Pregnancy Weight Gain as a Predictor of Fetal Wellbeing in Liver Transplant Recipients

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Background: Gestational weight gain (GWG) is an important index influencing perinatal outcomes. Inappropriate weight gain during pregnancy is strongly associated with multiple pregnancy complications. In pregnant liver transplant recipients whose risk of adverse pregnancy outcomes is already high, this aspect may be even more significant. The present study analyzed the gestational weight gain in female liver transplant recipients and its effect on neonatal complications.

Material/Methods: A cohort study of retrospective data was performed in the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. There were 23 patients who fulfilled all inclusion criteria. The gestational weight gain was analyzed in the context of pre-pregnancy BMI, immunosuppression, and perinatal outcomes.

Results: The preterm delivery rate was 39.13% and GWG increased according to the duration of pregnancy. The model adjusted to week of delivery revealed no association between weight gain and the length of pregnancy (p=0.82). GWG in liver transplant recipients did not affect hypotrophy incidence, adverse perinatal outcomes, or caesarian delivery rate. A positive correlation between GWG and neonatal birth weight was observed (p=0.06). One patient, with coexisting PIH, had a stillbirth at 23 weeks. In all other cases, the 5-min Apgar score was 10 points.

Conclusions: Current obstetrical recommendations do not consider patients with chronic diseases undergoing immunosuppressive treatment. Proper counselling and preparing liver transplant recipients for pregnancy, especially optimizing maternal pre-pregnancy BMI, may be an important element in improving perinatal outcomes by lowering the risk of maternal complications. GWG itself is not relevant as a predictor of term gestation, but it might be important in achieving eutrophic fetus growth.

MeSH Keywords: Infant, Small for Gestational Age • Liver Transplantation • Perinatal Care • Pregnancy, High-Risk

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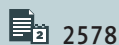
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Background

Pre-pregnancy body mass index (BMI) is a strong, modifiable factor affecting maternal and neonatal outcomes [1,2]. Maternal obesity not only affects perinatal outcomes, but may also lead to obesity of offspring and metabolic syndrome in the future [3]. In addition to pre-pregnancy BMI, gestational weight gain (GWG) is an important component influencing pregnancy outcomes. Inappropriate weight gain above or under the cut-off point during pregnancy may be associated with adverse pregnancy outcomes, such as gestational diabetes mellitus, gestational hypertension, preeclampsia, fetal macrosomia and hypotrophy, preterm delivery, and caesarian delivery [4]. In 2013, The American College of Obstetricians and Gynecologists (ACOG) established guidelines for optimal GWG based on BMI group [5].

Pre-pregnancy BMI and gestational weight gain may be influenced by many factors, including parity, obesogenic environment, smoking, drugs, socioeconomic status, and accompanying diseases [6]. Patients undergoing liver transplantation are at greater risk of developing obesity than non-transplanted patients due to chronic disease, leading to transplantation problems, metabolic changes, immunosuppressive therapy, and other factors [7,8].

Due to the increasing number of patients receiving liver transplantation, improved long-term survival, and better immunosuppressive therapy [9], more women of reproductive age consider the possibility of pregnancy after transplantation [10]. It is estimated that about 80–90% of female transplant recipients have potential to become pregnant at some point in their life [11,12]. Gestation in liver transplant recipients is a high-risk pregnancy [11,13] and may lead to numerous pregnancy complications such as preterm labor, low birth weight, caesarian delivery, and graft dysfunction [14]. Although the adverse effect of immunosuppression, especially steroid therapy, on metabolic syndrome is well established [15] – hypertension, diabetes and obesity are the most common adverse effects of steroids [16] – the impact of pre-pregnancy BMI and gestational weight gain in liver transplant recipients on pregnancy and neonatal outcomes is still unproven.

This study analyzed the associations of maternal weight gain during pregnancy and pre-pregnancy BMI with perinatal outcomes in liver transplant recipients.

Material and Methods

Study design and characteristics

A cohort study with retrospectively collected data was carried out in the 1st Department in Obstetrics and Gynecology, Medical University of Warsaw. The data were analyzed for 45 liver transplant recipients who delivered in the Department between January 2010 and June 2019. As the data were collected retrospectively and no medical intervention was included in study design, formal approval from the Ethics Committee was not necessary. During completion of the database, all patients were informed about the goals and conclusions of this study and asked for consent to use their results.

All patients qualified to the study had to fulfill the following eligibility criteria: patients after liver transplantation, singleton pregnancy, full medical history of mother and child available, delivery between 2010 and 2019, and informed consent for use of medical data in research purposes.

The exclusion criteria were as follow: inconsistent or incomplete medical history, multiple pregnancies, more than 2 transplantations, and co-transplantation of liver with other organs (kidney, pancreas, heart). Because most pregnancy-associated weight gain occurs during the late second trimester and third trimester, we decided to exclude patients with extremely preterm deliveries (<25 weeks).

