Il Diabete Gestazionale

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CLINICA OSTETRICA E GINECOLOGICA

AZIENDA OSPEDALIERO UNIVERSITARIA DI FERRARA

DIABETE GESTAZIONALE

Definizione

"intolleranza ai carboidrati, di variabile grado e severità con inizio o primo riscontro durante la gravidanza"

Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study Coopera>ve Research Group.N Engl J Med 358;19.May 8, 2008.

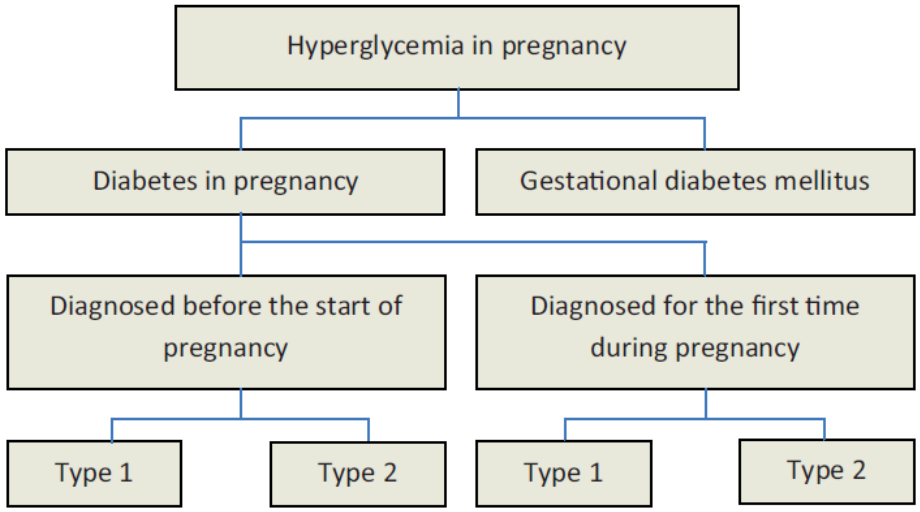


Figure 1 Types of hyperglycemia in pregnancy.

