Application of Rapid Rehabilitation Concept in Enhanced Recovery After Cesarean Section in Patients With Gestational Diabetes Mellitus: a Systematic Review

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Research Article

Keywords: gestational diabetes mellitus, enhanced recovery after surgery, cesarean section, maternal-neonatal complications

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-886638/v1

Abstract

Background: Gestational diabetes mellitus (GDM) is defined as all cases of diabetes observed during gestation, including pre-gestational diabetes and true GDM with its first onset during pregnancy. A rising number of parturient are diagnosed with GDM due to increased maternal weight, creating a serious global health concern. In order to improve maternal health and reduce childhood mortality, rapid rehabilitation approaches for postpartum recovery are of significant importance. However, most guidelines regarding this area remains extremely limited with poor quality,

Methods: All the references included in this work were either in English or in Chinese, enrolled via systematic selection from database PubMed, Web of Science (WOS) and CNKI. “Gestational diabetes mellitus”, “rehabilitation”, “cesarean”, “neonatal diabetes mellitus” etc. were selected as keywords during the search. No restriction was placed on publish date, quality or the setting of the studies.

Results: A total of 666 literatures were found in the initial selection. After sorting out 130 duplications, 536 articles had titles and abstracts read, among which 70 were thoroughly read. The contents of the articles include maternal-neonatal complications of GDM, maternal health managements in antenatal period, during labor and postpartum period, providing descriptions of maternal and neonatal outcomes after GDM patients receiving the interventions.

Conclusions: The application of rapid rehabilitation concept in enhanced recovery of cesarean section in pregnant women with GDM during perioperative period can significantly reduce the risk of multiple maternal-neonatal complications. However, the studies focusing on the discovery of new rapid rehabilitation approaches are still inadequate.

Introduction

Gestational diabetes mellitus (GDM) refers to any degree of either hyperglycemia or diabetes with onset or first recognition during pregnancy, induced by transitory form of glucose intolerance and pancreatic β-cell dysfunction, and remains below the cut-off value for manifest diabetes.[1, 2] It has become one of the most frequently diagnosed pregnancy complications in clinic, with the incidence rate of 9.0-25.1% worldwide, an average of 14.0%,[3, 4] yet the global prevalence is still on the rise.[5] GDM without appropriate antenatal and postpartum managements results in various severe maternal and fetal complications, such as premature delivery, fetal macrosomia and intrauterine growth retardation (IUGR).[6] Pregnant women with GDM and their neonates are identified to be predisposed to metabolic diseases including obesity, hyperglycemia and eventually type 2 diabetes mellitus (T2DM).[7] In addition, health economic consequences of GDM in pregnant women and related maternal-fetal complications are noticed, indicating direct substantial health-economic burden.[8]

Most importantly, as GDM usually accompanies preeclampsia, shoulder dystocia and fetal macrosomia,[9] if not applied with timely and effective intervention, maternal and neonatal health would be put in danger.

To guarantee the safety of parturient with GDM and the neonate, the use of cesarean section is remarkably enhanced. The overall cesarean section rate in pregnant women with GDM is significantly higher than that in nondiabetic pregnant women, as well as the acute cesarean section rate, which is 1.52 times the nondiabetic one is.[10, 11] However, cesarean section poses an enormous threat of surgical incision infection and maternal post-operative wound infection to pregnant women with GDM.[12] It is urgent to achieve rapid rehabilitation for post-cesarean section parturient. Fortunately, the outcome of GDM can be improved via standardized and appropriate managements, by significantly lessen the severity of maternal and natal complications, according to recent studies.[13] Therefore, standardized management of postpartum recovery in pregnant women with GDM is of great significance in levitation and prevention of the related complications and subsequent diseases.

At the present stage, numerous clinical guidelines on the rapid rehabilitation approach after cesarean section in nondiabetic pregnant women have been published.[14] Surprisingly, we found that there was not even one guideline regarding the postpartum rapid rehabilitation of pregnant women with GDM. In order to fill this gap, this review focuses on the maternal and natal adverse effects accompany the cesarean section in pregnant women with GDM and the application of rapid rehabilitation concept in perioperative care of cesarean section with GDM, which also aims to build the foundation for subsequent studies and encourage fellow researchers to pay more attention to this field.

