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Review Article

Effects of Gestational Diabetes Mellitus on Fetal Liver Length: A Systematic Review and Meta-Analysis

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Abstract

Background: Gestational diabetes mellitus (GDM) is a serious pregnancy complication that can affect various organs and organ systems of the mother and fetus. In diabetic mothers, increased blood glucose delivery to the fetus leads to fetal hyperglycemia and hyperinsulinemia, which promotes the growth of insulin-dependent organs such as the liver. Therefore, this systematic review and meta-analysis was conducted to more precisely estimate the association between GDM and fetal liver length (FLL).

Methods: Six electronic databases (PubMed, Scopus, Web of Science, ProQuest, Cochrane, and Wiley) were searched up to Aug 2023. Two reviewers independently extracted data and assessed the risk of bias using the Newcastle–Ottawa Scale. The pooled weighted and standardized mean differences in FLL were calculated using random-effects models. Heterogeneity, subgroup analysis, and publication bias were also assessed using funnel plots. All statistical analyses were performed using Stata Version 16.0.

Results: Twelve articles were included in the final meta-analysis. GDM was associated with increased FLL, as assessed by ultrasound, in both the second (SMD=1.56; 95% CI: 1.04, 2.08; *P*<0.001) and third (SMD=0.84; 95% CI: 0.07, 1.61; *P*<0.001) trimesters of pregnancy. The pooled mean difference in FLL between the GDM and non-GDM groups was 4.85 mm (WMD=4.85; 95% CI: 3.26, 6.45), indicating larger liver size in fetuses from mothers with GDM.

Conclusion: GDM is a significant risk factor for increased FLL, as assessed by ultrasound, which may reflect fetal overgrowth and metabolic dysfunction.

Keywords: Fetus; Gestational diabetes mellitus; Liver; Meta-analysis

Introduction

Diabetes mellitus (DM), one of the top 10 causes of death in the world (1), with an estimated prevalence of 783 million people in 2045 (2) imposes a considerable socioeconomic burden worldwide. Type 1, type 2, and gestational diabetes mellitus (GDM) are the three main types of DM (3). GDM, one of the most common complications of pregnancy, is defined as glucose intolerance

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with onset or first recognition during the second or third trimester of pregnancy, resulting in hyperglycemia of variable severity (4, 5).

In 2021, the International Diabetes Federation reported that the global prevalence of GDM was 14.0% (95% confidence interval: 13.97%–14.04%) (6).

GDM has short- and long-term consequences for the mother and the fetus. Maternal complications of untreated GDM include pregnancy-induced hypertension, cesarean delivery, induction of labor, and preeclampsia (7-9). These women are more likely to develop metabolic syndrome, DM, and cardiovascular diseases later in life (10-12).

Fetal/neonatal complications include fetal macrosomia, shoulder dystocia, birth injuries, neonatal hypoglycemia, and hyperbilirubinemia (7, 13). These children will more often suffer from obesity, metabolic syndrome, DM, and cardiovascular disease later in life (13-15).

In the study of Wang et al., (16), the incidences of fetal macrosomia, hyperbilirubinemia, hypoglycemia, premature births, and hypocalcemia in neonates in the GDM group were 24.15%, 12.29%, 17.80%, 19.07%, and 9.32% respectively, which were significantly higher than those in the control group.

The growth of the fetus is assessed throughout gestation by measuring different dimensions of the fetal body, one of which is fetal liver length (FLL) (17).

In diabetic mothers, increased blood glucose supply to the fetus leads to fetal hyperglycemia and hyperinsulinemia, which promotes the growth of insulin-dependent organs such as the liver (18-22).

Due to the importance of this issue, despite the existence of numerous preliminary studies worldwide, no comprehensive systematic review and meta-analysis has been conducted investigating the relationship between GDM and FLL. This systematic review aimed to provide a comprehensive analysis of the relationship between GDM and FLL through a meta-analysis. This review aimed to offer a more accurate estimation of this association, drawing upon a synthesis of relevant research studies to inform clinical practice and future research in this field.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (23).

Search Strategy

The following databases were searched up to Aug 2023: PubMed, Scopus, Web of Science, ProQuest, Cochrane, and Wiley. The main search strategy was as follows: "gestational diabetes" OR "GDM" AND "fetus*" OR "fetal" AND "liver length". The search strategy for each database is detailed in Appendix 1. Additionally, the reference lists of electronically retrieved manuscripts were hand-searched to identify additional relevant citations and included in Google Scholar.