There were 23 patients who met all the inclusion criteria; 13 of these 23 patients (56.5%) were on steroid therapy. Based on results of the association between BMI and GWG in the healthy population, we divided the patients into a normal BMI group and an overweight group. One patient with BMI=15 was excluded from this analysis due to being the only member of the underweight group. Adverse outcomes were postpartum hemorrhage, pregnancy-induced hypertension, gestational diabetes mellitus, caesarian section, and preterm birth. The median age at the time of delivery was 28 years old and the median time between transplantation and delivery was 6 years. All patients in analyzed groups had stable graft function at the time of conception.

Statistical analysis

To estimate the effect of GWG on adverse outcomes, we used multivariate logistic regression analysis. Descriptive statistics of all deliveries are presented in Table 1.

All results were adjusted for gestational age and mother's age as known cofounding factors and are presented in Table 2.

Results

The data were collected and analyzed for the following factors: age, pre-pregnancy BMI, patient's weight shortly before delivery, indication for transplantation, immunosuppression, pregnancy complications (i.e., gestational diabetes mellitus, hypertension, and preeclampsia), preterm birth, fetal birth weight,

Table 1. Gestational weight gain in relation to pre-pregnancy BMI [kg] in analyzed patients.

	n=	Min	Max	Median	Q1	Q3	* (%)	** (%)	*** (%)
Total	23	3	24	12	10	14	12 (52.2)	6 (26.1)	4 (17.4)
Underweight	1	20	20	20	20	20	–	–	1 (4.3)
Normal	14	5	14	12	10	13	10 (43.5)	–	4 (17.4)
Overweight	8	3	24	18	9	20	2 (8.7)	6 (26.1)	–

* In range of ACOG gestational weight gain guidelines; ** over the ACOG gestational weight gain guidelines; *** under the ACOG gestational weight gain guidelines.

Table 2. Relation between gestational weight gain and adverse outcomes.

Outcome n, aOR (95% CI) (for each 5kg of GWG)	Obese and normal weight BMI n=22	p	Normal weight BMI n=14	p	Overweight BMI n=8	p
Adverse outcome	20, 0.7 (0.1–5.4)	0.78	14, –	–	6, 1.32 (0.1–11.5)	0.80
Preterm delivery	9, 0.01 (0.0–>100)	0.84	7, 3.7 (0.0–>100)	0.98	2, 0.0 (0.0–>100)	0.83
PPH	2, 0.16 (0.00–5.21)	0.30	2, 9.7 (0.0–>100)	0.63	0, –	–
PIH	1, –	–	0, –	–	1, –	–
GDM	2, 0.69 (0.057–8.326)	0.77	1, –	–	1, –	–
Hypotrophy	1, –	–	1, –	–	0, –	–
Cesarean section	15, 0.88 (0.2–3.8)	0.86	11, 0.00 (0.0–13.0)	0.17	4, >100 (0.0–>100)	0.25

the route of delivery, and neonatal outcomes. The indications to liver transplantation in this cohort were: Wilson's disease (n=7, 30.43%), autoimmune hepatic disease (n=6, 26.01%), viral hepatitis (n=3, 13.04%), toxic hepatic disease (n=2, 8.70%), biliary atresia (n=2, 8.70%), idiopathic hepatitis (n=2, 8.70%), and Budd-Chiari disease (n=1, 4.35%). None of the patients fulfilled the metabolic syndrome criteria before pregnancy.

The median pre-pregnancy BMI was 23 kg/m^2 and the median gestational weight gain was 12 kg. Full characteristics of the relationship between pre-pregnancy BMI and gestational weight gain are presented in Table 1.

In the presented results, 1 patient had to be considered separately and was excluded from statistical analysis – a 26-year-old woman transplanted due to autoimmune hepatitis, with chronic colitis ulcerosa. Her pre-pregnancy BMI was 15 and her weight before pregnancy was 41 kg. Her gestational weight gain was 20 kg (nearly 50% of primary weight), much more than the ACOG guidelines recommend. The patient delivered by caesarean section after 37 weeks of pregnancy and the baby

had severe hypotrophy (2080 g, 1st percentile). In this extreme case, the gestational weight gain had an inverse correlation with fetal weight. Concerning immunosuppressive treatment, 6 patients (8.70%) received a regimen based on tacrolimus and azathioprine, 2 received a regimen based on cyclosporine, and 15 received a regimen based on tacrolimus. We did not find any differences according to drug treatment.

As we expected, a theoretical dependency was observed between gestational weight gain and patient age at the time of delivery (p=0.04) and the length of pregnancy (p=0.03).