Methods

Inclusion and exclusion criteria

Inclusion criteria: 1) the language used in the paper was English or Chinese; 2) studies involving perioperative management strategies for maternal and neonatal complications of GDM; 3) studies involving pregnant women suffered cesarean section with GDM; 4) reported perioperative outcomes, such as blood glucose level, adverse effects etc.

Exclusion criteria: 1) non-English and Chinese published literature; 2) not related to post-cesarean section rehabilitation

Literature search

A systematic selection was conducted in three distinct database, PubMed, Web of Science (WOS) and CNKI, focusing on studies related to “application of rapid rehabilitation concept in postpartum recovery of cesarean section in pregnant women with gestational diabetes mellitus”. However, no direct result was found associating this aspect. Thus, a second round of selection was conducted, using the following strings in PubMed MeSH:

"diabetes, gestational/complications"[MeSH Major Topic] OR "diabetes, gestational/diet therapy"[MeSH Major Topic] OR "diabetes, gestational/drug therapy"[MeSH Major Topic] OR "diabetes, gestational/metabolism"[MeSH Major Topic] OR "diabetes, gestational/nursing"[MeSH Major Topic] OR

"diabetes, gestational/therapy"[MeSH Major Topic]) AND ("caesarean"[All Fields] OR "caesareans"[All Fields] OR "cesarean"[All Fields] OR "cesareans"[All Fields] and in WOS: “gestational diabetes mellitus (Topic) and neonatal (Topic) and cesarean (Topic)”.

No restriction was placed on the settings and quality of the studies, and no time range was set. All citations were imported into EndNote for further screening.

Screening of studies

The studies selected were screened according to the following three steps. First, all duplicates were found and removed using EndNote; second, all the directly or partially related studies were selected by reviewing the titles and abstracts; finally, the full texts of the selected papers were read.

Results

A total of 666 literatures were identified in the initial search. After 130 duplicates were removed, 536 records’ titles and abstracts were reviewed and 70 articles were retrieved full-text reviewing. The publish dates range from 1954 to 2021, most of which were published in the recent decade.

Discussion

Adverse maternal outcomes

Hypertensive disorders: Hypertensive disorders during pregnancy and postpartum period are classified into three pathological categories: chronic hypertension, pre-eclampsia and gestational hypertension, which are all recognized as risk factors of subsequent diseases, such as T2DM, metabolic disorders and CVD.[15] Several studies indicated that GDM contributes to the onset of hypertension during pregnancy and postpartum period.[16] Hyperglycemia, as a characteristic of GDM, can damage endothelial cells, resulting in vascular hypertensive dysfunction.[17, 18] In addition, hyperinsulinemia in patients with GDM that influences weight gain and renal sodium retention, is also a nonnegligible risk factor for developing hypertension.[19] For the purpose of resolving the questions regarding the optimal diagnostic cutpoints of GDM, the National Institutes of Health and other health care organizations sponsored and launched an international prospective cohort study, termed HAPO.[20] The HAPO study suggested that pregnant women who were obese with GDM and high BMI, had risks of developing pre-eclampsia higher than normal women by eight folds.[20, 21] However, contradictory results were observed in a recent retrospective study, demonstrating GDM and chronic hypertension could be protective against the development of pre-eclampsia and gestational hypertension.[21]

Preterm birth: Infants born alive prior to 37-week gestation are recognized as preterm births.[20, 22] Pregnant women with GDM face a frequency of 6.9% of encountering preterm birth, which was demonstrated to be in correlation with increased post oral glucose tolerance test (OGTT) maternal glucose.[20]

Cesarean section: Due to the requirement to overcome one or several adverse complications with GDM, such as shoulder dystocia and fetal macrosomia, cesarean section is commonly applied to patients with GDM, to guarantee the safety of parturient and neonate. According to a cross-section study, the most frequent maternal complications were induction of labor (66%) and cesarean section (32%). Among women went through labor induction, the majority (81%) proceeded to have a cesarean section.[23] The frequency of cesarean section application in patients with GDM is indicated to be associated with increased post OGTT maternal glucose and fasting glucose levels.[20] It bears high risk of wound infection, hemorrhage, thrombosis and wound dehiscence.[24] In addition, recent study shows that despite reduced neonates' birth weight, cesarean sections are still conducted in patients with GDM, which suggests that GDM alone can be an indicator for cesarean section.[25]