Eligibility Criteria

There was no restriction on years of publication; however, only English-language articles were considered for inclusion.

Only cohort, case-control, and cross-sectional studies were included that met the following criteria: 1) Studies evaluating FLL during pregnancy 2) Studies comparing pregnancies with and without GDM 3) Studies that reported FLL as mean and standard deviation or mean difference and standard error. The exclusion criteria were 1) studies with qualitative data and 2) duplicate publications of the included studies.

Article Selection

Two authors (S.A. and A.R.) independently screened the titles and abstracts for eligibility. Any disagreements were resolved through discussion and consultation with another author (M.J.G.). The full texts of the potentially relevant articles were obtained and independently assessed against the inclusion criteria by the authors (M.G. and G.R. and A.R.), and, again, disagreements

were resolved through discussion with another author (M.J.G.).

Data Extraction

Data were extracted independently by two authors (S.A. and M.G.) using a customized data extraction form for data extraction and management. The form included information on article characteristics, including the first author's name, year of publication, initial sample size, mean participant age, study design, trimester of pregnancy, diagnostic criteria for GDM, and mean and standard deviation of FLL.

Assessment of Risk of Bias

We assessed the quality of the included studies using the Newcastle–Ottawa Scale (NOS), which evaluates non-randomized studies for selection bias, comparability, and outcome/exposure assessment (24). Studies with less than 5 stars were considered low quality, studies with 5 to 7 stars were considered fair quality, and studies with more than or equal to 7 stars were considered high quality.

Two authors (A.R. and S.A.) evaluated each study independently and resolved any disagreement through discussion and consensus.

The scale was chosen for this context due to its reliability, validity, and relevance to the variables being measured. It has been widely used in previous research and is well-established in the field. Additionally, researchers considered the ease of scale administration and interpretation in this context.

Data Analysis

Pooled mean differences in FLL between the GDM and non-GDM groups were estimated using a random-effects model and presented as weighted mean differences (WMDs) with 95% confidence intervals (CIs). Furthermore, to examine the impact of GDM on FLL, the standardized mean difference (SMD) was estimated using a random-effects model to synthesize the findings. Heterogeneity among the included studies was assessed using Cochrane Q and I^2 statistics. Cochrane Q with a $P<0.05$ and $I^2 > 50\%$ demonstrated substantial heterogeneity among the included studies. Finally, subgroup analyses were performed on study features, including quality level, trimester, study design, and country. Publication bias was evaluated by examining the asymmetry of the funnel plot and Egger and Begg's test ($P<0.05$ considered as significant). When publication bias existed, the trim-fill adjustment method was used to assess the effect of this bias on outcomes. All analyses were performed using Stata Version 16.0 (StataCorp, College Station, TX, USA).

Results

Literature Search

According to the predefined search strategy, 3402 records were initially found through the systematic literature search in electronic databases. Overall, 3130 studies were screened for eligibility after removal of duplicates (n=272). 2974 studies were removed by reviewing the titles and abstracts. The full texts of the remaining 156 articles were assessed for eligibility, 146 of which were removed for various reasons (Fig. 1).

Study Characteristics

Twelve studies were included in the systematic review, and the extracted data are summarized in Table 1.