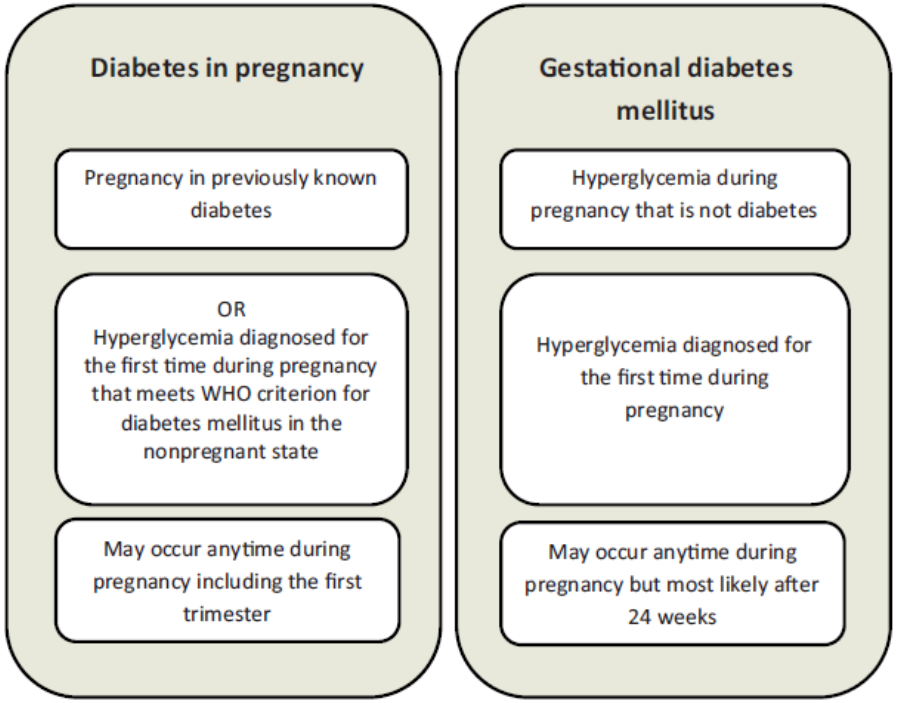
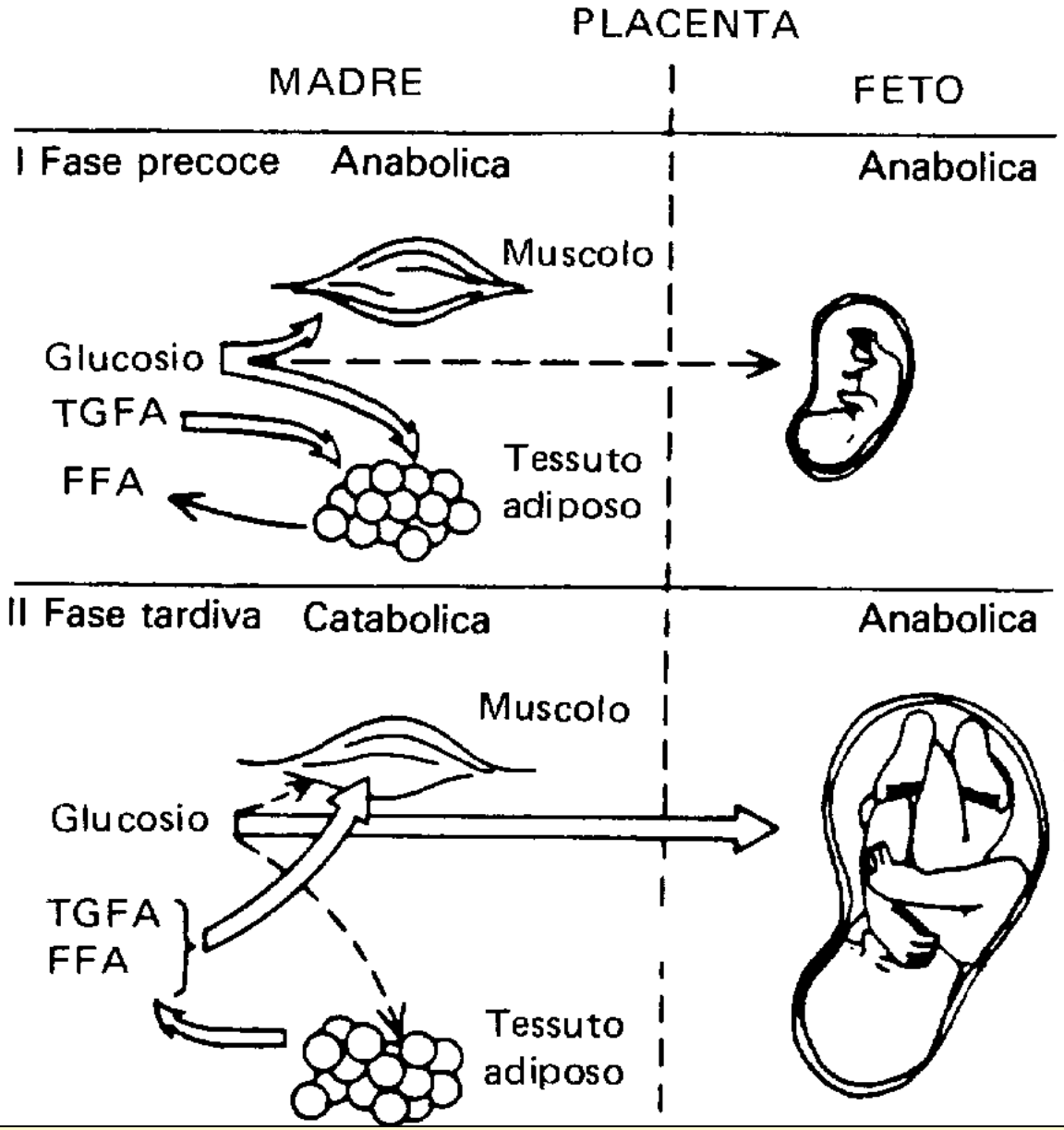


Figure 2 The difference between diabetes in pregnancy and gestational diabetes mellitus.



Modificazioni metaboliche nella gravidanza normale

Cambiamenti metabolici fisiologici durante la gravidanza

1. Iperplasia delle β -cell pancreatiche dovuta all'incremento di estrogeni e progesterone della madre
2. Aumento della sensibilità al glucosio:
- aumento dell'immagazzinamento di glicogeno
- diminuzione della gluconeogenesi nel fegato
- aumento dell'utilizzazione periferica del glucosio
3. Diminuzione del glucosio plasmatico a digiuno
4. Aumento dell'immagazzinamento dei grassi
5. Ormoni placentari antagonisti dell'insulina

All'inizio della gravidanza

L'hPL è responsabile dello "Stato diabetogeno" della gravidanza:
- aumenta la lipolisi
- riduce la sensibilità dei tessuti periferici all'insulina
- risparmio del glucosio e degli amminoacidi per il feto

Durante la gravidanza

1. Diminuzione della tolleranza glucidica
2. Diminuita sensibilità all'insulina (specialmente nel muscolo scheletrico)
- diminuzione dei depositi epatici di glicogeno,
- aumento della gluconeogenesi
- shift mobilizzazione dei grassi