Long-term metabolic comorbidities: GDM with no intervention conducted significantly increases the lifetime risk of developing type 2 diabetes mellitus (T2DM).[26, 27] Approximately 50% of women with a history of GDM will develop T2DM within a decade.[28] A strong correlation between increasing pre-pregnancy BMI, higher fasting glucose level, early gestational age at GDM diagnosis and post-partum impaired glucose tolerance, and subsequent onset of T2DM, was observed in recent studies.[28] Furthermore, an estimated frequency of one-third of the female patients with T2DM has a history of GDM, indicating that GDM could be a convincing predictor of subsequent T2DM.[29]

Adverse neonatal outcomes

Neonatal hypoglycemia: Occurs in around 2.1% of the offspring of patients with GDM, as a result of fetal hyperinsulinemia responding to exposure to high glucose level from the mother.[24] The risk of neonatal hypoglycemia is considered in correlation with increased post OGTT maternal glucose instead of fasting glucose levels.[20] In addition, some neurological sequelae might be induced by the nadir glucose concentration and the duration of neonatal hypoglycemia.[30]

Hyperbilirubinemia: Increased maternal blood glucose level and subsequent fetal hyperinsulinemia decrease fetal oxygen consumption, resulting in increased fetal red cell mass, which may be responsible for subsequent hyperbilirubinemia.[24] An estimated frequency of 8.3% of offspring of GDM patients was founded with hyperbilirubinemia. However, this comorbidity is relatively less associated with maternal OGTT glucose levels.[20]

Fetal macrosomia: Recent study indicated that 24.7% of GDM patients had neonates with macrosomia (birthweight >4 kg), and those with a previous baby weight >4 kg were facing higher risks of having further babies with fetal macrosomia.[23] It is assumed as a consequence of fetal hyperinsulinemia and increased umbilical C-peptide in responding to increased trans-placental flow of glucose from the mother.[31]

Neonatal hypocalcemia: Low maternal vitamin D status and hypomagnesemia of GDM patients may be a reason for the cause of neonatal hypocalcemia.[32, 33] Nevertheless, the frequency of hypocalcemia in

neonates of women with GDM remains relatively low and of little clinical importance.

Other comorbidities in neonates of GDM patients includes respiratory distress syndrome,[34] hypertrophic cardiomyopathy[35] and major congenital malformations[36], which were found to be less frequent.

Long-term metabolic comorbidities: It is noticed that offspring of mothers with GDM are at increased risks of developing T2DM, obesity, cardiovascular diseases and structural hypothalamic changes.[37] In a follow-up study of adult offspring of women with GDM, the risk of prediabetes/diabetes and metabolic syndrome was eight and four folds higher than that of offspring of background population.[28] Evidences are that the development of subsequent T2DM in offspring is associated with fetal β-cell hypertrophy, relatively impaired insulin secretion and impaired insulin sensitivity resulted from fetal exposure to intrauterine hyperglycemia.[27, 31, 38]

Enhanced Recovery After Surgery (ERAS) managements

Enhanced Recovery After Surgery (ERAS) protocols has made remarkable progress in the field of surgery in recent years, though the literature search in this work indicated the lack of research papers and standardized guidelines regarding the application of ERAS protocols to cesarean section with GDM. ERAS is not a fixed operation process. Instead, it is a multidisciplinary, multi-pattern perioperative rehabilitation concept based on evidence-based medicine, continuously optimizing the operation plan in each diagnostic and treatment process, including outpatient evaluation, preoperative preparation, intraoperative management and postoperative rehabilitation, and the clinical effect examination.