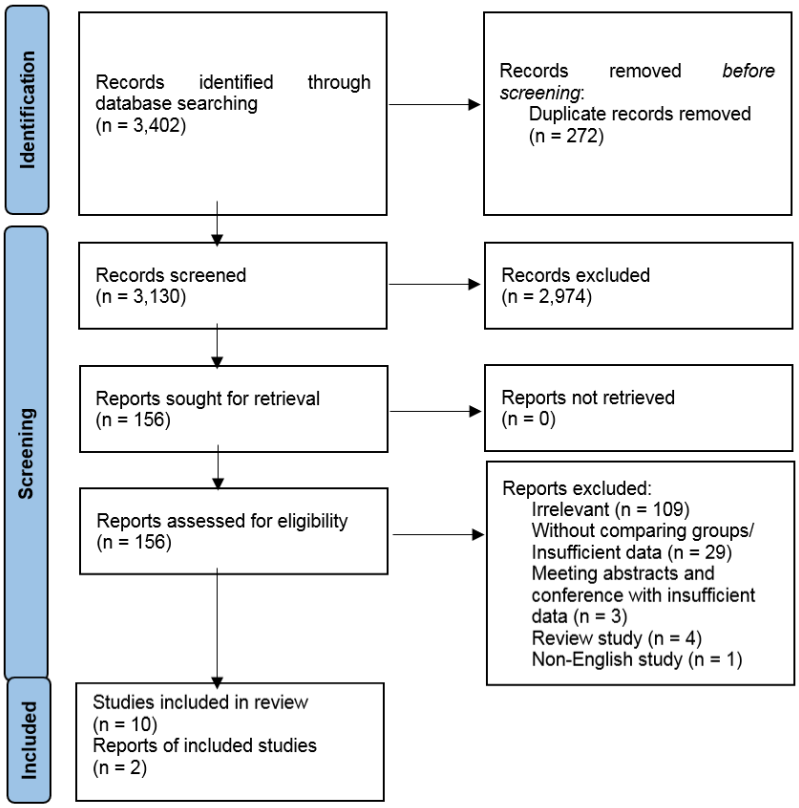

Fig. 1: PRISMA flow diagram of the study selection

Table 1: Characteristics of included studies

First author, year	Country	Study design	Trimester of pregnancy	Maternal age (Mean ± SD)		GDM criteria
				Case	Control	
Rahman N, et al. 2016	Bangladesh	Case-control	Second	aged from 18-35 yr		WHO
Showman H.A.K, et al. 2019	Iraq	Cross-sectional	Second	27.9 ±3.3	28.1± 3.9	NICE
Perovic M, et al. 2015	Serbia	Case-control	Second	28.8 ± 4.9	28.9 ± 5.9	ADA
Mirghani H, et al. 2007	United Arab Emirates	Cross-sectional	Second	NR		WHO
Mackic M, et al. 2013	Serbia	Case-control	Second	NR		ADA
Fattah E.A.A.EI, et al. 2017	Egypt	Cross-sectional	Second	NR		WHO
Cevik M, et al. 2020	Turkey	Case-control	Second	31.04±6.39	29.32±5.23	IADPSG
Abd Elwahab A.M, et al. 2018	Egypt	Case-control	Second	30.92 ± 4.51	28.54 ± 4.78	IADPSG
Gharib W.F, et al. 2019	Egypt	Case-control	Second	28.3 ± 5.8	28.1 ± 5.5	ADA
Gharib W.F, et al. 2019	Egypt	Case-control	Third	28.3 ± 5.8	28.1 ± 5.5	ADA
Elhassany H.H.A, et al. 2019	Egypt	Cross-sectional	Third	29±4		ADA
Stanirowski P.J, et al. 2021	Poland	Cross-sectional	Third	Median:32.5 (IQR:28.85-36.6)	Median: 30 [IQR:27.7–32]	WHO
Pouya E.K, et al. 2022	Iran	Case-control	Third	32.85±5.89	30.55±5.94	NR

GDM: gestational diabetes mellitus; IADPSG: International Association of Diabetes and Pregnancy Study Groups; WHO: World Health Organization; ADA: American Diabetes Association; NICE: National Institute for Health and Care Excellence; NR: not reported; IQR: Inter quantile range

One study was published in 2007 (25), while the other studies were published from 2013 (17, 26-35) onwards. Seven were case-control studies (17, 26, 28, 30-32, 35) and five were cross-sectional studies (25, 27, 29, 33, 34). Four were from Egypt, two from Serbia, and the remaining were from Bangladesh, Iraq, Turkey, Poland, Iran, and the United Arab Emirates.

WHO criteria, International Association of Diabetes and Pregnancy Study Groups (IADPSG), National Institute for Health and Care Excellence (NICE), and American Diabetes Association criteria (ADA) were used for GDM diagnosis.

Studies evaluated FLL using ultrasound. Sonographic assessment of FLL was performed in the second or third trimesters of pregnancy. Among these studies, Gharib et al.'s study (32) examined FLL in both the second and third trimesters.

Table 1 presents the characteristics of the studies included in this meta-analysis. Overall, 1901 pregnant women were included in the analysis. Of these, 1625 were in the second trimester (case=310, control=1315) and 276 were in the third trimester (case=129, control=147).

