Fetal Liver and Gestational Diabetes

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Gestational diabetes mellitus (GDM) is a relatively common pregnancy pathological condition that was recently defined by the American Diabetes Association (ADA) as hyperglycemia, with no obvious cause, first appearing or discovered during the pregnancy's second or third trimester. It was suggested to include in this definition the preexisting, nonidentified cases of type 2 diabetes mellitus ("overt diabetes") and type 1 diabetes mellitus, but these are detected very early after the onset of the pregnancy. However, GDM develops later during the pregnancy and is usually detected between week 24 and week 28 of gestation.

Keywords: fetal liver ; gestational diabetes ; dietary patterns ; obstetrical ultrasound ; pregnancy ; pregnancy complications

1. Introduction

Gestational diabetes mellitus (GDM) is a relatively common pregnancy pathological condition that was recently defined by the American Diabetes Association (ADA) as hyperglycemia, with no obvious cause, first appearing or discovered during the pregnancy's second or third trimester [1][2][3][4][5]. It was suggested to include in this definition the preexisting, nonidentified cases of type 2 diabetes mellitus ("overt diabetes") and type 1 diabetes mellitus, but these are detected very early after the onset of the pregnancy [6][7]. However, GDM develops later during the pregnancy and is usually detected between week 24 and week 28 of gestation [8].

A relatively recent meta-analysis of 40 studies involving a total of 177,063 subjects displayed that the prevalence of GDM in Europe is 5.4% [9]. The incidence of GDM differs depending on the diagnostic guidelines and the cutoff values employed, respectively, and is currently estimated at 14% of all pregnancies worldwide. Thus, GDM affects around 18 million pregnancies annually [2]. The exact incidence is difficult to establish as the limits of the range vary significantly, i.e., from 2% to 37% [10][11][12]. The International Diabetes Federation estimated that 21.3 million live births worldwide are affected by some type of hyperglycemia in pregnancy, out of which 83% are due to GDM. Meanwhile, one in six pregnancies is affected by GDM [13]. The prevalence of hyperglycemia in pregnancy varies between different geographical areas from 10.4% in North America and the Caribbean Region to 25.0% in Southeast Asia [14]. Ethnicity influences the risk of GDM, with Asian women having an increased risk versus other ethnic groups [15]. The incidence of GDM has been steadily increasing, mainly due to the increase in the age of the pregnancy and, most importantly overall, the weight of women [16]. Risk factors for the development of GDM include a family history of maternal overweight/obesity or diabetes, age of the mother >35 years, smoking, use of a Western diet, micronutrient deficiencies, multiparity, a history of dysglycemia, personal history of GDM or previous pregnancy with a macrosomic fetus (newborn above 4 kg). (**Figure 1**) [17][18][19][20][21][22]. A personal history of hyperglycemia or the presence of GDM in a previous pregnancy increases the risk of GDM recurrence in subsequent pregnancies [21]. Women in whom the presence of hirsutism and/or hyperandrogenism without a diagnosed polycystic ovary syndrome or other clinical conditions associated with insulin resistance (e.g., obesity, acanthosis nigricans) is noted seem to display elevated odds of GDM versus females without polycystic ovary syndrome or the aforementioned conditions [20][23][24]. In addition, women diagnosed with hypertension have an increased risk of GDM versus normotensive females [25]. The use of several drugs, e.g., antidepressants, antipsychotics, beta-adrenergics, or corticosteroids, has been linked with an increased risk of GDM as well [26][27][28]. In addition, some other factors that can be incriminated in the development of GDM are macrosomia (exaggerated somatic development of the fetus) during the current pregnancy or 2 or more episodes of glycosuria during the second or third trimester of gestation [2][5].

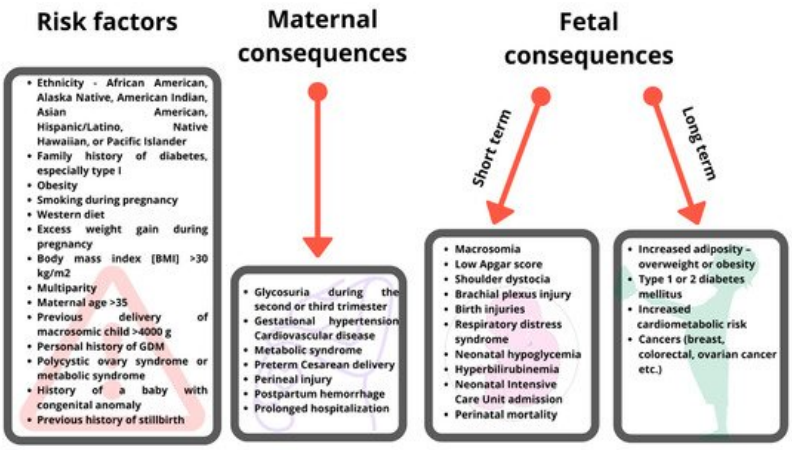

Figure 1. Consequences of gestational diabetes mellitus (GDM) on the mother, fetus, and offspring.

