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Full length article

## The association between second trimester ultrasound fetal biometrics and gestational diabetes

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## ABSTRACT

**Objective:** Gestational diabetes mellitus (GDM) is the most common metabolic complication of pregnancy. The incidence of GDM is increasing worldwide and 5–25% of pregnancies are diagnosed with GDM depending on screening strategies and diagnostic criteria. GDM may lead to obstetric complications and increases the risk of adult metabolic disease in the offspring. Timely identification of GDM allows for regulation of maternal glucose levels which may reduce the obstetric complications considerably. The aim of this study is to investigate the association between second trimester ultrasound biometrics and GDM.

**Study Design:** This is a retrospective cohort study including 2697 singleton pregnancies attending second trimester ultrasound scan at 20 + 0 to 20 + 6 weeks' gestation and giving birth at Aalborg University Hospital in the year 2020. Ultrasound measurements included head circumference (HC), abdominal circumference (AC), femur length (FL) and estimated fetal weight (EFW) by Hadlock's formula. Women with pregestational diabetes were excluded. GDM screening was performed on indication using oral-glucose-tolerance-test (OGTT) including 75 g glucose and a 2-hour serum glucose value  $\geq 9$  mmol/L was considered diagnostic. The association between fetal biometrics and GDM was investigated by logistic regression.

**Results:** A total of 174 (6.5 %) were diagnosed with GDM. The incidence of GDM in pregnancies with biometrics above the 90th centile was; FL: 10.5 %, HC: 8.8 %, AC: 7.6 %, EFW: 9.3 %. Fetal biometrics above the 90th centile was significantly associated with GDM;  $OR_{FL} = 2.07$ ,  $p = 0.001$ ;  $OR_{HC} = 1.89$ ,  $p = 0.001$ ;  $OR_{AC} = 1.63$ ,  $p = 0.033$ ;  $OR_{EFW} = 1.64$ ,  $p = 0.036$ . This association remained significant for HC and FL when adjusted for maternal obesity (Body Mass Index  $\geq 27$ ):  $OR_{HC(adj)} = 1.56$ ,  $p = 0.019$ ;  $OR_{FL(adj)} = 1.57$ ,  $p = 0.049$ .

**Conclusion:** At the second trimester scan, fetal biometrics above the 90th centile increase the risk of GDM. In pregnancies that are later diagnosed with GDM fetal growth is increased already at the second trimester scan. Such knowledge underlines the importance of early identification of GDM.

## Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic complication of pregnancy [1,2]. 5–25 % of pregnancies are currently affected worldwide depending on diagnostic criteria and population [3,4] and the incidence is increasing.

During pregnancy, changes regarding the maternal carbohydrate metabolism ensure a continuous high supply of nutrients to the growing

fetus despite fluctuations in maternal food intake [5]. This requires increased insulin resistance in the peripheral tissue [6,7] mediated by placental hormones such as growth hormone, cortisol and progesterone [5,8]. Women with GDM are unable to meet the increased demands of insulin due to inadequate  $\beta$ -cell hyperplasia in the pancreas resulting in maternal and fetal hyperglycemia [2,5–7,9]. Hyperglycemia leads to fetal hyperinsulinemia and high levels of maternal, placental and fetal insulin-growth factors which increases fetal growth and the risk of

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macrosomia [10–12]. Fetal macrosomia increases the risk of cesarean section, preterm delivery, shoulder dystocia and neonatal hypoglycemia [13–15]. In well-regulated cases of GDM, the risk of obstetric complications is similar to the general population [16].

Fetal overgrowth late in GDM pregnancies is well known [2,17–19], however, the timing of such manifestation of GDM has been investigated with inconsistent results. Studies found increased fetal biometrics in gestation week 24–28 and suggest increased fetal growth in GDM pregnancies may be present prior to the GDM diagnosis [17,20]. This current study aims to investigate the association between fetal biometrics and GDM at gestation 20. Such knowledge could provide important information on the optimal timing of GDM screening.

## Methods

### Study population

This was a retrospective cohort study in 2697 women with a singleton pregnancy attending the routine second trimester fetal ultrasound examination at 20 + 0 to 20 + 6 weeks' gestation and giving birth at Aalborg University Hospital, Denmark in the year 2020. Women with pregestational diabetes mellitus and delivery before 22 + 0 weeks' gestation were excluded.