Of the 23 patients, 9 (39.13%) delivered before 37 weeks of pregnancy. The impact of time of delivery on gestational weight gain was clear – the longer the pregnancy, the greater the weight gain. Nevertheless, this model adjusted for week of delivery revealed no association between weight gain and the length of pregnancy (p=0.82).

For analysis of neonatal birth weight and gestational weight gain, we considered only patients who delivered at 37 or more

weeks of pregnancy (n=14, 60.87%). In this case, the positive correlation between GWG and neonatal birth weight was observed, and the p value was on the border of statistical significance (p=0.06).

While considering perinatal outcomes, especially time of delivery in relation to weight gain, we decided to analyze patients who delivered at term. This model was performed based on previous statistical analysis, revealing a direct positive correlation between gestational weight gain and time of delivery.

Several pregnancy complications occurred: gestational hypertension (n=1), gestational diabetes mellitus (n=2), fetal hypotrophy (n=2), and postpartum hemorrhage (n=2). None of these outcomes were significantly associated with GWG (Table 2).

The caesarian section rate was 69.57% (n=16), and in most of cases (n=15) it was performed due to obstetrical conditions. The main indications were threatening intrauterine fetal asphyxia n=6 (26.09%), previous caesarian (n=8, 34.78%), labor arrest (n=2, 8.70%), and rapidly increasing intrahepatic cholestasis of pregnancy (n=2, 8.70%). The gestational weight gain was positively correlated with the rate of caesarian section; however, the p value was 0.07.

There was 1 stillbirth, at 23 weeks of pregnancy, in a patient who had gestational hypertension, and the remaining 22 women all delivered neonates with a 5-min Apgar score of 10 points. No statistically significant difference was observed in correlation to GWG (p=0.98).

Discussion

The present study assessed the importance of gestational weight gain and pre-pregnancy BMI in a specific subpopulation of female liver transplant recipients. Several factors should be taken into consideration when analyzing this problem.

First of all, liver transplantation is not just one moment in a woman's life – it is a process – and obesity and metabolic syndrome in liver transplant recipients have multifactorial etiologies [7,17–19]. The role of the basic disease leading to liver transplantation can have a significant impact—patients transplanted because of non-alcoholic steatohepatitis had higher risk of death from cardiovascular episodes than patients requiring liver transplantations because of other reasons [8]. In the present study, patients transplanted due to biliary atresia had greater gestational weight gain than women with other indications for transplantation. However, due to the very small sample size, the risk of bias cannot be excluded and more research is needed before making further conclusions.

Immunosuppressive therapy and immunosuppressive drugs are reported to be significantly associated with pre-pregnancy BMI and weight gain [19]. The adverse effects of systemic steroids are well established and include obesity, steroid-induced diabetes, and metabolic syndrome [20]. In the study performed by Bianci et al., patients after liver transplantation who were taking tacrolimus had a lower BMI, lower rate of dyslipidemia, and higher blood pressure than patients taking cyclosporine [19]. Thus, immunosuppression based on tacrolimus monotherapy is becoming more popular as a safe alternative for polytherapy for liver graft recipients [21]. In the present study, 13 of 23 patients (56.5%) were on steroid therapy and – surprisingly – the mode of immunosuppression, especially steroids intake, did not correspond with gestational weight gain or with perinatal outcomes.

The environmental components present in healthy people, such as obesity preceding transplantation or obesogenic environment, also have a significant impact on pre-pregnancy obesity in female liver transplant recipients [18]. Richards et al. found that 67% of patients undergoing liver transplantation were overweight or obese 3 years after transplantation, and this was correlated with immunosuppression and excessive food intake [22]. In our study, patients who were overweight before pregnancy were more predisposed to gain weight over the ACOG guidelines during pregnancy, in comparison with patients with normal BMI. This result was on the border of statistical significance; thus, more research is needed to assess this association. Nevertheless, appropriate periconceptional counselling and optimizing BMI before getting pregnant seems to have potential to improve perinatal outcomes in liver transplant recipients.

When considering pre-pregnancy BMI and gestational weight gain, it is important to remember that even obesity and excessive GWG, as well as underweight and insufficient GWG, are important risk factors for adverse pregnancy outcomes in the general population [4]. According to the metanalysis performed by Voerhal et al., pre-pregnancy BMI may be a more important risk factor for adverse perinatal outcomes than is gestational weight gain [4]. However, both GWG and pre-pregnancy BMI depend mostly on maternal dietary patterns [23].

In the present study, we did not observe an effect of GWG on perinatal outcomes. However, even in this small population, consisting only of cases of live deliveries after 24 weeks of gestation, many variables were on the edge of statistical significance and more research with larger sample sizes should be performed before making conclusions.