The pathophysiology of GDM is not fully understood, but the latest studies point out that in GDM there is an elevated insulin requirement and a progressive peripheral resistance to the action of this hormone, most often present but not expressed before the pregnancy. Various circulating cytokines, e.g., interleukin 6 (IL−6) or tumor necrosis factor-alpha (TNF-alpha), seem to be culprits in exacerbating insulin resistance in pregnancy [3].

Although the above tests have an undeniable diagnostic value, new noninvasive diagnostic methods, e.g., ultrasonography, have emerged as useful tools in identifying patients at risk of developing GDM. Thus, Perovic et al. (2012) highlighted the advantages of an ultrasound GDM screening score as a predictor of GDM development by screening pregnant females who were at least in the week 24 of gestation and who harbored risk factors for GDM. The ultrasound GDM screening score proposed by the aforementioned researchers exhibited a specificity and a sensitivity of over 89% and took into consideration several relevant parameters, i.e., subcutaneous fetal adipose tissue, the immature appearance of the placenta, and the placental thickness [29]. Moreover, another study by Gojnic et al. (2012) revealed that subcutaneous fetal adipose tissue exhibited the best specificity and sensitivity in predicting GDM if the evaluation was performed in week 32 of gestation [30]. Furthermore, prior to week 24 of gestation, other ultrasound parameters, i.e., head circumference below the 10th percentile and femur length below the 10th percentile have been linked with a 13–17% elevated risk of GDM [31].

2. Fetal Consequences of Maternal Gestational Diabetes Mellitus and Maternal Diet

Maternal hyperglycemia causes diabetic embryopathy, which represents multiple impairments in embryogenesis and diabetic fetopathy, translated as complications in fetal development [32]. Maternal hyperglycemia in the first trimester of pregnancy has an effect similar to that of ionizing radiation, hypoxia, alcohol, and high-risk drugs inhibiting the uptake of myoinositol which is indispensable in the stage of gastrulation and neurulation, resulting in congenital malformations, e.g., caudal regression, neural tube defects, atresia and digestive agenesis [33]. GDM with poor glycemic control causes fetal hyperglycemia (normally, the glycemia of the fetus is always 23–30 mg/dL below the maternal one), resulting in fetal hyperinsulinism and β-pancreatic cell hypertrophy [34]. These manifestations of fetal adaptation to the hyperglycemic environment cause organomegaly (especially cardiomegaly) and weight gain. Insulin excess causes the stimulation of fetal adipogenesis and leads to macrosomia [35]. Fetal macrosomia is defined as the fetal weight above the 90th percentile, i.e., over 4000 g; this value is calculated by a mathematical distribution of the birth weight of all newborns at 39 weeks of gestation [36].

The anabolic action of insulin is manifested at the fetal level by increasing the tissue production of amino acids and glucose while increasing the transplacental gradient for glucose and resulting in excessive intake [37]. Moreover, Naeye et al. (1965) reported that in postmortem specimens, the liver size of fetuses born to diabetic mothers was approximately 80% elevated versus healthy counterparts due to both cellular hyperplasia and hypertrophy and an elevated amount of hematopoietic tissue [38].

Fetal hyperinsulinism, in turn, causes stimulation of glycogen accumulation in the liver, increased lipid synthesis with the accumulation of subcutaneous adipose tissue, and disproportionate growth of insulin-sensitive tissues, namely, the liver tissue, muscle tissue including the myocardium, and the subcutaneous adipose tissue [39]. The fetus exposed to the hyperglycemic environment develops cardiomegaly with cellular changes, e.g., aggregation of ribosomes and vacuoles in

the cytoplasm, structural changes in the myocardial tissue such as myoblast proliferation and increased rate of induction of apoptosis in myocardial cells, functional changes such as a high level of vascular endothelial growth factor (VEGF), and a very low amount of nitric oxide (NO) [40].