Quality Assessment

The quality of the included studies was evaluated using the Newcastle–Ottawa Quality Assessment scale, and most (66.67%) were found to be of good quality (Table 2). The mean of quality score was 7±1.15 (min=5 and max=9).

Table 2: NOS scores of case-control studies and cross-sectional studies

Case-control studies										
	Selection				Comparability	Exposure			Total	Score
Rahman N, et al. (26)	*	*	*	*	*	*	*	*	8	Good
Perovic M, et al. (17)	*	*	*	*	-	*	*	*	7	Good
Mackic M, et al. (28)	*	*	*	*	-	*	*	-	6	Fair
Cevik M, et al. (30)	*	*	*	*	-	*	*	*	7	Good
Abd Elwahab A.M, et al. (31)	*	*	*	*	-	*	*	*	7	Good
Gharib W.F, et al. (32)	*	*	*	*	-	*	*	*	7	Good
Pouya E.K, et al. (35)	*	-	-	*	-	*	*	*	5	Fair
Cross-sectional studies										
	Selection				Comparability	Outcome			Total	Score
Showman H.A.K, et al. (27)	*	-	*	**	**	**	*		9	Good
Mirghani H, et al. (25)	*	-	-	**	-	**	*		6	Fair
Fattah E.A.A.EI, et al. (29)	*	-	-	**	-	**	*		6	Fair
Elhassany H.H.A, et al. (33)	*	-	*	**	-	**	*		7	Good
Stanirowski P.J, et al. (34)	*	-	*	**	**	**	*		9	Good

Results Of Meta-Analysis

GDM had a large significant association with FLL (SMD=1.35; 95% CI: 0.87, 1.83; P<0.001; I^2 =92.48%) (Fig. 2A). This association was large and significant both in the second trimester (SMD= 1.56; 95% CI: 1.04, 2.08; P<0.001; I^2=91.44%) and the third trimester (SMD=0.84; 95% CI:0.07, 1.61; P<0.001; I^2=86.47%) (Fig. 2A). Since all studies used the same units of measurement (millimeters), WMD was also calculated in the meta-analysis. The results of the WMD in FLL between the two groups showed that the liver length of the GDM group was significantly higher than that in the control group (WMD=4.85; 95% CI: 3.26, 6.45). Moreover, in the second trimester, 5.04 mm (WMD=5.04; 95% CI: 3.16, 6.91) and 4.46 mm (WMD=4.46; 95% CI: 0.7, 8.21) in the third trimester, the FLL in GDM was higher than in the control group (Fig. 2B).

