

## NARRATIVE REVIEW

### Timing of delivery in women with gestational diabetes mellitus: still an open question

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## ABSTRACT

Gestational diabetes mellitus (GDM), is a pregnancy-related glucose intolerance, and it represents one of the most common metabolic disorders during pregnancy. GDM is associated with serious short- and long-term maternal and fetal morbidity.

The prevalence of both pre-gestational and gestational diabetes mellitus is increasing among women due to older maternal age at childbearing and the growing prevalence of obesity and overweight worldwide.

This review summarizes the recommendations of the main scientific societies on mode and time of delivery in GDM women, highlighting the absence of unique clinical management.

Moreover, analyzing the literature, only three Randomized clinical trials (RCTs) on this topic are available, and also the largest of these appears underpowered and it does not provide statistically significant data.

In conclusion, the lack of evidence and meta-analyses, suggests the necessity of further studies to draw up guidelines about time and mode of delivery to help clinicians in their decision making

## Key words

Gestational diabetes; Induction of labour; labour; RCT; Pregnancy; Timing of delivery.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is the most common complication of pregnancy and it is defined as a glucose intolerance of varying degree that develops in the second or third trimester of pregnancy and it generally resolves after delivery (1).

GDM is associated with an increase of maternal-fetal morbidity as well as short and long term complications (2). Long-term neonatal complications not only arise from the hyperglycemia to which fetuses are exposed, but are also a consequence of epigenetic mutations in the offspring, namely in Large for Gestational Age (LGA) newborns (3). The main complications in GDM pregnancies are Cesarean delivery and birth trauma. Little is the available evidence to guides us in the delivery management of these pregnancies. The poorly controlled GDM (elevated BMI, marked insulin resistance as manifested by insulin requirements, polyhydramnios and increased fetal abdominal circumference) should likely be managed considering earlier induction. In other way, the “low risk” well-controlled primiparous GDM patient with an unfavorable cervix is likely to benefit from expectant management (4).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed there is a continuous and graded relationship between maternal hyperglycemia and risk for adverse perinatal outcome, independent of other risk factors (5).

A large retrospective study (6) evaluated the risk of stillbirth (SB) and infant death stratified by gestational age, in women with GDM; the SB and neonatal death risk for 36-42 week was higher in GDM women compared to the population without diabetes. Such risk displayed a U-shaped curve, highest at 36 weeks, decreasing to a nadir at 39-40 weeks (also in women without GDM), increasing again at 41 and 42 weeks. This result suggested that planning delivery at 39 weeks would be a strategy preventing SB. In a retrospective study, the differences between deliveries with and without iatrogenic intervention in GDM pregnancies were analyzed (7). The incidence of cesarean delivery at  $\geq 41$  gestational weeks was significantly higher than that at 39<sup>0/6</sup> weeks. The rate of macrosomia was not significantly different between the different gestational weeks, except that no macrosomia was present at  $< 37$  weeks. The incidences of postnatal hypoglycemia and vomiting and moaning at  $< 37$  gestational weeks were significantly higher than those in the 39<sup>0/6</sup> gestational weeks group. The results give in this way an indication for the delivery at 39-40 weeks.

### ***Prevalence of GDM is increasing***

The prevalence of GDM has increased by more than 30% in several countries, including developing countries Africa, Southeast Asia, the western Pacific regions (8), forming an emerging worldwide epidemic (9). This increase may be related to the older maternal age, the epidemic of obesity and diabetes, and the reduction in physical activity with the adoption of the worst western lifestyles in developing countries (10). According to Emilia Romagna Birth certificates, in 2020, the mean age at delivery was 32 years, there were 10.3% obese and 20.7% overweight women at beginning of pregnancy. The obesity rate has increased compared to 7.7% detected in 2012 in Emilia Romagna (11). European data shows that the mean age at delivery was 29.5 years and 30-50% of women were obese or overweight at beginning of pregnancy(12).