According to Danish guidelines, GDM screening was performed on indication using OGTT including 75 g glucose and a 2-hour serum glucose value  $\geq 9$  mmol/L was considered diagnostic of GDM [21]. In Denmark, selective screening is performed in high-risk pregnancies at 24–28 weeks' gestation and in very high risk also at 10–20 week's gestation (Table 2). The treatment of GDM is through dietary and lifestyle counseling combined with self-monitoring of blood glucose [22]. Insulin therapy is indicated if the glycemic goals are not obtained within two weeks (Table 2) [21].

Maternal obesity was defined as pregestational body mass index (BMI)  $\geq 27$ , according to danish guidelines for GDM screening [21].

Data on maternal characteristics, pregnancy outcome and infant birthweight were obtained from the hospital records.

The study was approved 21 May 2021 by the Regional Danish Patient Safety Authority (Journal number 2021–01066).

### Ultrasound examination

Ultrasound data were retrospectively collected from a local Fetal Medicine database (Astraia software gmbh version 1.24.10). All routine ultrasound examinations in first and second trimester were performed by certified sonographers.

Gestational age was determined from the first trimester ultrasound examination at 12 + 0 to 13 + 6 weeks' gestation from the measurement of the fetal crown-rump length [23].

In the second trimester scan fetal biometrics included head circumference (HC), abdominal circumference (AC) and femur length (FL). Estimated fetal weight (EFW) was calculated using Hadlock's formula [24].

### Statistical analysis

The second trimester fetal biometrics and EFW were converted into centiles adjusted for gestational age based on the current cohort. The association between the fetal biometrics and GDM was investigated by logistic regression adjusted for maternal obesity. Bar charts were created to demonstrate the incidence of GDM in groups based on biometry centiles  $\leq 10$ th, 10th–90th and  $\geq 90$ th.

The association between fetal biometrics and gestational age was investigated by linear regression and illustrated in scatterplots.

The statistical software package Stata®15.1 (StataCorp LP, College Station, TX, USA) was used for all calculations, and the significant statistical level was set at a P-value  $< 0.05$ .

## Results

A total of 174 (6.5 %) were diagnosed with GDM. Maternal and pregnancy characteristics are presented in Table 1. In our cohort, 27 % of GDM pregnancies had caesarean section, compared to 16.5 % of non-GDM pregnancies. Furthermore, the incidence of large for gestational age at birth (Birthweight  $\geq +22$  % of the expected for gestational age) was 7.5 % among GDM pregnancies and 4.2 % in the group of non-GDM pregnancies.

In Fig. 1, the incidence of GDM is illustrated by centile groups. For fetal biometrics above the 90th centile the incidence of GDM was the following: FL: 10.5 %, HC: 8.8 %, AC: 7.6 % and EFW: 9.3 %.

Fetal biometrics  $> 90$ th centile were significant risk factors of GDM (Table 3); FL (OR<sub>FL</sub> = 2.07, 95 %-CI 1.34–3.19,  $p = 0.001$ ), HC (OR<sub>HC</sub> = 1.89, CI-95 % 1.32–2.7,  $p = 0.001$ ), AC (OR<sub>AC</sub> = 1.63, 95 %-CI 1.04–2.57,  $p = 0.033$ ) and EFW (OR<sub>EFW</sub> = 1.64, 95 %-CI 1.03–2.59,  $p = 0.036$ ). This association remained significant for HC and FL when adjusted for maternal obesity; OR<sub>HC(adj)</sub> = 1.56 (95 %-CI 1.08–2.25,  $p = 0.019$ ) and OR<sub>FL(adj)</sub> = 1.57 (95 %-CI 1.0–2.46,  $p = 0.049$ ).

In average GDM pregnancies showed a rather small but significant increase in EFW when compared to non-GDM pregnancies; 4.24 g (95 %-CI 0.5–7.99,  $p = 0.027$ ). For HC, AC and FL the mean difference between groups was not significant (Fig. 2).

## Discussion

This study demonstrates that the incidence of GDM is increased in pregnancies with biometrics above the 90th centile at second trimester scan. Accordingly fetal growth is increased already at 20 weeks' gestation, suggesting, that the fetus is influenced by the abnormal maternal glucose metabolism prior to the GDM diagnosis.