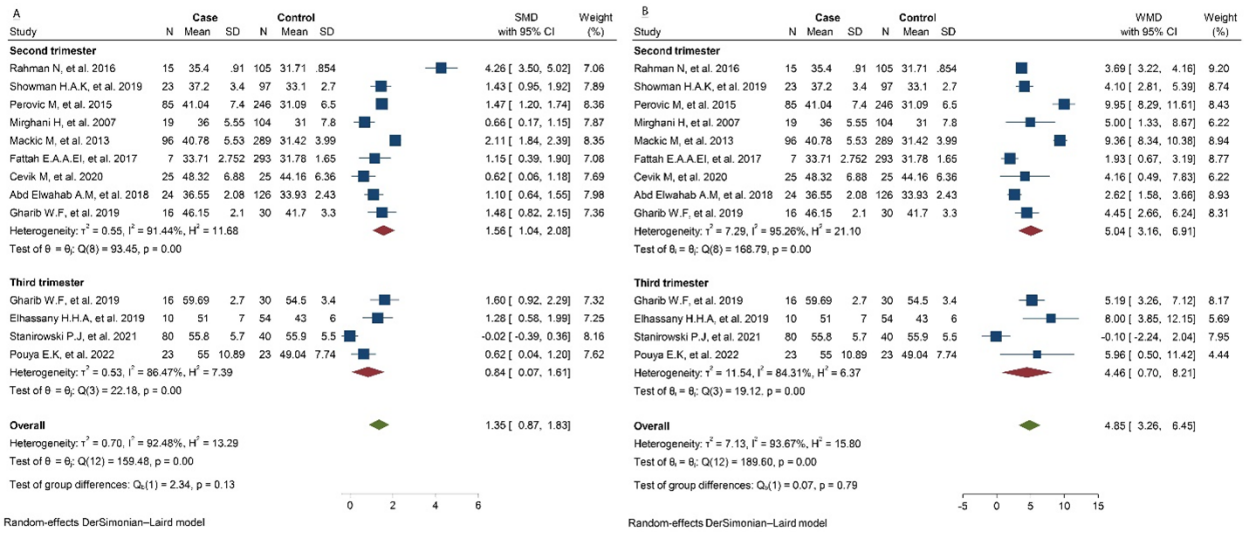

Fig. 2: Forest plots of meta-analyses of the effects of gestational diabetes mellitus and fetal liver length by trimester

A. For Standardized Mean Difference (Hedges g)
B. For Weighted Mean Difference (WMD)

For second-trimester studies, the subgroup analysis for the quality level of the study revealed significant mean differences in FLL among good-quality studies (WMD = 4.79; 95% CI: 3.08, 6.51) (Fig.3B). The results of other subgroups showed that the mean FLL was significantly higher in the GDM group compared to the control group (Fig. 3B). The results of other subgroups are presented in Fig. 3 A and B.

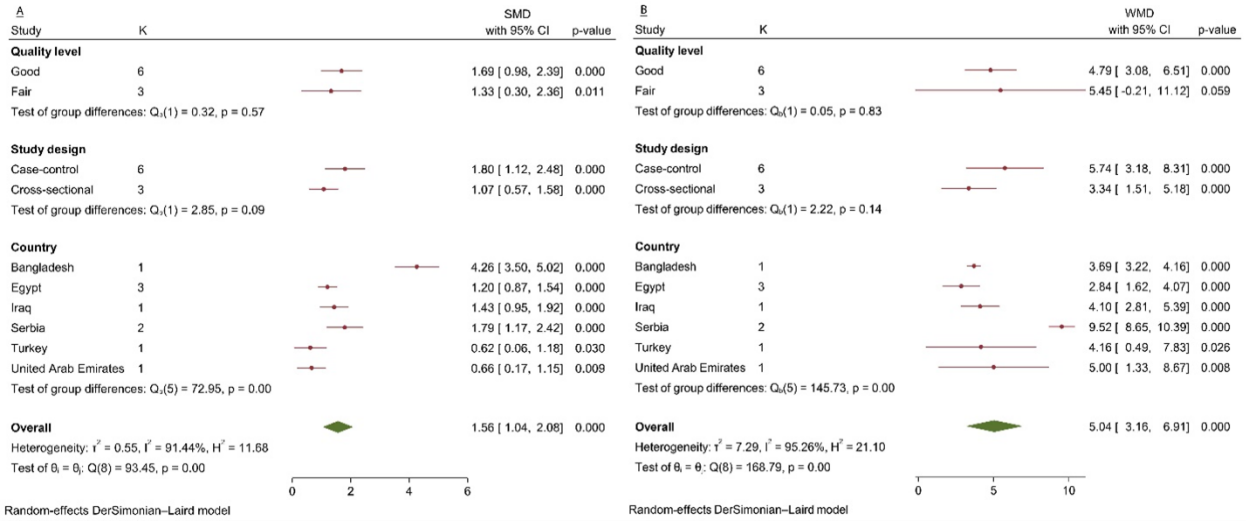

Fig. 3: Subgroup meta-analyses of the effects of gestational diabetes mellitus and fetal liver length in second trimester

A. For Standardized Mean Difference (Hedges g)
B. For Weighted Mean Difference (WMD)

For third-trimester studies, the subgroup analysis for the quality level of the study did not find significant mean differences in FLL among good-quality studies (WMD=4.13; 95% CI: -0.31, 8.56) (Fig. 4B). Subgroup analysis based on the type of study showed that the mean difference of FLL was significant in case-control studies (WMD=5.28; 95% CI: 3.46, 7.09); however, it was not significant in cross-sectional studies (WMD=3.75; 95% CI: -4.18, 11.67) (Fig. 4B). The results of other subgroups are presented in Fig. 4.