The growing incidence of GDM consequently increased the interest in this metabolic disorder, leading to the development of more stringent screening. The international Association of Diabetes and Pregnancy Study Groups (IADPSG) developed a consensus statement for a new strategy to diagnose GDM (13) with a reduction of threshold values measured at glucose challenge. These changes were associated with an increased detection rate of GDM, 23.1% according to IADPSG compared with previous values of 17.8% (14). Similarly, there was an increased prevalence the

GDM when the IADPSG criteria were compared with 1999 WHO criteria, respectively 12,4% vs 9,4% respectively (15).

However, easily accessible and systematically organized data on global prevalence estimates of GDM are lacking. Furthermore, lack of consensus and uniformity in the screening standards, definition, and diagnosis criteria of GDM challenges the comparative assessment of the GDM prevalence across countries and regions (9). At the same time, the need to standardize obstetric management, that appears to be very heterogeneous in terms of mode and timing of delivery, becomes urgent.

### ***Timing and mode of delivery in GDM women***

#### **A) Guidelines**

Individual providers, practices, and medical institutions traditionally developed protocols for labor management in women with GDM by incorporating a combination of anecdotal experience, published literature, and recommendations by national clinical organizations. Different scientific associations provided some guidance for labor management of pregnancies complicated by GDM. A summary of the main international guidelines is reported in Table 2.

Delivery management options in women with GDM include expectant management, labor induction, elective cesarean sections (CS). (16)

GDM is not by itself an indication for caesarean delivery or for delivery before 38 completed weeks of gestation (17) and is not a contraindication for a vaginal delivery.

The American College of Obstetricians and Gynecologists (ACOG) states that elective CS may be indicated in women with GDM whose estimated fetal weight (EFW) is  $\geq 4,500$  g. Women with GDM with good glycemic control (only with diet and exercise) and no other complications are commonly managed expectantly up to 40 6/7 weeks of gestation while for women with GDM that is well controlled by medications, delivery is recommended from 39 0/7 weeks to 39 6/7 weeks of gestation. Expert opinion has supported earlier delivery for women with a poorly controlled GDM. Clear guidance about the degree of glycemic control that indicates earlier delivery, however is lacking, and the clinical choice must be made on a risk-benefit balance considering the risks of prematurity vs the ongoing risks of stillbirth. In such a setting, delivery between 37 0/7 weeks and 38 6/7 weeks of gestation may be justified, on the contrary delivery in the late preterm period from 34 0/7 weeks to 36 6/7 weeks of gestation should be reserved for women with lack of blood glucose control with no others strategy of intervention or with evidence of fetal distress. (18)

The World Health Organization (WHO) in 2021 does not recommend induction of labour before 41 weeks for GDM women whose glycemic level is controlled only with diet and exercise. For GDM women under medication, induction of labour may be necessary, but not in the case of suspected macrosomia, although the quality of the evidence is low, and the recommendation is weak (19).

The National Institute for Health and Care Excellence (NICE) guidance, recommends elective birth (induction of labor or CS) before 40 6/7 weeks in case of maternal or fetal complications (20).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) suggests more frequent fetal assessments, in women with poorly controlled GDM and /or associated with other maternal/fetal diseases. The induction of labour may be offered at 39 weeks with the purpose to reduce the risk of stillbirth and the risk of CS. Earlier or later induction of labour should be considered if GDM is not well controlled or maternal and/or fetal pathologies overlap (21).

According to the Polish Society of Gynecologists, in the event of an EFW  $> 4000$  g, induction of labour is contraindicated due to the increased risk of shoulder dystocia. When GDM is well managed, patients are compliant, no other maternal/fetal complications coexist and the estimated

fetal weight is between the 10<sup>th</sup> and 90<sup>th</sup> percentile, or does not exceed 4000 g, pregnancy may continue until 39–40<sup>th</sup> weeks. Individuals with poorly managed GDM, or other maternal and/or fetal pathologies, should be individually assessed (22).