Kaido et al. [24] emphasized the role of sarcopenic obesity as an important factor affecting overall survival in living donor liver recipients. In the present research, we did not assess

sarcopenia as a risk factor for pregnancy complications, but more research is needed on this topic.

Pre-pregnancy obesity is associated with several pregnancy complications: preeclampsia, hypertension, gestational diabetes mellitus, premature birth, and small or large for gestational age [4]. In women categorized as overweight, the risk for any adverse perinatal outcome increases to above 37.3% [4], which affects not only the perinatal outcomes, but, perhaps more importantly, plays a significant role in the child's future development. Maternal obesity in pregnancy is associated with higher risk of obesity and type 2 diabetes mellitus and higher mortality rate due to cardiovascular diseases in the children's adolescent and adult life [25]. Moreover, infants of overweight and obese women have higher blood pressure and higher BMI than infants from normal-weight mothers [1,26]. Maternal pre-pregnancy BMI and eating behavior are linked to the pattern of infant gut microbiota at 12 months of life [27]. A positive correlation between maternal BMI and skinfold thickness in the children at the age of 6 years was also noted [6]. Another study suggested that maternal obesity during pregnancy was associated with an earlier age of attaining most pubertal milestones in both sons and daughters [28]. Furthermore, a meta-analysis observed higher pre-pregnancy BMI as a risk factor for attention deficit hyperactivity disorder (ADHD) in adolescents [29]. Optimal pre-pregnancy BMI differ in particular sub-populations – in Asian populations, overweight is considered as BMI 23 kg/m^2, and from this value the rate of cardiovascular complications increases [30]. This fact should be taken into consideration while analyzing large, multi-population metanalyses.

Excessive gestational weight gain affects not only the perinatal outcomes, but can also lead to long-term maternal overweight and obesity [31,32]. Although the ACOG guidelines [5] suggest the optimal gestational weight gain (Table 3), it has several limitations in that the guidelines do not include separate recommendations for extremely obese or cachectic women; these guidelines concern the whole population of pregnant women, without divisions for ethnicity, age, drug use, or accompanying chronic diseases. A metanalysis by Voerman et al. [4] evaluated 25 cohorts to assess the association between gestational weight gain and perinatal adverse effects according to baseline status of underweight, normal weight, overweight, and obesity grade 1, 2, and 3, showing that the lowest rate of adverse perinatal outcome (26.7%) was in underweight women, where GWG was 26–27.9 kg. In lean and overweight patients, the optimal GWG was 14–15.9 kg and 2–3.9 kg, respectively, and the rate of adverse outcomes was 39.2% and 37.3%, respectively. Moreover, the risk of adverse perinatal outcomes in obese patients was 63.7%, 67.7%, and 78.8% for grade 1, 2, and 3, respectively, while the maximum GWG was more than 28 kg for grade 1 and more than 16 kg for grades 2 and 3.

Table 3. Recommended gestational weight gain – ACOG guidelines 2009.

	Pre-pregnancy BMI [kg/m^2]	Recommended pregnancy weight gain [kg]
Underweight	<18.5	12.5–18
Normal weight	19–24.9	11.5–16
Overweight	25–29.9	7–11.5
Obese	>30	5–9

The optimal weight gain for obese women was established in a study performed by Kiel et al., which suggested the optimal weight gain according to maternal obesity: 4.5–11.3 kg for grade 1, 0–4.1 kg for grade 2, and weight loss up to 4 kg for grade 3 [33].

A strength of the present study is that it is the first to analyze weight gain during pregnancy in liver transplant recipients, whereas limitations are the small sample size and use of a historical cohort. Pregnant patients after liver transplantation are a highly selected group of patients who survived liver disease and transplantation and were able to get pregnant and deliver at a minimum of 23 weeks. Thus, we cannot exclude the risk of selection bias, and more research is needed to improve perinatal outcomes.

Conclusions

Current recommendations, despite their usefulness, do not address patients with chronic diseases, such as those who underwent solid graft transplantation and are undergoing immunosuppressive treatment. Multiple factors concerning liver transplant recipients (i.e., basic disease leading to transplantation and mode of immunosuppressive treatment) may interfere with analyzing the perinatal results in this group. Our study confirms that GWG itself is not relevant as a predictor of term gestation, as the model adjusted to week of delivery revealed no association between weight gain and the length of pregnancy (p=0.82), and a positive correlation between GWG and neonatal birth weight was observed (p=0.06). GWG in liver transplant recipients did not affect hypotrophy incidence, adverse perinatal outcomes, or caesarian delivery rate.

Due to lack of research assessing pre-pregnancy BMI and gestational weight gain in liver transplant recipients, it is impossible to establish the exact value of GWG correlated with the lowest rate of perinatal outcomes. Thus, more research is needed, and appropriate patient counselling is advised.

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