**Table 1**

Characteristics of the cohort, non-GDM and GDM.

Characteristics	Cohort (n = 2697)	Non-GDM (n = 2523)	GDM (n = 174)	P-value
Maternal age (years)	29 (27–32)	29 (27–32)	31 (28–34)	0.000
Body mass index (kg/m <sup>2</sup> )	24.1 (21.5–27.8)	23.9 (21.4–27.3)	29.1 (24.8–34.9)	0.000
Nulliparous	1294 (48)	1215 (48.2)	79 (45.4)	0.482
Conception				0.397
Spontaneous	2465 (91.4)	2309 (91.5)	156 (89.7)	
Assisted conception	232 (8.6)	214 (8.5)	18 (10.3)	
Smoking	146 (5.4)	131 (5.2)	15 (8.6)	0.053
Gestational age at ultrasound (weeks)	20.4 (20.3–20.6)	20.4 (20.3–20.6)	20.4 (20.3–20.7)	0.009
Gestational age at delivery (weeks)	40.1 (39.0–41.0)	40.1 (39.1–41.0)	39.7 (38.7–40.7)	0.002
Spontaneous delivery	1490 (55.3)	1437 (57)	53 (30.5)	0.000
Caesarean	464 (17.2)	417 (16.5)	47 (27)	0.000
Preterm delivery $< 37$ weeks	92 (3.4)	85 (3.4)	7 (4)	0.646
Birthweight (g)	3550 (3210–3900)	3540 (3210–3900)	3635 (3340–3900)	0.084
LGA at birth ( $\geq +22$ %)	118 (4.4)	105 (4.2)	13 (7.5)	0.039
SGA at birth ( $\leq -22$ %)	103 (3.8)	99 (3.9)	4 (2.3)	0.279
Fetal sex				0.96
Female	1359 (50.4)	1271 (50.4)	88 (50.6)	
Male	1338 (49.6)	1252 (49.6)	86 (49.4)	

GDM, Gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age.

Data are presented as median (25th, 75th quartiles) and n (%). P-values are for difference between non-GDM and GDM groups using Mann-Whitney test for continuous variables and Pearson  $\chi^2$  test for binary variables.

**Table 2**

Risk factors for GDM screening and glycemic goals according to the Danish National Pregnancy Screening Guidelines [21,38].

Risk factors	GA 10–20*	GA 24–28
1. History of GDM in previous pregnancies	X	X
2. Family disposition to GDM		X
3. Pregestational maternal overweight (BMI $\geq 27$ )		X
4. Previous child with fetal macrosomia (BW $\geq 4500$ g)		X
5. Multiple gestation		X
6. PCOS		X
7. Glycosuria		X
Glycemic goals for treatment of GDM regardless of GA	Blood glucose (mmol/L)	
Pre-prandial	4–6	
1½ hour post-prandial	4–8	
Fasting	$\leq 5$	
HbA1c	$< 37$	

GA, gestational age; GDM, gestational diabetes mellitus; BMI, body mass index; BW, birth weight; PCOS, polycystic ovary syndrome.

\*Women with  $\geq 2$  risk factors 2–6 should undergo screening for GDM in GA 10–20 and GA 24–28.

A strength of this study is the relatively large non-selected study population. The cohort is derived from a specific geographic area attending routine care, and thereby representative of the entire population. The ultrasound examinations were performed by certified and experienced sonographers.

A limitation of the study is the selective GDM screening including only high-risk pregnancies which may lead to undiagnosed cases in the group of non-GDM pregnancies. Thereby, the difference between GDM and non-GDM pregnancies may be underestimated. Furthermore, the diagnostic criteria used in this current study was 2-hour OGTT value  $\geq$

9.0 which is in accordance with the Danish national guidelines. Accordingly, we did not include potential GDM cases diagnosed by 1-hour fasting blood glucose or OGTT 2-hour values between 8.5 and 9.0, which is the frequently used diagnostic criteria defined by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [25]. Thus, the association between GDM and second trimester biometrics demonstrated in this current study may only apply to severe GDM cases with OGTT  $\geq 9.0$ . In general, a direct comparison between studies is challenged by large variations in GDM diagnostic criteria and screening strategies.