Prospective randomized controlled studies to track the effects of maternal nutritional factors on the fetal liver are limited due to ethical implications. Thus, on human subjects, these effects can be followed only in retrospective studies. However, in the literature, there are data collected from animal studies that may show the possible effects of the maternal diet on fetal liver fat. A study on guinea pigs found that feeding the mother during pregnancy a Western diet is associated with a lower overall fetal fat level but with an increase in fetal liver fat ($p < 0.02$) [41]. In their study, Garcia-Contreras et al. demonstrated that maternal hydroxytyrosol supplementation alters the energy availability and content of fatty acids in the fetal tissues, diminishing the gross energy content of the fetal liver with an overall decreased amount of saturated fatty acids and an increased amount of polyunsaturated fatty acids [42]. Furthermore, Xue et al. demonstrated in a study conducted on sheep that maternal malnutrition is associated with changes in fetal metabolism such as increased oxidation processes and ketogenesis, increased triglyceride synthesis, decreased degradation of triglycerides and phospholipids, and decreased steroid synthesis [43].

3. The Size of Fetal Liver as a Predictive Parameter for the Evolution of GDM

Fetal growth and fetal liver development are influenced by the nutrient intakes of the fetus. The glucose tolerance of the mother and fetus and the insulin /insulin-like growth factor axis act as mediators of the relationship [44][45].

Fetal screening by ultrasound examination (2D, 3/4D) performed between 18 and 23 weeks of gestation is a noninvasive, effective, fast, and relatively inexpensive method of monitoring fetal development that can replace the OGTT as a diagnostic method for GDM [4][5]. The evaluation of fetal dimensions is performed by measuring some biometric indices. In addition to the standard ones evaluated in all routine OUS during pregnancy, such as fetal biparietal diameter, abdominal diameter, head diameter, or femur length, there are also some specific indices to the GDM-complicated pregnancy, such as fetal liver length (FLL) or volume (FLV), abdominal wall thickness, abdominal fat layer or Wharton's gelatin thickness [4][5][46]. Of these, the most important is the FLL and the FLV because the liver of the fetus is directly influenced by the fetal blood glucose levels via excess glycogen deposition under the action of fetal insulin [4][46].

Given the direct relationship between GDM and various parameters related to fetal growth, particularly liver indices, which can be assessed by ultrasound, we wanted to evaluate the effectiveness of OUS as a method of diagnosis and monitoring complicated pregnancies with GDM.

Thus, we computed a search in PubMed/MEDLINE, Clarivate Analytics Web of Science, SCOPUS, and ScienceDirect for articles published up to 1 April 2021 that evaluated the relationship of fetal liver indices with GDM. For inclusion in this review, we selected the articles published in English, French, Italian, and Romanian (the languages spoken by the authors) with full texts that could be accessed and presented relevant information on OUS parameters useful in the evaluation of GDM. The exclusion criteria were (1) articles with full texts in another language than the aforementioned ones; (2) articles whose full-texts could not be accessed; (3) case reports, letters to the editor, reviews, or abstracts presented at various scientific conferences. The keywords and word combinations employed were "fetal liver", "obstetrical ultrasound", "gestational diabetes", "pregnancy", "gestational diabetes mellitus", "midtrimester ultrasound", "fetal liver length measurement", "fetal growth", "fetal liver blood flow", "umbilical venous volume flow", and the results are systematized in the following paragraphs and in **Table 1** .

Table 1. Fetal liver-related parameters evaluated by obstetric ultrasound.