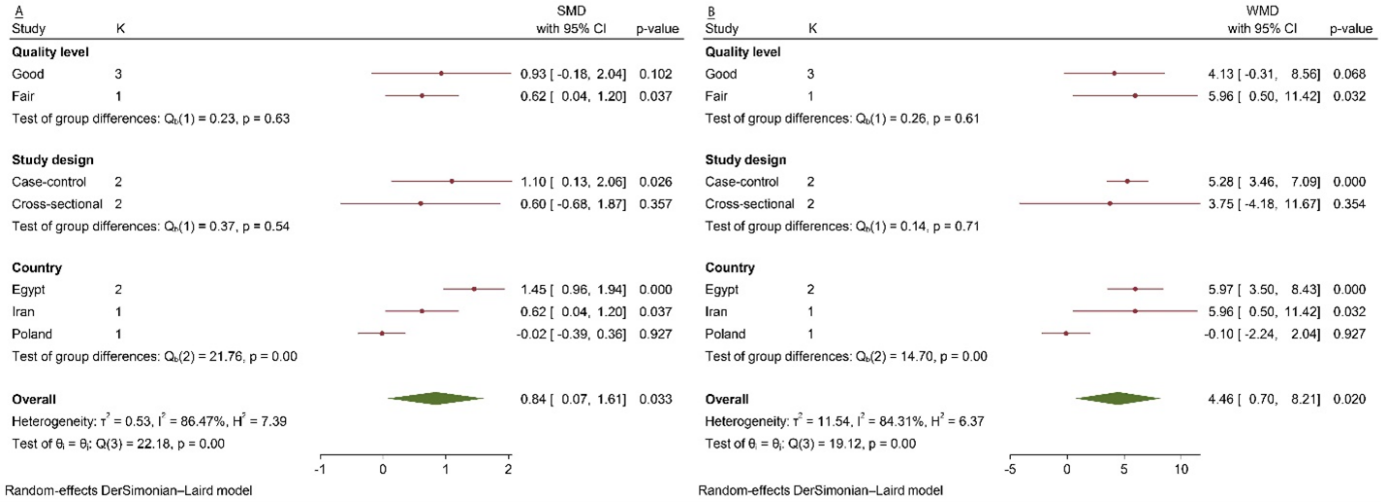

Fig. 4: Subgroup meta-analyses of the effects of gestational diabetes mellitus and fetal liver length in third trimester
A. For Standardized Mean Difference (Hedges g)
B. For Weighted Mean Difference (WMD)

Heterogeneity Analysis

Galbraith plot analysis was used to identify potential sources of heterogeneity. For the pooled WMD analysis, no study was identified as an outlier or a potential source of heterogeneity in the second trimester (Fig. 5A) and third trimester (Fig. 5B).

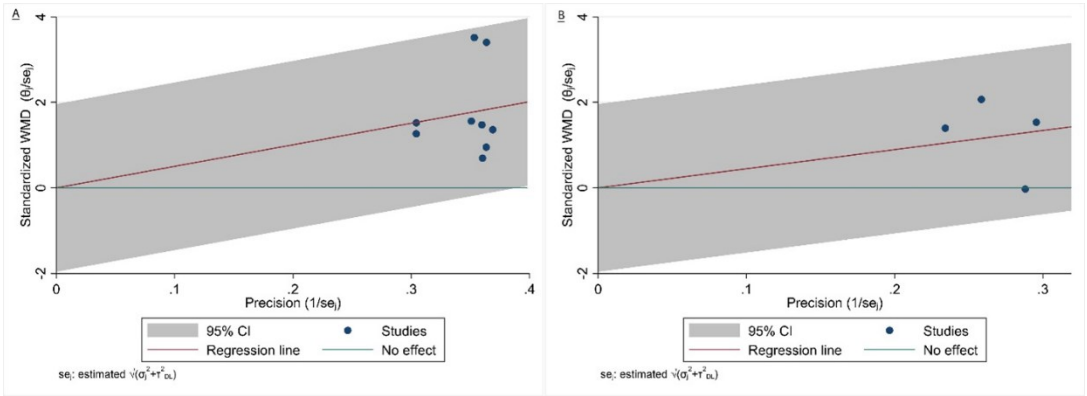

Fig. 5: Galbraith plots for the for-heterogeneity exploration of the effects of gestational diabetes mellitus and fetal liver length
A. For second trimester
B. For third trimester

Publication Bias

Publication bias was examined via visual inspection of funnel plots and Egger's regression asymmetry test. For the pooled WMD analysis, the shape of the funnel plots revealed no evidence of publication bias for second and third trimester studies. Egger and Begg's test further confirmed this (P=0.76, and P=0.42) (Fig. 6).