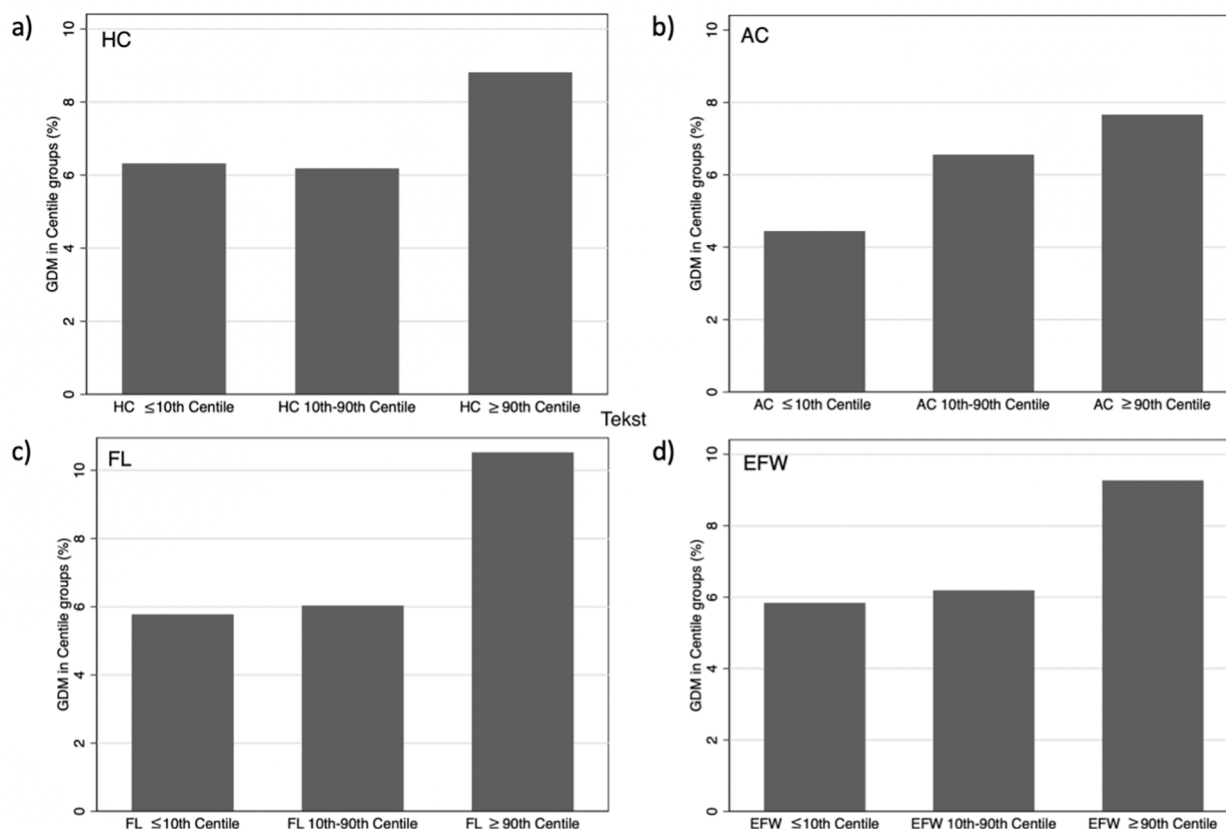
Previous publications have reported fetal overgrowth at birth [26] and even at the time of the GDM diagnosis [17,20]. However, evidence of fetal overgrowth already at 20 weeks' gestation in pregnancies that are later diagnosed with GDM is limited.

