Con il Patrocinio di

ASR ABRUZZO
AGENZIA SANITARIA REGIONALE

IL DIABETE IN GRAVIDANZA

Chieti, 19-20 aprile 2018

DALLA RICERCA ALLA PRATICA CLINICA



Il parto nella donna con diabete

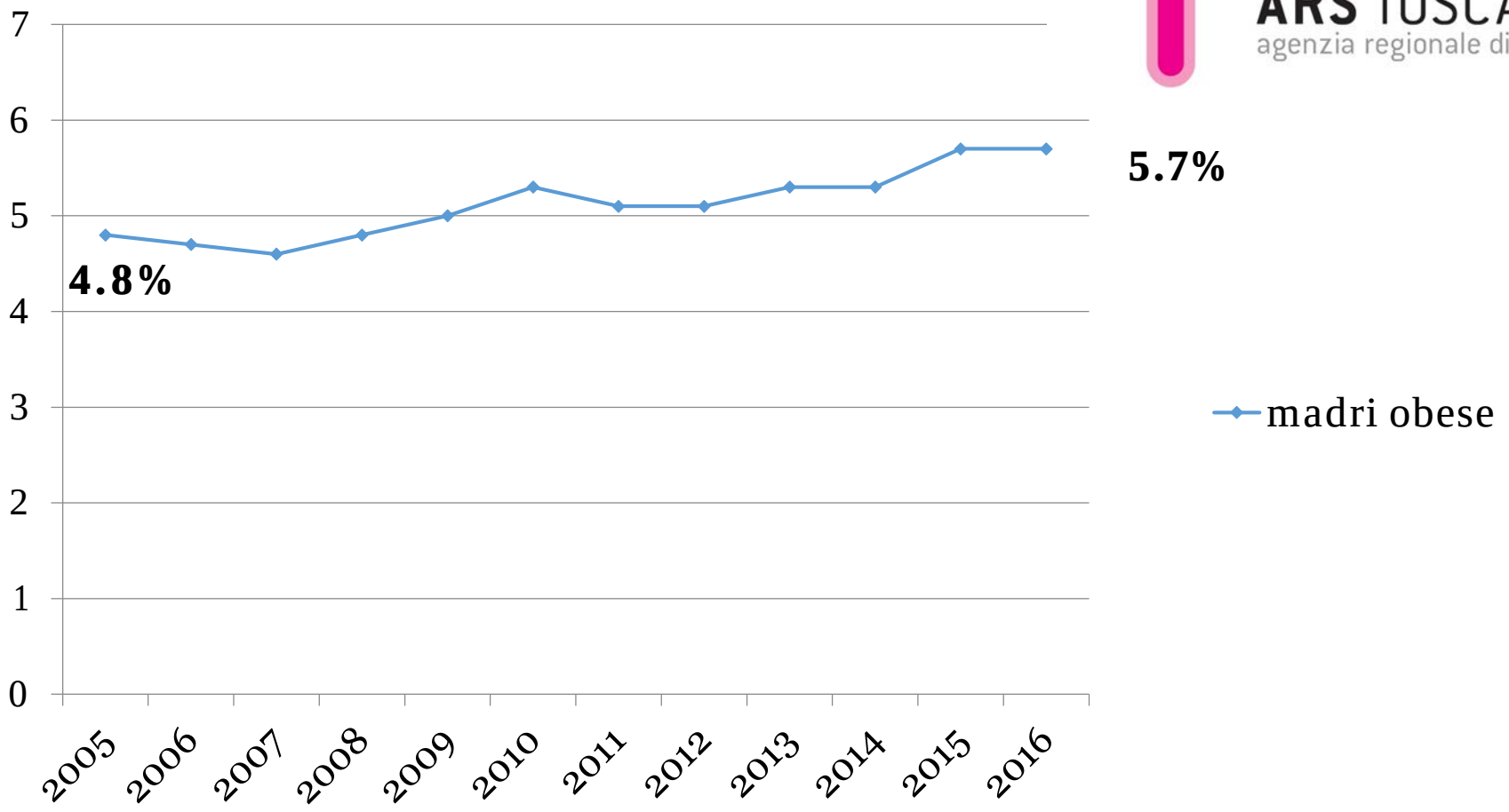
Federico Mecacci

Prenatal Medicine
High Risk Pregnancy Unit
Careggi Universitary Hospital
Newborn's and Women's Health Department

