defined as the antepartum weight minus pre-pregnancy body weight, while the pregnancy interval referred to the interval between delivery and the next pregnancy.

Statistical analysis

A machine learning technique called Random Forest tree classification was used for the statistical analyses. In Python 3.7 environment, after simple preprocessing of formatted table data, the Random Forest model in SK-Learn was used for training and testing. At the same time, the Random Forest model under SK-Learn provided the use of information entropy to judge the impact of various feature attributes (risk factors) on the category (outcome).

Results

As shown in Figure 2, for maternal outcomes of pregnant women with initial GDM, pre-pregnancy BMI and GWG contributed more to cesarean sections, hypothyroidism, premature rupture of membranes, hypertension during pregnancy, preeclampsia, fetal distress, and premature birth. Pre-pregnancy BMI and FBG during early pregnancy contributed significantly to postpartum hemorrhage. For the maternal outcomes of pregnant women with recurrent GDM (Figure 3), the time between pregnancies and the abdominal circumference in the first obstetric examination had a greater influence on the mode of delivery and the occurrence of gestational hypertension. Pre-pregnancy BMI, GWG and FBG level during early pregnancy had a greater influence on pregnancy associated with hypothyroidism, while FBG level during early pregnancy, pre-pregnancy BMI, and GWG had a greater influence on premature rupture of the membrane. Pre-pregnancy BMI and HDL level in early pregnancy contributed more to preeclampsia, and abdominal circumference. Pre-pregnancy BMI and FBG level during the first prenatal examination contributed more to fetal distress; while TG level in early pregnancy and GWG contributed more to preterm delivery, pre-pregnancy BMI, and GWG contributed more to postpartum hemorrhage.

For the neonatal outcome of initial GDM (Figure 4), GWG and pre-pregnancy BMI contributed more to hypoglycemia, macrosomia, neonatal infection, and congenital heart disease. GWG and HDL level in early pregnancy contributed significantly to hyperglycemia. Pre-pregnancy BMI and FBG level in early pregnancy had greater effects on neonatal jaundice and neonatal septicemia, while FBG level in early pregnancy and GWG had greater effects on respiratory failure. For the neonatal outcomes of women with recurrent GDM (Figure 5), pre-pregnancy BMI and TG level in early pregnancy contributed more to hypoglycemia, while TG and HDL levels in early pregnancy contributed significantly to hyperglycemia. GWG and FBG level during early pregnancy had a greater effect on macrosomia, while FBG and TG levels in early pregnancy had a greater effect on neonatal infection. Pre-pregnancy BMI and FBG level in early pregnancy had greater effects on neonatal jaundice and neonatal sepsis, while pre-pregnancy BMI and GWG had a greater influence on respiratory failure. In addition, FBG and HDL levels in early pregnancy had a greater influence on neonatal congenital heart disease.

Discussion

Our study showed that pre-pregnancy BMI and GWG had a significant impact on the maternal and neonatal outcomes of both the initial and recurrent GDM, and also that the time between pregnancies and FBG level during early pregnancy had an impact on the maternal and neonatal outcomes of recurrent GDM. In addition, we found that maternal lipid levels during early pregnancy had a significant impact on the neonatal outcomes of recurrent GDM. Many studies have focused on the risk factors for initial GDM although the results have been inconsistent, with most studies showing that pre-pregnancy BMI and GWG have an important impact on maternal and child outcomes^{9–11}. Mastella, L.S et al. concluded that inflammatory cytokines produced by adipose tissue induced by obesity promoted an imbalance in the expression of inflammatory and anti-inflammatory cytokines, leading to insulin resistance (IR) and inhibition of insulin secretion. An increase in maternal fat and insulin desensitization of placental

hormones also synergistically increased IR. In addition, obesity increases the accumulation of liver cholesterol and toxic effects in liver cells, resulting in a deterioration in liver glycogen storage function and elevations in circulating blood sugar levels ^{12,13}. As the new theory of developmental origins of health and disease (DOHaD) has become generally accepted around the world, a growing number of people consider that nutrition in early life is related closely to fetal and placental development and disease in adulthood ^{14,15}. Wong et al. reported that pre-pregnancy BMI and GWG have a major effect on the recurrence of GDM, including, but not only, cesarean delivery, premature delivery, premature rupture of the membrane, fetal distress, and neonatal jaundice ^{16–18}. Furthermore, the results of Yang et al. are consistent with our finding that the interpregnancy interval and FBG level during early pregnancy has a noticeable effect on the recurrence of GDM and pregnancy outcomes ^{19–22}. It is possible This effect may be associated with the level of β -cell reserves ², with a raised FBG indicating insulin resistance and impaired insulin secretion. It is interesting to note that this study also showed that maternal lipid levels during early pregnancy had a significant impact on neonatal outcomes in women with recurrent GDM. It is well established that dyslipidemia leads to insulin resistance in pregnant women and plays a role in the development of GDM ^{2,23}. Compared with incipient GDM, pregnant women with recurrent GDM in early pregnancy and abnormal blood lipid levels are more likely to experience adverse neonatal outcomes. The mechanism of this association is worthy of further study.

The strength of our study was that it achieved complete data collection, attributes that increased the credibility of the study. Because of the use of the Random Forest model, which incorporates an integration algorithm, the accuracy of our study was better than most previous studies that only used a single algorithm.

There were several limitations in our study. Because it was a single-center study in Fujian Provincial Maternity and Children's Hospital, it is likely more adverse outcomes occurred than observed normally. A multi-center research study is recommended to address these limitations. Moreover, because our study was a retrospective design it was difficult to avoid selection bias. A larger scale research is recommended to address the limitations.

Conclusion

This study shows pre-pregnancy BMI and GWG affect maternal and child outcomes of the first and second onset of GDM. On the basis of this result, weight management should be closely monitored before and during pregnancy. For planning of the second pregnancy with a previous history of GDM, a reasonable time between pregnancies is ideal. Moreover, in the next pregnancy, control of FBG and lipid levels during the first trimester is necessary to improve both maternal and child outcomes.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee, the study was legally approved by the institutional ethics committee of Fujian Maternity and Child Health Hospital and conducted in accord with the guidelines of the Declaration of Helsinki, and the rights of all participants were protected.

Availability of data and materials The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

Funding

Guide Fund for the Development of Local Science and Technology from the Central Government (2020L3019); National Health and Family Planning Commission Science Foundation(2019-WJ-04); Fujian Maternity and Child Health Hospital (YCXN 19-12), Fujian Maternity and Child Health Hospital (YCXN 20-16).

Authors' contributions

WJX, XX and JYY made substantial contributions to conception and design. WJX and XX took part in drafting the article and JYY revised it critically for important intellectual content. WJX, YNG and JL collected and analyzed the data. WJX and XX contributed to the work equally. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to express their gratitude to EditSprings (<https://www.editsprings.cn/>) for the expert linguistic services provided.

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Figures

Figure 1

Flowchart of the population.

Figure 2

Risk factors of incipient GDM and maternal complications.

Figure 3

Risk factors of incipient GDM and neonatal complications.

Figure 4

Risk factors of recurrent GDM and maternal complications.

Figure 5

Risk factors of recurrent GDM and neonatal complications.