3. Costante apporto di nutrienti al feto

FISIOPATOLOGIA

SUPERAMENTO DELLA RESISTENZA FISIOLOGICA ALL'INSULINA

peggioramento di una cronica resistenza all'insulina

anomalia autoimmune o genetica della funzionalità delle B cell pancreatiche

5% dei GDM hanno mutazioni della glucochinasi

GDM

Diabete Gestazionale : si verifica nella gravida quando la fisiologica insulino-resistenza non viene compensata dall'aumento della secrezione insulinica in modo
da mantenere nella norma i livelli di glucosio.

PREVALENZA

5 – 10 % in relazione a

- **test impiegato per la diagnosi**
- **gruppo etnico**

1--14% in Italia

Variabilità di frequenza in relazione alle diverse razze ed etnie esaminate, in parte dovuta alle diverse modalità di diagnosi e screening utilizzate

Diagnosis and Classification of Diabetes Mellitus. ADA. Diabetes Care. Volume 30, Supplement 1, January 2007.

DIAGNOSTIC THRESHOLDS
GDM

Measure	Value (mmol/L)	Value (mg/dL)	Cumulative %
Fasting VPG	≥ 5.1	≥ 92	8.3
1 hr VPG	≥ 10.0	≥ 180	14.0
2 hr VPG	≥ 8.5	≥ 153	16.1

- **One or more** of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM
- **Universal**

SCREENING PER GDM: A CHI E QUANDO

Tabella II. *Criteri ADA per la valutazione del grado di rischio per GDM*

Basso rischio Screening non indicato	**Medio** Screening fra 24a -28a s.g.	**Alto** Screening appena possibile
Appartenenza a gruppo etnico con bassa prevalenza GDM		Familiarità positiva per diabete in parenti di I° grado
Familiarità negativa per diabete mellito		Pregresso riscontro di intolleranza glucidica
Anamnesi ostetrica priva di esiti sfavorevoli	Caratteristiche intermedie tra basso e alto rischio	Pregresso riscontro di intolleranza glucidica
Nessun precedente di anormale tolleranza al glucosio		Obesità
Età inferiore a 25 aa		Glicosuria marcata nella gravidanza in corso
Normopeso		

SCREENING PER GDM IN ITALIA

Glicemia BASALE al primo controllo in gravidanza
(entro le 12 sett di EG)

DIAGNOSI DI DIABETE PREGRAVIDICO SE:

- due valori di glicemia plasmatica a digiuno ≥ 126 mg/dl
- glicemia plasmatica random ≥ 200 mg/dl
- Hba1C>=6,5%

Conferenza nazionale di consenso per raccomandazioni e implementazione delle nuove linee guida per screening e diagnosi del GDM 2011,

SCREENING PER GDM IN ITALIA

OGTT a *16-18 sett* se almeno uno dei seguenti *FATTORI DI RISCHIO*:

- diabete gestazionale in una gravidanza precedente
- indice di massa corporea (IMC) pregravidico ≥ 30 (OBESITA!)
- riscontro, precedentemente o all'inizio della gravidanza, di valori di glicemia plasmatica compresi fra 100 e 125 mg/dl (5.6-6.9 mmol/l)

Conferenza nazionale di consenso per raccomandazioni e implementazione delle nuove linee guida per screening e diagnosi del GDM 2011,

SCREENING PER GDM IN ITALIA

OGTT da 75 g a *24-28 sett* se almeno uno dei seguenti FATTORI DI RISCHIO:

- eta ≥35 anni
- OGTT negativo a 16-18 sett
- indice di massa corporea (IMC) pregravidico ≥25 kg/m2
- macrosomia fetale in una gravidanza precedente (≥4,5 kg)
- GDM in una gravidanza precedente
- anamnesi familiare di diabete (parente di primo grado con diabete tipo 2)
- famiglia originaria di aree ad alta prevalenza di diabete: Asia meridionale, Caraibi, Medio Oriente

Conferenza nazionale di consenso per raccomandazioni e implementazione delle nuove linee guida per screening e diagnosi del GDM 2011,

FIGO – Main Messages
Universal Testing 2017

- FIGO adopts and supports the **IADPSG/WHO/ IDF**

position that :

all pregnant women should be tested for hyperglycemia during pregnancy using a one-step procedure

- FIGO encourages **all countries**… to ensure ***universal testing of all pregnant women*** for hyperglycemia

FIGO – Main Messages Universal Testing 2017

Table 4
Options for diagnosis of gestational diabetes mellitus based on resource settings.