The Emilia Romagna guidelines of 2019 recommend induction of labour between 39 0/7 and 40 6/7 weeks in GDM women managed with diet and exercise, while for women under medication delivery is recommended from 39 0/7 – 39 6/7 weeks. Poorly controlled GDM women should be induced between 37 0/7 and 38 6/7 weeks (23).

This variety of guidelines on GDM management, underlines that a) GDM is not a homogenous entity with diverse clinical presentation and b) scientific evidences are scanty, based primarily on retrospective studies that summarize individual hospitals' policies. Moreover, each GDM woman faces unique challenges with respect to her ethnicity, biomedical condition, psychological makeup, and social support system and all these factors may potentially impact obstetric decision-making (24).

## **B) Randomized controlled trials**

### Search Strategy

To summarize the best evidence on the timing and mode of delivery in GDM women, we carried out a computerized literature search using PubMed. Eligibility criteria were predetermined by reviewers to prevent bias in the inclusion or exclusion of articles and to improve the precision of the search. We included the most recent experimental studies exclusively published in English until 2021, involving women with GDM randomized to expectant management versus induction of labor (IOL). We found only three randomized clinical trials (RCT) available on the timing and mode of delivery in GDM women (25-27). The first one was conducted by Kjos et al (25) to assess whether the CS rate could be safely reduced by expectant management versus induction of labor (IOL) at 38 weeks. It included 200 women with insulin-requiring GDM or uncomplicated pre-gestational diabetes, which were randomly assigned to IOL within 5 days or expectant management (EM), at 38 weeks. The EM group was monitored weekly. The rate of CS was not different between the two arms. However, more cases of shoulder dystocia occurred in EM group (only three cases), with a significant increase in LGA infants compared with IOL. Therefore, the authors concluded that there is no advantage in delaying delivery in women with insulin requiring diabetes past 38 to 39 weeks' gestation. If delivery is postponed, careful monitoring of fetal size and growth must be performed (26) (Table 3).

The GINEXMAL (26) is the largest RCT so far carried out and it has been included in the most recent Cochrane review (28). The aim of this multicenter open-label RCT was to provide evidence on the best management of women with diagnosis of GDM in terms of maternal and neonatal outcomes (26, 29). Eligible patients, according to inclusion/exclusion criteria were enrolled and randomized between 38 and 39 weeks of gestation to expectant management or IOL. The main outcomes were the incidence of CS and the rate of operative vaginal delivery, the latter considered risk factor for shoulder dystocia and other adverse outcomes. Secondary outcomes were assessed at the time of delivery and/or during maternal and neonatal admission until discharge. They included mode of delivery, spontaneous or assisted third stage of labour, perineal tears, postpartum hemorrhage, gestational age and weight at birth, shoulder dystocia, neonatal respiratory distress, Apgar score, arterial cord pH, biochemical hypoglycaemia and hyperbilirubinemia (Table 3). No difference was detected between the two arms both in caesarean section rate and in non-spontaneous delivery rate. A few cases of shoulder dystocia occurred and were solved without significant birth trauma. Maternal and neonatal outcomes were similar in the two groups except for hyperbilirubinemia, significantly higher in the IOL group. As expected, gestational age and birthweight were lower in the induction group. Although this study is the largest

published focusing on women affected exclusively by GDM, it resulted underpowered, including low-risk population and having the two arms unbalanced for GDM treatment.

Recently Worda et al. planned a RCT (27) to evaluate fetal and maternal morbidity in women with insulin-treated GDM, comparing IOL at 38 weeks vs IOL at 40 weeks. Out of 100 randomized women, only 91 were eligible for final analysis focused on neonatal outcomes (LGA newborns, neonatal hypoglycemia and hyperbilirubinemia, Apgar score at 5<sup>th</sup> min, cord arterial pH-values and rates of NICU admission). Secondary outcomes IOL to delivery interval and the rate of CS. The main limitation of this study is the sample which makes findings less meaningful. However, although this RCT does not provide statistically significant differences among groups, the authors conclude suggesting routine induction of labor at 40 weeks, considering a lower rate for CS and significantly lower rates of hypoglycemia and hyperbilirubinemia.