Antenatal managements

Studies have demonstrated adverse maternal and neonatal outcomes of most women (80%-90%) with GDM can be significantly reduced through effective intervention, such as dietary management and exercise.[39-41] Screening and lifestyle management are two important factors for improvement of maternal and neonatal health. According to a guideline for the diagnosis and treatment of GDM developed by the Department of Perinatal Medicine in the Chinese Medical Association, all pregnant women are recommended to receive diagnostic test with a 75g OGTT test at 24-28 weeks of gestation and health education regarding GDM.[42] The same is also recommended by the World Health Organization (WHO).[43] Women diagnosed with GDM should be provided with lifestyle management composing medical nutrition therapy (MNT), weight management, exercise intervention and self-monitoring of blood glucose (SMBG). If lifestyle management occurs ineffective, pharmacological intervention is necessary. [24]

MNT: The purpose of conducting MNT is to attain normal glycemic control without the development of ketosis and fetal compromises induced by reduced maternal blood glycose level, and maintain the adequate weight gain based on prenatal BMI.[24] The mainstay of MNT for GDM patients, which is widely accepted, has been limited caloric intake. However, the extent of the limitation should be strictly

controlled. On the one hand, a reduced caloric intake from 2400 kcal/d to 1200 kcal/d results in significant ketosis in women with GDM.[44] On the other, though a caloric intake > 25 kcal/kg per day can prevent both ketosis and fetal growth compromise, the efficacy of this dietary intervention is not promising.[45] Therefore, a reduction of caloric intake to approximately 24 kcal/kg per day is recommended by the American College of Obstetricians and Gynecologists (ACOG), along with the composition and distribution throughout the day.[45]

Maternal weight management: Weight monitoring plays a significant role in ensuring a recommended weight gain during pregnancy. However, due to the increasing incidence of obesity and glucose intolerance during pregnancy, the standard for appropriate weight gain during pregnancy has been repeatedly altered. Most recently, a revised guideline conducted by the Institute of Medicine (IOM) in America was released to assist weight management for pregnant women based on the individual primary weight (Table 1), and has been endorsed by the ACOG.[46] The quality of the IOM guidelines was then examined in a study, demonstrating that the guidelines' recommended weight gain during pregnancy can significantly reduce the risks for several maternal-neonatal complications, such as pre-eclampsia, cesarean delivery and fetal macrosomia.[47]

Table 1

The guidelines of the institute of medicine (IOM) in America

Weight gain during pregnancy (kg)	Primary BMI (kg/m^2)
12.5-18	<19.8 (underweight)
11.5-16	19.8-26.0 (healthy)
7-11.5	26.0-29.0 (overweight)
≤7	≥29.0 (obese)

Physical activity: For approximately 39% of GDM patients, physical activity is necessary in addition to MNT and weight managements for meeting targeted glucose level.[48] Physical activity is capable of improving insulin sensitivity[49] by boosting muscle glucose uptake and glycogen synthesis,[50] therefore improve maternal glucose tolerance, which can to some extent avoid the use of insulin and other drugs. At least 30 minutes of physical activity on several days a week is recommended generally.[50] If possible, more tailored exercise schedules based on individual condition might be more effective at glucose level and weight managements for GDM women.[51]

SMBG: In addition to dietary management and physical activity, SMBG is recommended to assist in glucose monitoring of pregnant women and determining whether pharmacological intervention is required.[52] Frequent SMBG based on postprandial instead of pre-prandial monitoring has been reported to be associated with reduced adverse outcomes in insulin treated pregnant women.[53] Moreover,

continuous glucose monitoring (CGM), a novel technology allowing a 24-h monitoring of glucose levels, can significantly lower the risks of maternal-neonatal complications.[54]

Pharmacological intervention:

When dietary management and tailored physical activity fail to maintain the glycemic targets for pregnant women with GDM, pharmacological intervention is necessary.

Insulin: In most cases, insulin should be the first-line therapy for GDM. Types of insulin that can be used during pregnancy include short-acting and neutral protamine Hagedorn (NPH) insulin and rapid-acting analogues, which are lispro and aspart. The dose and regimen applied is determined based on individual severity of hyperglycemia in order to maintain glycemic targets.[54] If the fasting glucose is elevated in the morning, NPH-insulin can be applied at an initial dose of 0.2 units/kg body weight. If postprandial glycemic levels are increased, short-acting insulin can be used at doses of 1.5 units per 10 g per carbohydrate per breakfast and 1.0 units per 10 g per carbohydrate per lunch and dinner. If both pre- and postprandial glucoses are elevated, injection at a dosage of 0.9-1.0 units/kg can be applied four times a day.[55] In cases of limited insulin provision, inaccurate insulin dosing, or severe needle phobia, glyburide can act as an ideal substitute.[56]