	Strategy			
Setting	Who to test and when	Diagnostic test	Interpretation[a]	Grade
Fully resourced settings	All women at booking/first trimester	Measure FPG, RBG, or HbA1c to detect diabetes in pregnancy		1|⊕⊕⊕○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT		
Fully resourced settings serving ethnic populations at high risk[b]	All women at booking/first trimester	Perform 75-g 2-hour OGTT to detect diabetes in pregnancy		2|⊕○○○
	24–28 weeks	If negative: perform 75-g 2-hour OGTT		
Any setting (basic); particularly medium- to low-resource settings serving ethnic populations at risk	All women between 24 and 28 weeks	Perform 75-g 2-hour OGTT		1|⊕⊕⊕○

While this is the optimal recommendation, alternatives are given in acknowledgement of limitations faced in diverse settings

Pragmatic guides for **testing**, **diagnosis** and **management** must be based on each country's available:

- **Finances**
- **Human Resources**
- **Infrastructure Resources**

GDM a major global health problem

Hyperglycemia is one of the **most common medical conditions women encounter during pregnancy**

1 in 6 live births occur to women with some form of hyperglycemia

84% *of which are due to GDM*

HYPERGLYCEMIA/GDM IS ASSOCIATED WITH:

- Leading causes of **maternal mortality**
- Higher incidence of **maternal morbidity**
- Higher incidence of **perinatal and neonatal morbidity**
- **Later long term consequences** for both mother and child

GDM a major global health problem

- Higher incidence of maternal morbidity, including cesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy [including preeclampsia] and subsequent development of type 2 diabetes.

- Perinatal and neonatal morbidities are also increased : macrosomia, birth injury, hypoglycemia, polycythemia and hyperbilirubinemia. Long term sequelae in offspring with in-utero exposure to maternal hyperglycemia may include higher risks for obesity and diabetes later in life.

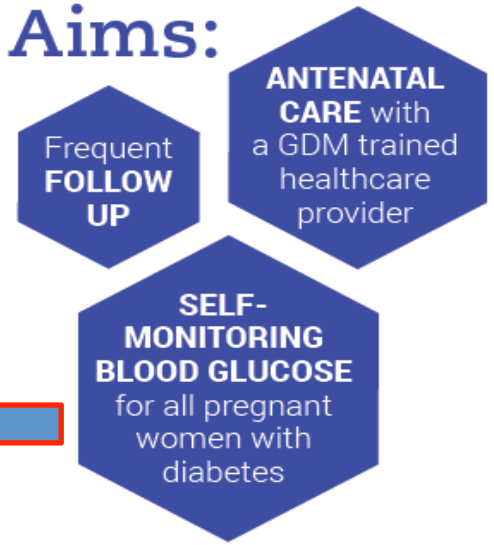
In most parts of the low, low middle and upper middle income countries (which contribute to over 85 % of the annual global deliveries) the majority of women are not properly screened for diabetes during pregnancy.

Table 3
Maternal and fetal morbidity associated with gestational diabetes mellitus.

Maternal morbidity	Fetal/neonatal/child morbidity
Early pregnancy	Stillbirth
Spontaneous abortions	Neonatal death
Pregnancy	Nonchromosomal congenital malformations
Pre-eclampsia	Shoulder dystocia
Gestational hypertension	Respiratory distress syndrome
Excessive fetal growth (macrosomia, large for gestational age)	Cardiomyopathy
Hydramnios	Neonatal hypoglycemia
Urinary tract infections	Neonatal polycythemia
Delivery	Neonatal hyperbilirubinemia
Preterm labor	Neonatal hypocalcemia
Traumatic labor	Erb's palsy (as consequence of birth injury)
Instrumental delivery	Programming and imprinting; fetal origins of disease: diabetes, obesity, hypertension, metabolic syndrome
Cesarean delivery	
Postoperative/postpartum infection	
Postoperative/postpartum hemorrhage	
Thromboembolism	
Maternal morbidity and mortality	
Hemorrhage	
Puerperium	
Failure to initiate and/or maintain breastfeeding	
Infection	
Long-term postpartum	
Weight retention	
GDM in subsequent pregnancy	
Future overt diabetes	
Future cardiovascular disease	

Care for women with GDM

Management of GDM: Management should be in accordance with available national resources and infrastructure even if the specific diagnostic and treatment protocols are not supported by high-quality evidence, as this is preferable to no care at all.