Liver Ultrasound Timing (Weeks of Gestation)	No. of Subjects	Condition	Evaluated Parameters	Main Results	Reference
18, 28, 36	104	T1D, T2D, obesity	FL, WC, FLL, LS	FL↑, WC↑, FLL↑ versus reference values ($p < 0.001$) FLL↑ at all-time points during pregnancy ($p < 0.001$) Mean excess size of FL, WC: steady between 18–36 weeks ↑LS: 12.0% (18 weeks) → 16.7% (24 weeks) → 19.3% (36 weeks) ($p < 0.02$) T1D versus T2D: no differences at 18, 28, 36 weeks Postpartum: weight of newborns from diabetic mothers = 1.79 x controls	Roberts et al. (1994) [47]
21–24	123	GDM, healthy women	SFL, LRLL, CM, PT, WJA	LRLL↑ ($p < 0.01$) in GDM females FLV and maternal HbA1c were connected: liver volume is increased by 8.1% for each unit increase in HbA1c (95% CI 3.5–13.0%) and by 14% (95% CI 13.0–15.8%) per week of gestational age	Mirghani et al. (2006) [48]
18–36 (median 26)	64	IDDM, healthy women	FWC, FLV, FLV/EFWR, UEFW, UVV/kg FW	IDMM: ↑FLL, ↑FLV/EFWR = 1.20 x controls IDMM: ↑FWC, ↑FLV, ↑UEFW, ↑FLV/EFWR IDDM: ↓UVV/kg FW No differences in FLV at 32 and 36 weeks in NGT versus GDM if appropriate treatment	Boito et al. (2007) [49]
32, 36	27	GDM, NGT	FLV, FW	GDM versus NGT: no difference in FLV, FW FLV (32 weeks)-BW correlation (ρ = 0.42, $p = 0.03$) FLV (36 weeks)-BW correlation (ρ = 0.61, $p < 0.001$)	Dubé et al. (2011) [16]
23	331	GDM, healthy women	FLL	GDM: ↑BMI, ↑second parity, ↑ fetal liver measurements ($p < 0.001$) FLL-FPG positive correlation during OGTT ($p < 0.001$) FLL-BMI correlation (r = 0.586; $p < 0.001$) no FLL-parity correlation FLL-GDM association (OR = 1.401; 95% CI 1.308–1.501; $p < 0.001$; R2 = 0.597) independent of BMI/parity FLL = 39 mm, cutoff value for predicting GDM (sensitivity: 71.76%, specificity: 97.56%, positive predictive value: 91.0%, negative predictive value: 90.9%)	Perovic et al. (2014) [46]
24–28	97	GDM, healthy women	FLV, EFW	no differences in standard fetal biometric measurements, EFW GDM: ↑FLV ($p < 0.01$), ↑BMI, ↑BW no FLV-BMI correlation BW-FLV positive correlation ($p < 0.05$)	g et al. (2018) [4]
24	120	GDM, healthy women	FLL	midtrimester connection of FLL and FPG (OGTT)GDM: ↑FLL [37.2 (3.4)] versus controls [33.1 (2.7)], $p < 0.001$ FLL (GDM) = 1.6 x controls (OR 1.6; 95% CI 1.305–1.962), specificity 95.9%, negative predictive value 95.9%	Showman et al. (2019) [5]
28, 37	60	PGM, GDM, healthy women	FLL	PGM, GDM vs. controls: ↑FLL (28 weeks), 48.9 ± 3.4 mm vs. 41.7 ± 3.3 mm, $p < 0.001$ PGM, GDM vs. controls: ↑FLL (37 weeks), 65.6 ± 4.8 mm vs. 54.5 ± 3.4 mm, $p < 0.001$ PGD vs. GDM: ↑FLL (28 weeks), 50.55 ± 2.35 mm vs. 46.15 ± 2.1 mm, $p = 0.01$ PGD vs. GDM: ↑FLL (37 weeks), 66 ± 2.65 mm vs. 59.69 ± 2.7 mm, $p = 0.01$ FLL correlated with WC (r = 0.82), AFI (r = 0.86), HbA1c levels (r = 0.83), EFBW (r = 0.82), BW (r = 0.80)	Gharib et al. (2019) [50]
18–21, 22–25, 26–30	69	Healthy human fetuses	FLV	↑FLV 6.57 cm^3 (18–21 weeks) → 14.36 cm^3 (22–25) → 20.77 cm^3 (26–30 weeks) ↑FLV by 20%/week of gestation vs. normal	Szpinda et al. (2015) [51]

Liver Ultrasound Timing (Weeks of Gestation)	No. of Subjects	Condition	Evaluated Parameters	Main Results	Reference
24–36	49	PGM: T1D, T2D	LPVFV, TVSPFL, UVLF	↑LPVFV, ↑TVSPFL vs. reference no difference in PVF ↑UVLF in GDM vs. reference mean	Lund et al. (2019) [52]
18, 20	137	Healthy women	LF, UVLF	postprandial ↑ liver flow in NW postprandial ↓ liver flow if ↑BMI prepregnancy ↑UVLF in NW regardless of fetal size ↓UVLF in the overweight	Opheim et al. (2019) [53]