**Table 3**

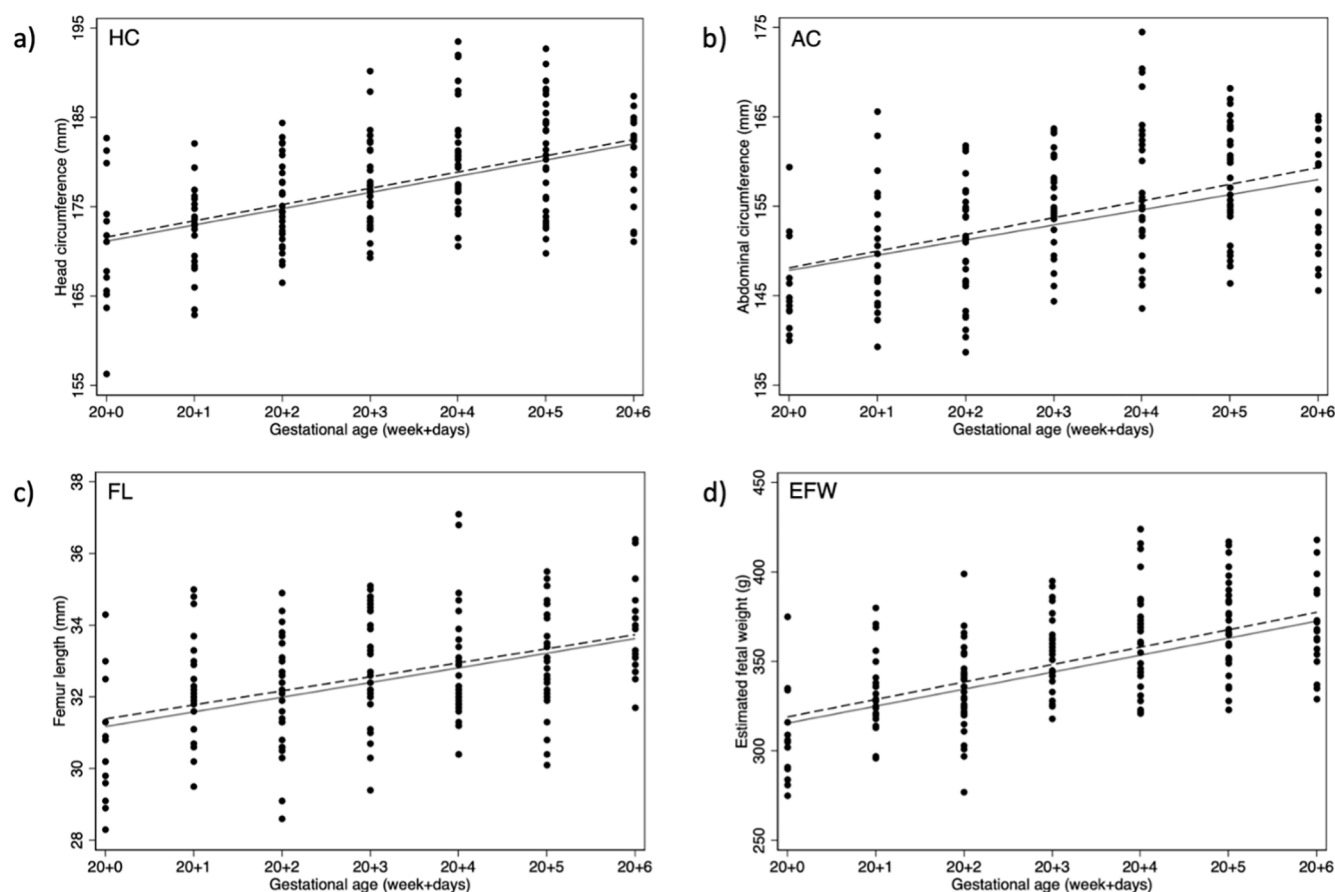
Risk of GDM for each fetal biometry  $>90$ th centile investigated by logistic regression adjusted for BMI ( $\geq 27$ ).

Fetal biometry	OR	95 %-CI	P-value	AUC	OR <sub>(adj)</sub>	95 %-CI	P-value
FL $> 90$ th centile	2.07	1.34, 3.19	0.001	0.54	1.57	1.00, 2.46	0.049
HC $> 90$ th centile	1.89	1.32, 2.70	0.001	0.55	1.56	1.08, 2.25	0.019
AC $> 90$ th centile	1.63	1.04, 2.57	0.033	0.52	1.31	0.82, 2.09	0.253
EFW $> 90$ th centile	1.64	1.03, 2.59	0.036	0.52	1.32	0.82, 2.15	0.253

GDM, gestational diabetes mellitus; BMI, body mass index; OR, odds ratio; 95%-CI, 95%-confidence interval; AUC, area under the curve; FL, femur length; HC, head circumference; AC, abdominal circumference; EFW, estimated fetal weight.



**Fig. 1.** Bar charts illustrating the incidence (%) of GDM stratified on three centile groups:  $\leq 10$ th centile, 10-90th centile and  $\geq 90$ th centile. a) HC, head circumference, b) AC, abdominal circumference, c) FL, femur length and d) EFW, estimated fetal weight.