Fasting venous plasma < 95 mg/dl
1 hour postprandial <130 mg/dl
2 hour postprandial <120 mg/dl (140)

Box 5

Recommendations for glucose monitoring in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Self-monitoring of blood glucose is recommended for all pregnant women with diabetes, 3–4 times a day: • Fasting: once daily, following at least 8 hours of overnight fasting • Postprandial: 2-3 times daily, 1 or 2 hours after the onset of meals, rotating meals on different days of the week	All	2|⊕⊕○○
Self-monitoring of blood glucose is recommended for all pregnant women with diabetes at least once daily, with documented relation to timing of meal	Low	2|⊕○○○

Quale TERAPIA per il GDM ?

- Dieta
- Esercizio fisico
- Terapia FARMACOLOGICA

Trattamento dietetico nel DMG

Le calorie totali vengono calcolate in base al peso pregravidico e aumentate del 25% ogni trimestre.

- L'intake nutrizionale dovrebbe essere suddiviso: 35-40% di carboidrati complessi; 20-25% di proteine, e 35-40% di lipidi (almeno il 10% polinsaturi)
- frazionando i pasti in piccole assunzioni si può ridurre la necessità insulinica
- Eccessive restrizioni dietetiche possono determinare chetonuria con effetti sia su madre che sul feto

NICE Clinical Guidelines, July, 2008

GDM : NUTRITION AND PHYSICAL ACTIVITY

Box 9

Recommendations for nutrition therapy in women with gestational diabetes mellitus

Recommendations
We recommend that the following principles should be adhered for all pregnant women with diabetes: • Design an appropriate diet with respect to prepregnancy BMI, desired body weight, physical activity, habits, and personal and cultural preferences. • Provide routine follow-up and diet adjustments throughout pregnancy to achieve and maintain treatment goals. • Offer training, education, support, and follow-up by a qualified dietician experienced in care of women with diabetes. Issues for discussion include: weight control, food records, carbohydrate counting, prevention of hypoglycemia, healthy foods, and physical activity. We suggest that caloric intake be calculated based on prepregnancy BMI and desirable weight gain as follows: • 35–40 kcal/kg desirable body weight for underweight women • 30–35 kcal/kg desirable body weight for normal weight women • 25–30 kcal/kg desirable body weight for overweight women We recommend limiting carbohydrate intake to 35%–45% of total calories, with a minimum of 175 g carbohydrate per day, distributed in three small-to-moderate sized meals and 2–4 snacks. For obese women, caloric intake may be reduced by 30%, but not below 1600–1800 kcal/d For women with diabetic nephropathy, protein may be lowered to 0.6–0.8 g/kg ideal body weight

- FIGO recognizes that nutrition counseling and physical activity are the primary tools in the management of GDM.
- FIGO recommends that women with GDM receive practical nutrition education and counseling that empowers them to choose the right quantity and quality of food.
- Women with GDM must be repeatedly advised to continue the same healthy eating habits after delivery to reduce the risk of future T2DM.

Box 10

Recommendations for physical activity in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
We suggest that appropriate, personally adapted, physical activity be recommended for all women with diabetes: • Planned physical activity of 30 min/day • Brisk walking or arm exercises while seated in a chair for 10 min after each meal. • Women physically active prior to pregnancy should be encouraged to continue their previous exercise routine.	All	2⊕⊕○○

GDM :PHARMACOLOGICAL MANAGEMENT

Update on Gestational Diabetes Mellitus

2011

Ann E. Evensen, MD

Table 2
Safety of GDM medications in pregnancy and breastfeeding

Drug	Pregnancy Class	Breastfeeding Class
Insulin	B (regular, lispro, NPH) C (glargine, detemir)	All forms safe in breastfeeding (infants cannot absorb insulin intact through their gastrointestinal tracts)
Glyburide	B/C (manufacturer dependent)	Does not enter breast milk, but breastfeeding is not recommended by the manufacturer
Glipizide	C	Does not enter breast milk, but breastfeeding is not recommended by the manufacturer
Metformin	B	Small amount (<1% weight-adjusted maternal dose) enters breast milk, but breastfeeding is not recommended by the manufacturer

Experts consider insulin, glyburide, glipizide, and metformin safe to use in women who are breast-feeding despite the manufacturers' cautions.

Data from Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop—Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl 2):S251–60; and Lexi-Comp [Internet]. Ohio: Lexi-Comp, Inc.; 2011. Available at: http://www.lexi.com/. Accessed November 3, 2011.

GDM :PHARMACOLOGICAL MANAGEMENT

Pharmacological management: If lifestyle modification alone fails to achieve glucose control, metformin, glyburide, or insulin should be considered as safe and effective treatment options for GDM.