## **CONCLUSION**

Given the high incidence of gestational diabetes and the high risk of maternal and perinatal adverse outcomes, the identification of an algorithm for the labor and delivery management for GDM patients is mandatory. The insufficient quantity of evidences and meta-analyses, highlights the importance of further studies to provide high quality data on optimal terms and modes of delivery in diabetic pregnancies to help guide clinicians in their decision making. We recommend a well-designed multicentric RCT comparing expectant management with induction of labour in these women either under diet and exercise or medical treatment. Sample size should be large enough to allow for answers to rare neonatal outcomes, such as perinatal mortality and shoulder dystocia. The enrolled population should represent the general population, in order that the results could be transferable.

## **AUTHORS CONTRIBUTION**

All author contributed equally.

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## **DISCLOSURE OF INTERESTS**

The authors report no conflict of interest.

## **ETHICS APPROVAL STATEMENT**

This study is based on secondary data therefore the Ethics Approval was not required.

## **INFORMED CONSET**

N/A

## **DATA SHARING**

N/A

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**Table 1.** Summary of the main international diagnostic criteria for GDM

	IADPSG 2010 (any of one)	NICE 2015 (any of one)	WHO 1999 (any of one)
Fasting glucose, mg/dL	≥91.9	≥100.9	≥109.9
1 h glucose, mg/dL	≥180.2	-	-
2 h glucose, mg/dL	≥153.2	≥140.5	≥140.5



**Table 2.** Summary of the main international guidelines

	<b>ACOG (2018)</b>	<b>WHO (2011)</b>	<b>NICE (2015)</b>	<b>SOGC (2019)</b>	<b>Polish Gynecological Society (2017)</b>	<b>Emilia Romagna (2019)</b>
<b>GDM controlled only with diet and exercise</b>	No delivery < 39 wks, unless otherwise indicated. Expectant management up to 40 6/7 wks in the setting of indicated antepartum testing	IOL < 41 wks is not recommended. ( <i>Very-low-quality evidence/weak recommendation</i> )	IOL not later than 40 6/7 weeks		Delivery after 39 weeks ( <i>Level C</i> )	IOL between 39 0/7 and 40 6/7 weeks
<b>GDM requiring medications</b>	Delivery recommended at 39 0/7 to 39 6/7 weeks	IOL may be necessary	Consider elective birth < 40 6/7 wks with maternal or fetal complications	IOL at 39 wks could be considered		Delivery is recommended from 39 0/7 – 39 6/7 weeks
<b>Poorly controlled GDM</b>	Delivery 37 0/7 to 38 6/7 weeks. Delivery from 34 0/7 to 36 6/7 wks if failed in-hospital attempts to improve glycemic control or with abnormal antepartum fetal testing.					IOL is recommended between 37 0/7 and 38 6/7 weeks
<b>Suspected macrosomia</b>	Explain risks and benefits of a scheduled CS when the EFW $\geq$ 4,500 g	IOL at term is not recommended. ( <i>Low-quality evidence/weak</i> )	Explain risks and benefits of vaginal birth, IOL and CS		EFW > 4000 g and/or difference between AD and BPD > 2.6 cm, IOL is contradicted	

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IOL: Induction of labour; EFW: Estimated fetal weight; CS: Cesarean Section

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**Table 3.** Summary of RCTs characteristics