**Fig. 2.** Scatterplots illustrating the correlation between fetal biometrics and gestational age at the second trimester ultrasound scan. Pregnancies complicated by GDM ( $n = 174$ , black circle, dashed line). Trendline from non-GDM pregnancies ( $n = 2523$ , solid line). a) HC, head circumference (mm), b) AC, abdominal circumference (mm), c) FL, femur length (mm) and d) EFW, estimated fetal weight (g).

Sovio et al. investigated 4069 nulliparous women [17]. GDM was diagnosed at 28 weeks' gestation in 4.2 % using a 2-hour 75 g OGTT with a cut-off value of 8.5 mmol/L. They found AC to be significantly increased in GDM pregnancies at the time of diagnosis, but not at 20 weeks' gestation.

In another study by Kim et al. 7569 women were investigated [20]. GDM was diagnosed at gestational week 24–28 in 5.1 % using a 3-hour 100 g OGTT with a cut-off value of 7.8 mmol/L. They also found AC to be increased in GDM pregnancies at the time of diagnosis in selected pregnancies such as obese women ( $\text{BMI} \geq 25$ ) and women  $\geq 35$  years, but not in gestational week 20.

Both studies [17,20] used different diagnostic criteria of GDM than used in this current study. Accordingly, their GDM cases may have less severe hyperglycemia, which might explain why the previous studies failed to demonstrate fetal overgrowth at the second trimester scan.

GDM is most often revealed in the second or third trimester [27], however, as suggested by this current study abnormal glucose metabolism can develop earlier depending on the degree of insulin resistance and pancreatic dysfunction [5]. This challenges the screening strategy, as the timing of screening is debatable [5,22,28] and one could speculate if GDM screening is currently performed too late in pregnancy. The findings of this study suggest, that GDM screening should be performed early in pregnancy – as fetal growth is abnormal prior to the usual time for GDM screening in gestational week 24–28. Universal GDM screening at earlier gestation may improve diagnosis and treatment, and thereby tend to normalize fetal growth despite the development of GDM.

However, the benefits of earlier GDM screening in order to improve the obstetric outcomes have been investigated with inconsistent results. Harper et al. compared GDM screening at 14–20 weeks' gestation with

GDM screening at 24–28 weeks' gestation in 922 women [29]. Unfortunately, they found no improvement of perinatal outcome in the early screening group. This is a contrast to Ryan et al. who found an improvement in both maternal and neonatal outcomes in 576 women with early diagnosis of GDM [30].

The early manifestations of GDM are supported by several studies. Bozkurt et al. found evidence of maternal pancreatic  $\beta$ -cell dysfunction at 14–18 weeks' gestation in 211 GDM pregnancies, of which 23 % was diagnosed with GDM before 21 week's gestation [31]. Smirnakis et al. suggested that the non-fasting sex hormone-binding globulin assessed in the first trimester may be a significant predictor of GDM [32], and Mirghani et al. revealed that in GDM pregnancies the length of the fetal liver was significantly increased at 21–24 week's gestation when compared to non-GDM pregnancies [33]. These studies support the idea that metabolic changes are present in early pregnancy before the diagnosis of GDM, which may explain the findings of this current study.

It is well described, that GDM is associated with fetal overgrowth in late pregnancy and macrosomia at birth. Our study demonstrates that fetal overgrowth may be present already at 20 week's gestation in pregnancies that are later diagnosed with GDM. It is worth noticing, that fetal overgrowth in the second trimester is characterized by symmetric growth including the three fetal biometrics. This is in contrast to the well known asymmetric fetal overgrowth in the third trimester which is dominated by enlarged AC [18]. Thus, this current study indicates that these fetuses are exposed to a suboptimal intrauterine environment already from early gestation. The abnormal intrauterine environment in GDM pregnancies may lead to epigenetic changes of fetal DNA, which increase the risk of metabolic disease in adult life [10,11,22,34,35]. Earlier identification of GDM may have numerous benefits as it allows a



greater timeframe for adjustment of maternal blood glucose level by lifestyle interventions and optionally insulin treatment. The effect of lifestyle interventions is disputed [36,37], however, early awareness of GDM including screening and treatment may have the potential to decrease the risk of obstetric complications and long-term metabolic disease.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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