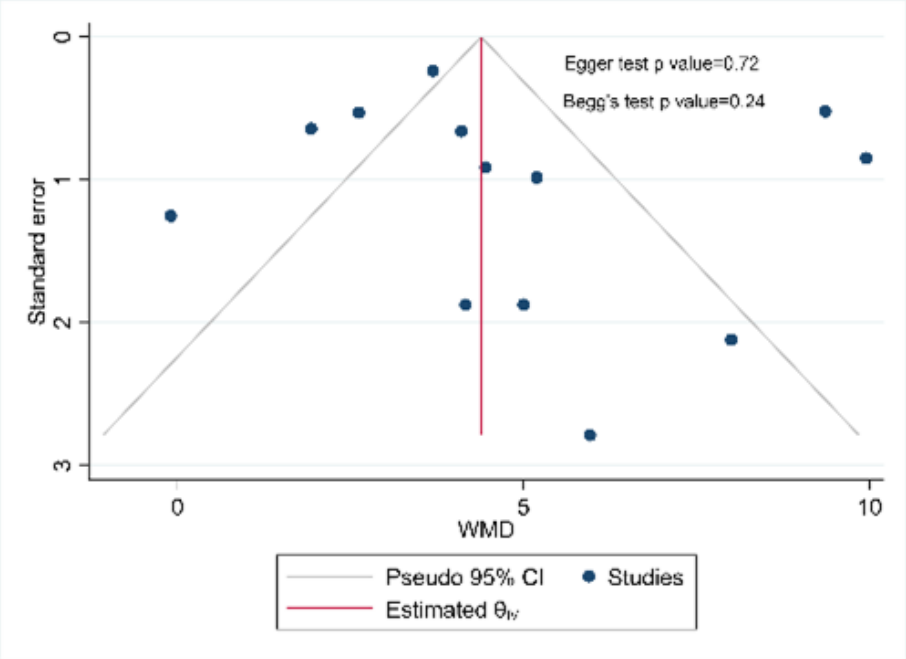

Fig. 6: Funnel plot of the publication bias

Discussion

GDM, one of the most frequent pregnancy complications, is associated with numerous maternal-fetal and neonatal complications (10, 36, 37).

This study evaluated the existing evidence on the ultrasound assessment of liver length in fetuses from mothers with and without GDM.

Our systematic review identified seven case-control studies and five cross-sectional studies involving 1901 participants to assess the association between GDM and FLL.

This study found a large significant association between GDM and FLL. It was also investigated in different subgroups and showed a consistent association across all subgroups. This association was large and significant both in the second (effect size=1.56) and third (effect size=0.84) trimesters of pregnancy.

The increase in the size of the liver in the fetuses of diabetic mothers can be attributed to maternal hyperglycemia with increased blood glucose delivery to the fetus, leading to fetal hyperglycemia and hyperinsulinemia, which promotes the growth of insulin-dependent tissues/organs such as the liver through cellular hyperplasia and cellular hypertrophy. In addition, hyperinsulinemia can induce an increased amount of hematopoietic tissue in the fetal liver. Long-term hyperglycemia also favors lipid storage in the liver of the fetus (18-22, 38).

Remarkably, the studies reviewed in this article have reported the use of FLL for various purposes, including GDM prediction, screening, early detection, evaluation, and the reduction of maternal and fetal complications.

In a study by Showman et al. on 120 Iraqi pregnant women at high risk for GDM, ultrasound measurement of FLL at 23 wk was reported as a

feasible alternative to OGTT for early GDM detection (27). In another study, evaluating the relationship between mid-trimester ultrasound measurements of FLL and GDM on three hundred and thirty-one pregnant women at high risk for GDM, a strong positive correlation was observed between ultrasound FLL and OGTT values in patients with GDM (17). In assessing the relationship between mid-trimester ultrasound FLL measurement in the screening of GDM in high-risk pregnant women, a highly significant correlation was found between FLL (at 20-24 wk gestation) and GDM development (31). On ultrasound measurements of the fetal liver, interventricular septum, fetal abdominal fat layer, and Wharton's jelly area between 21 and 24 wk gestation in 123 consecutive healthy pregnant women (19 pregnant women with GDM and 104 without GDM) by Mirghani et al., only FLL was significantly longer in women with GDM compared with women without GDM (25).