Box 11

Recommendations for pharmacological treatment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Insulin, glyburide, and metformin are safe and effective therapies for GDM during the second and third trimesters, and may be initiated as first-line treatment after failing to achieve glucose control with lifestyle modification. Among OADs, metformin may be a better choice than glyburide [109].	All	2|⊕⊕○○
Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on OAD therapy, including some of the following factors [129]: • Diagnosis of diabetes <20 weeks of gestation • Need for pharmacologic therapy >30 weeks • Fasting plasma glucose levels >110 mg/dL • 1-hour postprandial glucose >140 mg/dL • Pregnancy weight gain >12 kg	High	2|⊕⊕○○

Box 12

Recommendations for insulin treatment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
The following insulins may be considered safe and effective treatment during pregnancy: regular insulin, NPH, lispro, aspart and detemir.	All	1|⊕⊕⊕○

Care for women with GDM

Box 2

Recommendations for fetal growth assessment in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Clinical and sonographic growth assessments every 2–4 weeks from diagnosis until term	High	1|⊕○○○
Periodic clinical and sonographic growth assessments from diagnosis until term	Mid and Low	2|⊕○○○

Box 3

Recommendations for fetal well-being surveillance in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
Use cardiotocography and/or biophysical profile or kick-count as indicated according to local protocol	All	1|⊕○○○

MONITORAGGIO GDM in dietoterapia

- **Ecografia di accrescimento a 32-34 settimane, ricontrollo se CA > 95° centile o < 5° centile**
- **CTG da 39-40 sett di EG con misurazione AFI, poi a giorni alterni fino al parto**

ACOG 2009 – NICE 2008 – Fifth International Workshop-Conference on gestational diabetes mellitus, Metzger 2007, Kapoor, 2007 – Graves, 2007 – Hawkins, 2007

MONITORAGGIO GDM in insulinoterapia

(se CA>95° centile o profili glicemici alterati)

- **Visita ogni 1-2 settimane**
- **Ecocardiografia fetale a 20-22 sett se inizio terapia insulinica prima delle 20 sett di EG**
- **Ecografia di accrescimento a 32 e poi a 36 settimane di EG**
- **Controllo HbA1c mensile**
- **CTG settimanali da 34+0 sett di EG con misurazione AFI**

ACOG 2009 – NICE 2008 – Fifth International Workshop-Conference on gestational diabetes mellitus, Metzger 2007

GDM : TIME AND MODE OF DELIVERY

Box 4

Recommendations for timing and mode of delivery in women with gestational diabetes mellitus.

Recommendations	Resource setting	Strength of recommendation and quality of evidence
As per local protocol or as suggested in Figure 4	All	2|⊕○○○