Del 20% delle madri obese dal 2008 al 2016

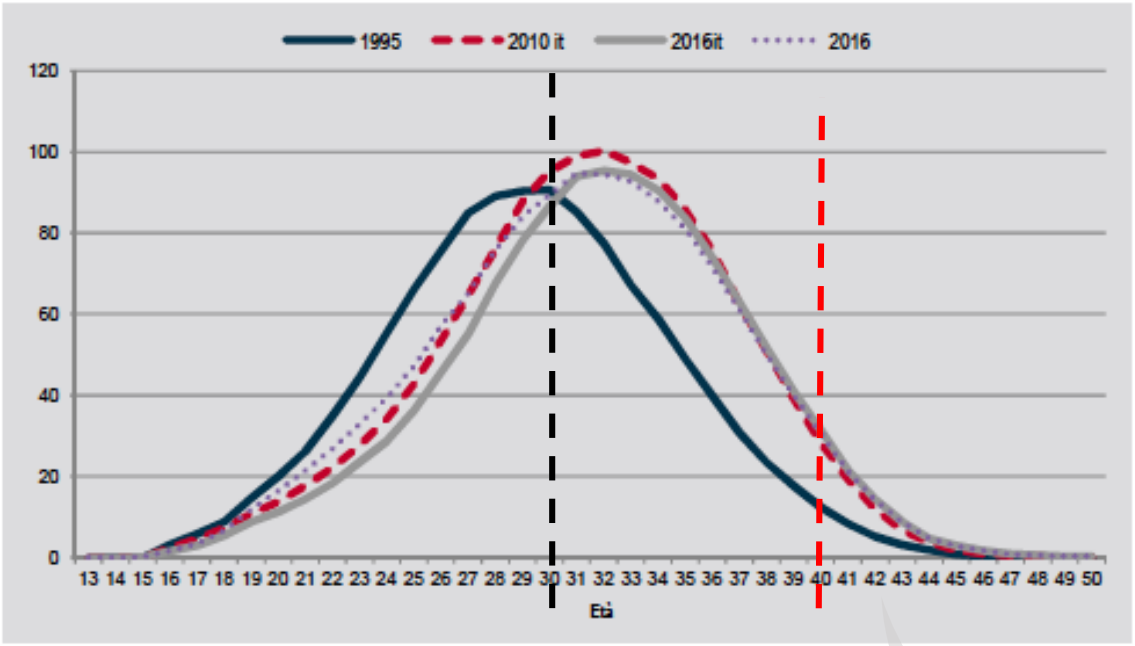
Dati regione Toscana

ARS TOSCANA
agenzia regionale di sanità



MATERNAL AGE , DELAYED CHILDBEARING AND METASBOLIC SYNDROME

Figura 1.3 - Tassi di fecondità specifici per età delle donne residenti in Italia - Anni 1995, 2010 e 2016 (per 1.000 donne) (a)