	<b>Kjos et al. 1993, California</b>	<b>Alberico et al. 2016, Italy, Slovenia and Israel</b>	<b>Worda et al. 2017, Vienna</b>
<b>Participants</b>	200 women with uncomplicated, insulin-requiring gestational or class B pregestational diabetes at 38 weeks' who were compliant with care and whose infants were judged appropriate for GA	425 women with singleton pregnancy, diagnosed with GDM by the IADPSG between 38+0 and 39+0 weeks of gestation, without other maternal or fetal conditions.	100 women with insulin-treated GDM
<b>Interventions</b>	IOL: between 38 and 38 + 5 weeks  EM: weekly monitoring by physical exam and twice a week nonstress tests and amniotic fluid volume estimation until delivery.	<u>IOL</u> between 38+0 and 39 + 0 weeks  <u>EM</u> until 41+0 weeks with electronic fetal heart rate monitoring and biophysical profile twice-weekly	<u>IOL</u> at 38 weeks  <u>IOL</u> at 40 weeks
<b>Primary outcome</b>	Caesarean section rate	Caesarean section rate  Non-spontaneous delivery rate	LGA, neonatal hypoglycemia and bilirubinemia, Apgar score at 5 <sup>th</sup> min, arterial pH-value and rate of NICU admission
<b>Secondary outcomes</b>	GA at delivery, birth weight, and numbers of infants defined as macrosomic (~4000 g) or LGA. Shoulder dystocia, hypoglycemia, perinatal death	Assisted 3 <sup>rd</sup> stage of labour, perineal tears, postpartum hemorrhage, GA and weight at birth, shoulder dystocia, neonatal respiratory distress, Apgar score, arterial cord pH, maternal blood transfusion, ICU admission, hypoglycemia and hyperbilirubinemia, NICU admission, maternal and perinatal death	Induction to delivery interval, rate of Caesarean section
<b>Follow-up</b>	Until discharge from the hospital	Until discharge from the hospital	Until discharge from the hospital

RCT: randomized controlled trial; IOL: Induction of labour EM: Expectant management; ICU: Intensive care unit; NICU: Neonatal intensive care unit; GA: Gestational Age

**Table 4.** Summary of RCTs findings

Outcomes	Kjos et al. 1993		Alberico et al. 2016		Worda et al. 2017	
	Study arms		Study arms		Study arms	
	IOL (N=100)	EM (N=100)	IOL (N=214)	EM (N=211)	IOL 38 w (N=44)	IOL 40 w (N=47)
Caesarean section (%)	25 (25.0)	31 (31.0)	27 (12.6)	25 (11.8)	7 (15.9)	3 (6.4)
Operative vaginal delivery (%)	NA	NA	18 (8.4)	22 (10.4)	NA	NA
Postpartum haemorrhage (%)	NA	NA	13 (6.1)	11 (5.2)	NA	NA
ICU admission (%)	NA	NA	3 (1.4)	2 (0.9)	NA	NA
Mean GA at birth (wks)	39 ± 2	40 ± 2	NA	NA	NA	NA
GA > 39 weeks (%)	NA	NA	47 (22.0)	157 (74.4)*	NA	NA
Birth-weight (g)	3446 ± 78	3672 ± 77	NA	NA	3246 ± 458	3352 ± 492
Macrosomia/LGA (%)	10 (10)	23 (23.0)*	13 (6.1)	24 (11.4)*	3 (6.8)	4 (8.5)
Apgar at 5 <sup>th</sup> minute < 7 (%)	NA	NA	2 (0.94)	0	NA	NA
Shoulder dystocia (%)	0/100 (0)	3 (3.0)*	3 (1.4)	1 (0.5)	NA	NA
Biochemical hypoglycaemia (%)	0	0	6 (3.0)	8 (4.1)	16 (36.4)	8 (17.0)*
Hyperbilirubinaemia (%)	NA	NA	20 (10.0)	8 (4.1)*	NA	NA
Respiratory distress (%)	NA	NA	3 (1.4)	2 (0.9)	NA	NA
NICU admission (%)	NA	NA	2 (0.9)	2 (0.9)	3/44	4/47
Perinatal death (%)	0	0	0	0	NA	NA

\* P value &lt; 0.05