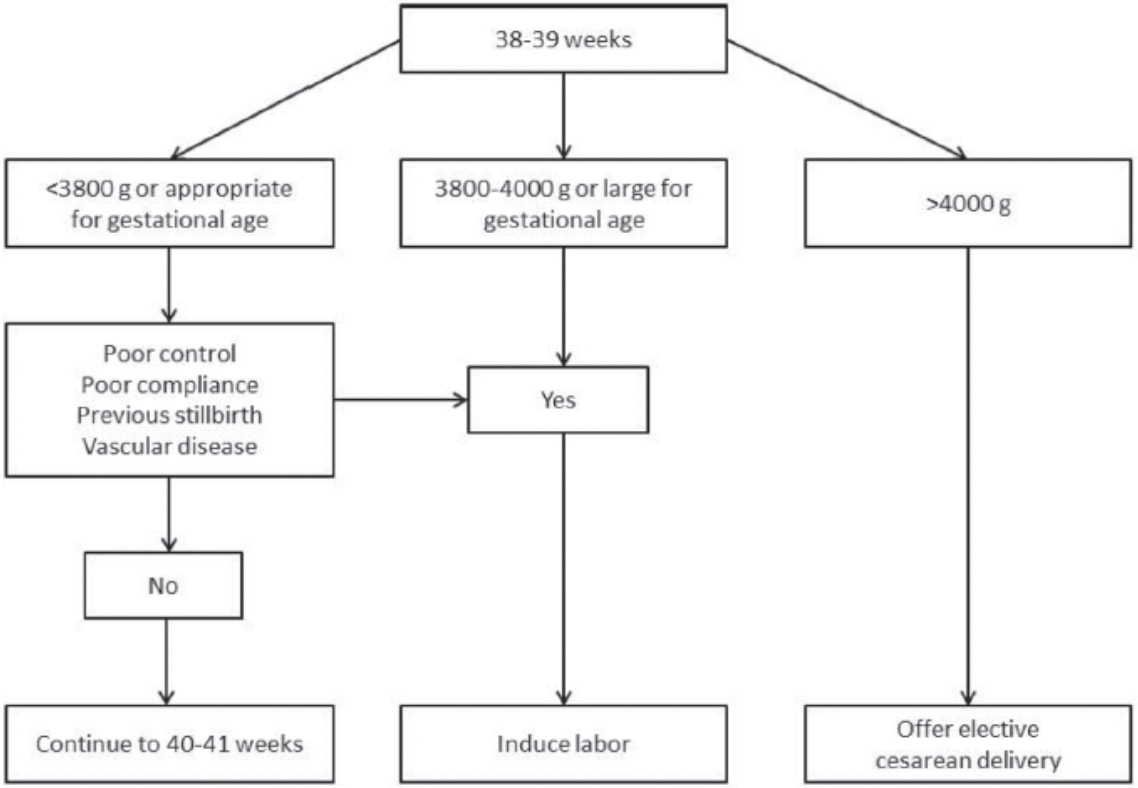


Figure 4. Timing of delivery in women with gestational diabetes mellitus and diabetes in pregnancy.

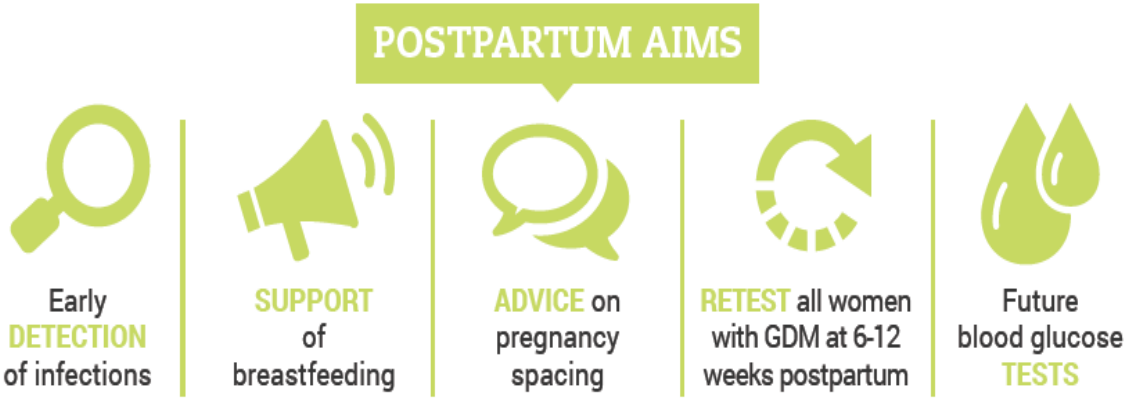
Includes recommendations for Postpartum care

- FIGO supports the concept that the postpartum period in women with GDM provides an important platform to initiate early preventive health for both the mother and the child who are both at a heightened risk for future obesity, metabolic syndrome, diabetes, hypertension, and cardiovascular disorders.
- FIGO encourages obstetricians to establish connections with family physicians, internists, pediatricians, and other healthcare providers to support postpartum follow-up of GDM mothers linked to the regular check-up and vaccination program of the child to ensure continued engagement of the high-risk mother–child pair.

PREGNANCY OFFERS A WINDOW OF OPPORTUNITY TO:

- **Establish** services
- **Improve** health
- **Prevent** intergenerational transmission of non-communicable diseases

- Glicemia basale a digiuno a 1 mese dal parto
- OGTT 75 g non prima di 6 settimane dal parto



COMPLICANZE FETALI

A BREVE TERMINE:

- policitemia, iperbilirubinemia, ipocalcemia, ipopotassiemia
- ipoglicemia
- neonato pretermine
- RDS
- polidramnios
- macrosomia / LGA
- distocia di spalla / fratture ossee / lesioni plesso brachiale
- MORTE ENDOUTERINA

•1 - 3% nel diabete pregravidico

•0.4% nella popolazione non diabetica

A LUNGO TERMINE:

- obesità
- intolleranza glicidica e diabete di tipo 2

MACROSOMIA

DIABETE non compensato

↓

Aumento passaggio di glucosio attraverso la placenta

↓

Iperinsulinizzazione fetale

↓

Crescita asimmetrica con deposizione di tessuto adiposo su spalle e addome

I picchi di iperglicemia postprandiale hanno un forte effetto sulla crescita intrauterina → ↑ R di MACROSOMIA fetale di 4 volte rispetto alla popolazione generale.