Metformin: Metformin is also one of the first-line treatments for GDM and T2DB to maintain glycemic control. The application of metformin can reduce the risks of gestational hypertension complications and maternal weight gain in GDM patients. Recent studies indicated that metformin can cross the placenta during pregnancy with an estimated rate of 10-16%,[57] exposing the fetus to high concentration of metformin which resulted in restriction of placental and fetal growth, followed by signs of catch up growth and obesity during childhood and inclination for cardiometabolic diseases later in life.[58, 59] Nevertheless, it is less likely to trigger severe neonatal hypoglycemia compared with insulin, since metformin neither stimulates pancreatic insulin release nor increases circulating insulin levels.[60]

Vitamin and omega-3 fatty acid co-supplementation: A recent study demonstrated that combined supplementation with vitamin D and omega-3 fatty acids for 6 weeks in GDM patients resulted in significantly improved outcomes, including suppressed glycemic and blood lipid levels, improved HOMA-β and insulin resistance.[59] However, the clinical effects of the co-supplementation of vitamin and omega-3 fatty acid remain poorly studied.

Managements during labor and post-cesarean section

Induction of labor (IOL): IOL is suggested when maternal or fetal risks associated with the process of pregnancy outweigh the risks associated with early delivery.[61] IOL conducted in early periods of pregnancy with GDM may reduce GDM-related maternal-neonatal complications, especially fetal macrosomia and stillbirth.[62, 63] However, it also carries the risks of other neonatal comorbidities, such as respiratory distress syndrome, mechanical ventilation, hypoglycemia and so on.[64]

Elective cesarean delivery: If the estimated fetal weight is over 4.0 kg, an elective cesarean section is recommended by the International Federation of Gynecology and Obstetrics (FIGO) to prevent birth trauma.[65] Unfortunately, cesarean section comes with increased risks of wound hematoma, anesthetic complications, major puerperal infection and severe hemorrhage which may result in hysterectomy. Therefore, pragmatic perioperative treatments should be applied to minimize these surgical risks. Recent study suggested that vitamin D supplement in antenatal period can decrease the risk of cesarean section.[66] During labor, insulin requirement is generally decreased and glucose infusion is even required in some cases, to prevent ketosis and provide for increased physical work and fasting time.[67] For women who received antenatal pharmacological therapies, insulin infusion and 2-hour glycemic check is still required to control blood glucose levels.[24]

Breastfeeding: Studies suggested that GDM can increase the risk of breastfeeding failure. Low breastfeeding rates were found to be associated with neonatal weight loss and admission to NICU.[68] It is recognized that intensive breastfeeding can improve weight and glucose tolerance during early post-partum period in obese women with GDM, therefore should be encouraged.[69]

Mobile health intervention and monitoring: Recent advances in medical devices coupled with artificial intelligence, Internet and remote-control technologies, such as mobile health application, allow mobile health intervention and self-monitor become reality. Evidences have verified the positive effects of the utilization of mobile health intervention in GDM patients.[70]

Conclusion

In conclusion, the application of rapid rehabilitation concept in enhanced recovery of cesarean section in pregnant women with GDM during perioperative period, can significantly reduce the risk of multiple maternal-neonatal complications. However, there is no precise guideline about the utilization of ERAS in cesarean section in GDM patients, hence the importance of exploring better ways to minimize the maternal-neonatal complications should be further stressed.

Abbreviations

GDM: Gestational diabetes mellitus

WOS: Web of Science

OGTT: oral glucose tolerance test

T2DM: type 2 diabetes mellitus

ERAS: Enhanced Recovery After Surgery

WHO: World Health Organization

MNT: medical nutrition therapy

SMBG: self-monitoring of blood glucose

CGM: continuous glucose monitoring

NPH: neutral protamine Hagedorn

IOL: Induction of labor

FIGO: the International Federation of Gynecology and Obstetrics

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Qiuhong Yang decided the subject of this work. Aiwen Jian did the screening and reading of the enrolled articles and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to give thanks to Yundi Zhang for her kind help.

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