However, contrary to these findings, in a study done to evaluate the diagnostic ability of the fetal ultrasound parameters (abdominal circumference, fetal truncal subcutaneous fat layer, biparietal diameter, estimated fetal weight, and FLL) in screening for GDM in the second trimester between 24-28 wk of gestation, a positive correlation was not found between FLL and GDM (29).

In a study by Rahman et al. on 120 pregnant subjects (15 women with GDM and 105 women without GDM), due to the increased liver length of the fetuses of gestational diabetic mothers compared with non-diabetic mothers in 2nd trimester (21-24 wk) of gestation, ultrasonographic measurement of FLL in the antenatal examination of diabetic pregnancies for decreasing maternal and fetal complications may be helpful (26).

Similar findings in a study on 60 pregnant women (subjects with DM either pre-gestational or GDM (n=30) and healthy subjects (n=30)) showed that ultrasound FLL measurements correlated well with the state of maternal glycemic control and as an easy, more precise, and reproducible index can be utilized for fetal macrosomia and maternal glycemic control (32).

Therefore, based on the reviewed studies, there was a statistically significant relationship between GDM and FLL. These findings are consistent with the results of the present study. However, there were contradictory findings, which may be attributed to a variety of factors, including differences in study design, sample size, and population characteristics. To provide a more definitive answer to this question, a systematic review and meta-analysis of the existing literature can be conducted. This can increase the statistical power of the analysis and help identify patterns or trends that may not be obvious in individual studies.

Regarding hyperglycemia in pregnant women, hyperglycemia can induce an increasing size of organs in the fetus; thus, the measurement of FLL by sonography during GDM pregnancy during antenatal checkups can help manage the control or treatment of GDM in pregnant women. Uncontrolled GDM can affect mothers and fetuses; thus, controlling GDM during pregnancy can help reduce complications in mothers and fetuses.

This is the first comprehensive systematic review and meta-analysis to investigate the relationship between FLL and GDM. One of the strengths of this systematic review and meta-analysis is the comprehensive and rigorous literature search conducted to identify all relevant studies on the association between FLL and GDM. The search strategy was based on well-defined inclusion and exclusion criteria and covered multiple electronic databases and reference lists of eligible studies. The quality of the included studies was also assessed using a validated scale, and most were found to be of good quality.

This study has some potential limitations that should be considered. One of the limitations of this systematic review and meta-analysis is the heterogeneity of the included studies regarding the diagnostic criteria for GDM, timing of FLL measurement, and confounding factors that may affect the association between FLL and GDM. Different diagnostic criteria for GDM may lead to different prevalence rates and degrees of glucose intolerance. Different timings of FLL meas-

urements may also affect the accuracy and comparability of the results. Moreover, some confounding factors, such as maternal age, body mass index, parity, gestational age, fetal sex, and fetal weight, may influence FLL and GDM, and not all studies adjusted for these factors in their analyses. Therefore, the results of this meta-analysis should be interpreted with caution, and further studies using standardized methods and adequate adjustments are needed to confirm the findings. Moreover, most studies did not specify the type of treatment for GDM patients.

Conclusion

GDM is a significant risk factor for increased FLL, as measured by ultrasonography, which may reflect fetal overgrowth and metabolic dysfunction. The association was evident in both the second and third trimesters, but was more pronounced in the second trimester. The findings were robust across various study characteristics, except for the quality level and type of study in the third trimester, which suggested potential sources of bias and heterogeneity. This study highlighted the importance of screening and managing GDM to prevent adverse fetal outcomes correlated with FLL. Future studies should explore the mechanisms and implications of FLL as a marker of fetal health in GDM pregnancies.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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This study was the preliminary part of an experimental research project conducted by the Congenital Malformations Research Center of Golestan University of Medical Sciences to review the literature on the impact of GDM on FLL. This work is part of the Ph.D. dissertation of S.A. This study was approved by the Ethics Committee of Golestan University of Medical Sciences, Gorgan, Iran (Code: IR.GOUMS.REC.1402.347).

Conflict of interest

The authors declare that there is no conflict of interests.

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