Boinpally and Jovanovic,2009

MACROSOMIA FETALE

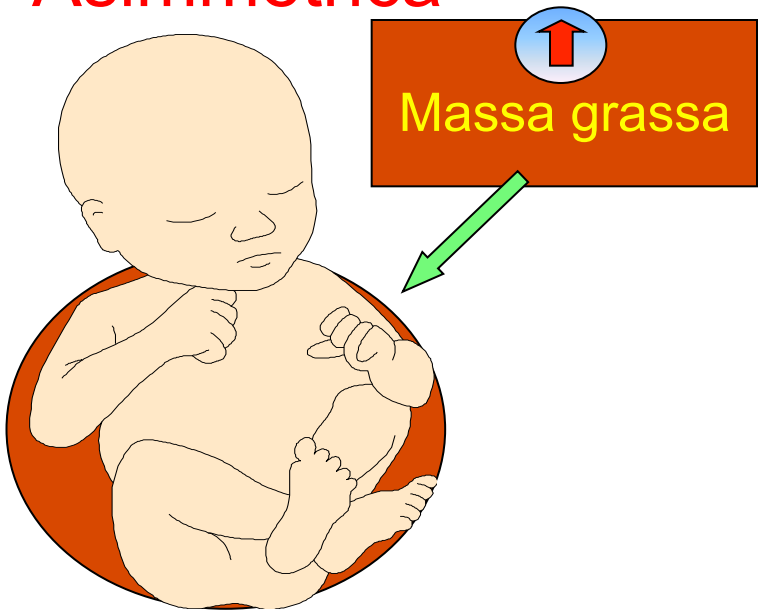
Classificazione

Simmetrica

MACROSOMA
Peso > 4000 gr
Peso > 4500 gr

INCIDENZA
5% - 20%
4% - 5%

Asimmetrica



PI: 10° - 90° percentile

Eziologia: fattori genetici

Eziologia: squilibrio nutrizionale intrauterino

Lepercq, 1999

MACROSOMIA FETALE

Rischi fetali a breve termine

- ✓ Morte intrauterina (2-3 volte)
- ✓ Travaglio prolungato
- ✓ Parto operativo
- ✓ Distocia di spalla
- ✓ Ipossia
- ✓ Lesioni del plesso brachiale (2-3 volte)
- ✓ Ipoglicemia (2-3 volte)
- ✓ Iperbilirubinemia (2-3 volte)

Rischi fetali a lungo termine

- ✓ Diabete
- ✓ Obesità
- ✓ Sindrome metabolica
- ✓ Asma
- ✓ Paralisi del plesso brachiale

MACROSOMIA FETALE

Quando effettuare l'esame ecografico?

Limitazioni tecniche dell'ecografia utilizzata presso **il termine di gravidanza**

- Rapporti dell'estremo cefalico con la pelvi materna
  - **Biometria dell'estremo cefalico non accurata o impossibile**
- Riduzione della quantità di L.A. presso il termine
  - **Influenza sull'accuratezza della biometria (in particolare sulla CA)**
- Impossibilità di valutazioni biometriche accurate nel caso di feti macrosomi
  - **Difficoltà nell'ottenere scansioni complete dell'estremo cefalico o dell'addome**

MACROSOMIA FETALE

Ecografia vs valutazione clinica

3844 Pz
EBW : Shepard
Macrosomia : 8,4 %

Accuratezza per un peso neonatale ≥ 4000 gr.

	SENS. (%)	SPEC. (%)	VPP (%)	VPN (%)
Val. clinica.	68	90	38	97
Val. US	58	68	***56***	70

Val. clinica: cut-off : ≥ 3700 gr.
Val. ecografica: ≥ 4000 gr.
N.B.: ECO dopo val. clinica di peso presunto ≥ 3700 gr

Weiner, 2002

MACROSOMIA ed ecografia

Diagnosi di macrosomia fetale ecografica
(peso fetale > 4000g)
SE 12 - 75% SP 68 – 99%

Bamberg et al, 2012

CA ≥ 35 cm:

VPP 93% di un peso alla nascita > 4000 g

Misure ripetute della CA sono in grado di prevedere pesi > 90° percentile (SE 84%, SP 100%)

L'accelerazione di crescita della CA è un buon predittore di macrosomia alla nascita e riflette l'asimmetria della crescita nelle gravidanze complicate da diabete

MACROSOMIA e PARTO

- **Mancato impegno della pp**
- **Rallentamento della progressione della pp**
- **Rallentata rotazione interna**
- **Distocia di spalle**

Acog 2005, Am J Obst Gyn 2006

MACROSOMIA

PREVENZIONE

- diminuire i picchi glicemici post-prandiali
- il target glicemico per le donne gravide è più basso rispetto alle non gravide
- l'automonitoraggio glicemico va personalizzato, evitando il R di ipoglicemie (soprattutto notturne)
- l'HbA1c non dovrebbe essere usata di routine per il controllo glicemico nel II e III trim

RCOG 2008