Abbreviations: GDM, gestational diabetes. FL, femur length. WC, waist circumference. FLL, fetal liver length. T1D, type 1 diabetes. 270 T2D, type 2 diabetes. GDM, gestational diabetes. SFL, subcutaneous fat layer. LRLL, length of the right lobe of the liver. CM, cardiac 271 muscle. PT, placental thickness. WJA, Wharton's jelly area. IDDM, insulin-dependent diabetes mellitus. FWC, fetal WC. FLV, fetal 272 liver volume. FLV/EFWR, FLV/estimated fetal weight ratio. UEFW, ultrasonically estimated fetal weight. UVV/kg FW, umbilical 273 venous volume flow per kilogram fetal weight. UAPI, umbilical artery pulsatility index. NGT, normal glucose tolerance. FPG, fasting 274 plasma glucose. BW, birth weight, OR odds ratio. EFW, estimated FW. PGD, pre-GDM. vs., versus. EFBW, estimated fetal BW. 275 LPVFV, left portal vein flow velocity. TVSPFL, total venous supply to the fetal liver. PVF, portal venous flow. UVLF, umbilical venous 276 liver flow. UVF, umbilical vein flow. NW, normal weight, LF, liver flow. ↑ increased. ↓ decreased. → to/at.

4. The Value of Nutrition Therapy in GDM

Currently, nutritional and lifestyle interventions have been recognized as the cornerstone of therapy for females diagnosed early with GDM. These approaches have emerged as attractive strategies with benefits that extend beyond pregnancy, being particularly helpful in decreasing the risk of CVD or T2DM [54][55][56]. It is estimated that 70–85% of cases can be controlled with such interventions alone [57]. These strategies are based on caloric restriction, the control of carbohydrate intake, and physical activity within tolerability limits. Some of the eight globally recognized diets that help pregnant women lose weight are the MedDiet or the DASH diet [54][56].

The caloric restriction remains a foundational strategy in preventing ponderal gain, controlling glycemia values, and preventing macrosomia in the offspring born to GDM mothers [54]. A strict dietary approach (based on an amount of 1500 daily, i.e., 50% reduction) has led to ketonuria and ketonemia, but a more moderate one has been more successful, managing to control weight gain and glucose levels without increasing ketonemia [54]. One study showed that decreasing the BMI by >2 points results in a subsequent decrease of the GDM risk by 74%, whereas an elevation of the BMI nearly doubles the risk of GDM [55].

Physical activity has shown multiple benefits, such as improving blood glucose control, reducing weight, insulin resistance, and cardiovascular risk. Thus, regular physical exercise might play an important role in GDM prevention [54][55][58][59]. Some studies showed a rapid effect of reducing glucose levels by 23 mg/dL at 30 min and a 69% reduced risk of GDM if sustained physical activity was performed [54][55]. Usually, if the target blood glucose levels are not reached within 1–2 weeks, pharmacotherapy should be initiated [57][60]. Historically, when that happened, the sole alternative was insulin because oral antidiabetic medications were contraindicated during pregnancy due to the possible risks of teratogenicity and life-threatening neonatal hypoglycemia [60]. Today, the most prescribed oral antidiabetics during pregnancy are metformin and glyburide, which, although not approved, are not banned by the United States Food and Drug Administration (FDA) and are recommended by a few key organizations, including the American Congress of Obstetricians and Gynecologists (ACOG), the Society of Maternal–Fetal Medicine (SMFM), or the American Diabetes Association (ADA) [61][62][63].

5. Conclusions

Given all the above, we conclude that an early diagnosis of GDM is crucial due to its potential complications, i.e., preeclampsia, birth defects, and possible development of CVD and T2DM later in the life of the newborn. Screening all pregnancies with an OGTT may not always be feasible due to several drawbacks. Since a midtrimester OUS is already a standard, future studies should investigate its feasibility and utility in the prediction, early diagnosis, and follow-up of GDM and, additionally, in estimating the birth weight prenatally. Measuring different fetal liver indices is an easy technique and could emerge as a reliable method to assess GDM pregnancies. Further research should clarify whether common

measurement parameters, i.e., FLL and FLV, could be strong predictors of GDM and to which extent they positively relate to maternal HbA1c levels. In addition, other indirect indicators, such as fetal liver blood flow, have been shown to be strongly connected to the glycemia of the GDM female in the first trimester of pregnancy. Finally, these studies highlighted the crucial role of a proper multidisciplinary approach to GDM treatment during pregnancy and maternal nutritional status, as the enhanced growth of the fetal liver can be modulated by controlling the mother's glycemia even in the late stages of pregnancy. Soon, medical nutrition therapy should also be integrated into the management of pregnancies at risk for GDM.

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