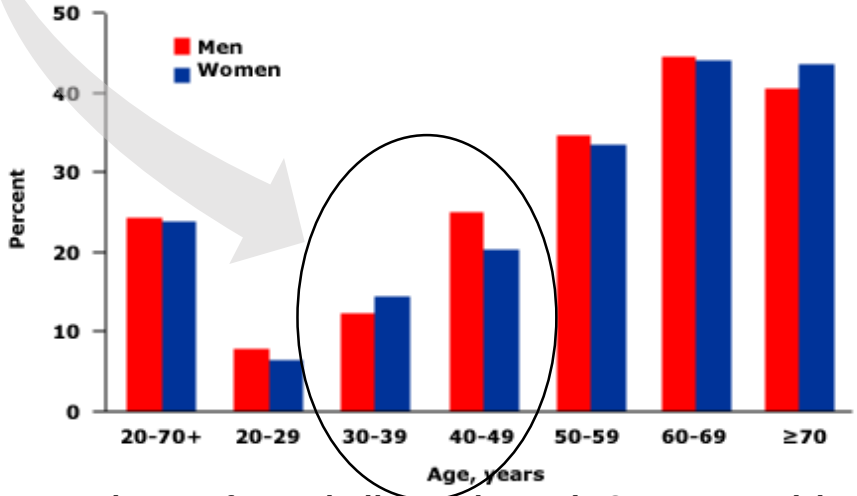
Istat 2016





36% of Europeans were observed at the age of 40-55 years with metabolic syndrome

Balkau B, Diabet. Metabol. 2002

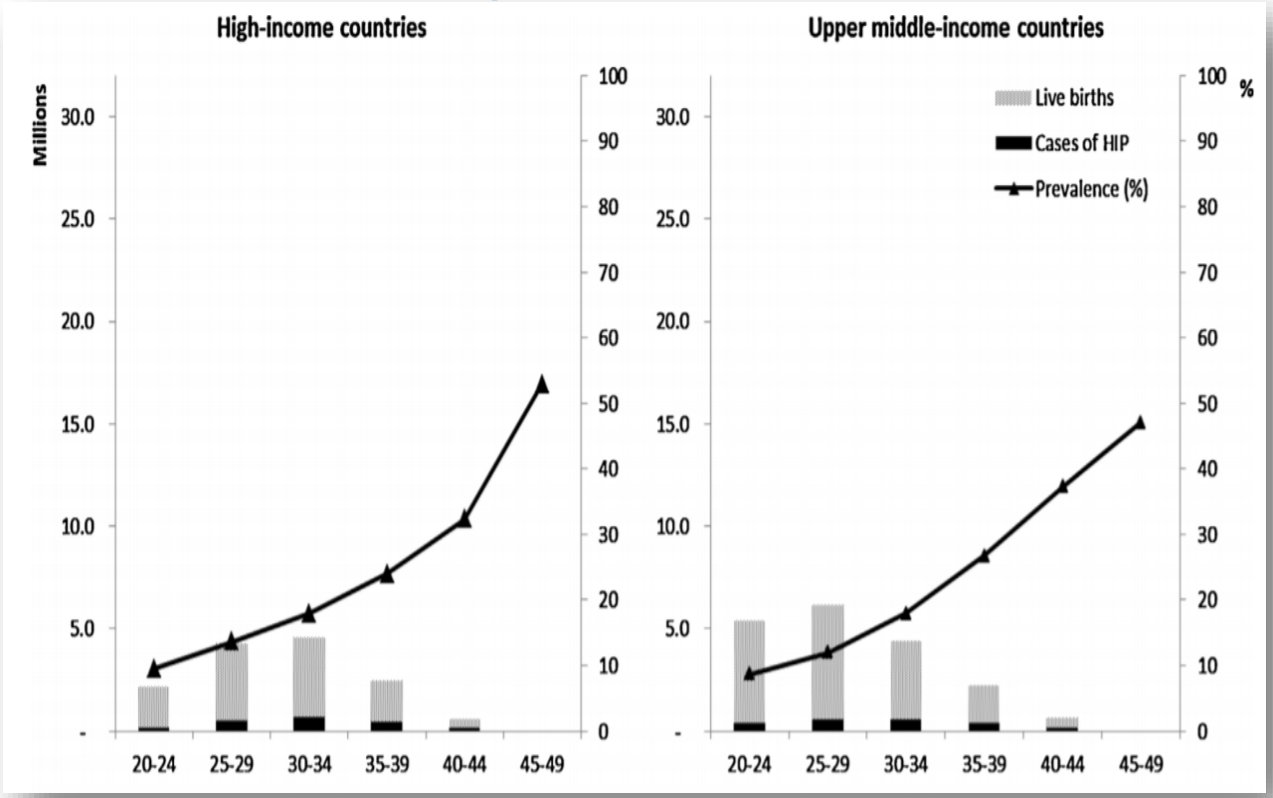


Prevalence of metabolic syndrome(NCEP ATP III) in the NHANES III survey

Ford ES, JAMA 2002; 287:356.

Prevalence of hyperglycaemia in pregnancy by age

Global prevalence of hyperglycaemia in pregnancy 16.9%





The prevalence of HIP increases sharply with age with a prevalence of **39.2%** in women **40–44** and up to 47.9% in women 45–59 years,

Global estimates of the prevalence of hyperglycaemia in pregnancy L. Guariguata et al. Diabettes research and clinical practice 2014

IN CHE MODO IL DIABETE INFLUENZA IL TIMING, LA MODALITÀ E L'OUTCOME DEL PARTO?



THE EFFECTS OF HYPERGLYCEMIA/METABOLIC SYNDROME

GESTATIONAL DIABETES

OBESITY

INSULIN RESISTANCE

↑ **Glucose**

↑ **FFA**
(fat mobilization)



↑ insulin

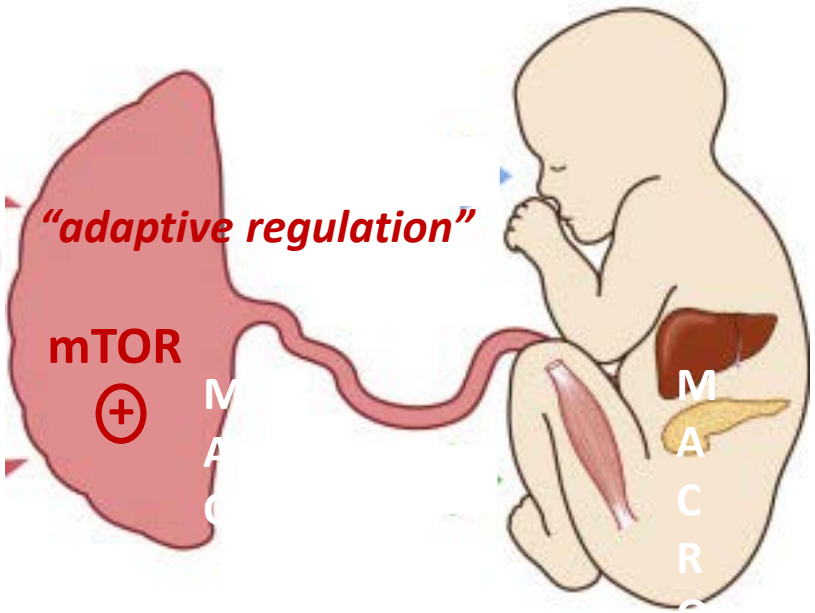
↑ IGF1

↑ leptina

↓ Adiponectina

↑ FETAL NUTRIENT AVAILABILITY

↑ PLACENTAL TRASPORT OF NUTRIENTS



FETAL OVERNUTRITION-MACROSOMIA/LGA

↓ **DISTOCIA**

↓ **STILLBIRTH**

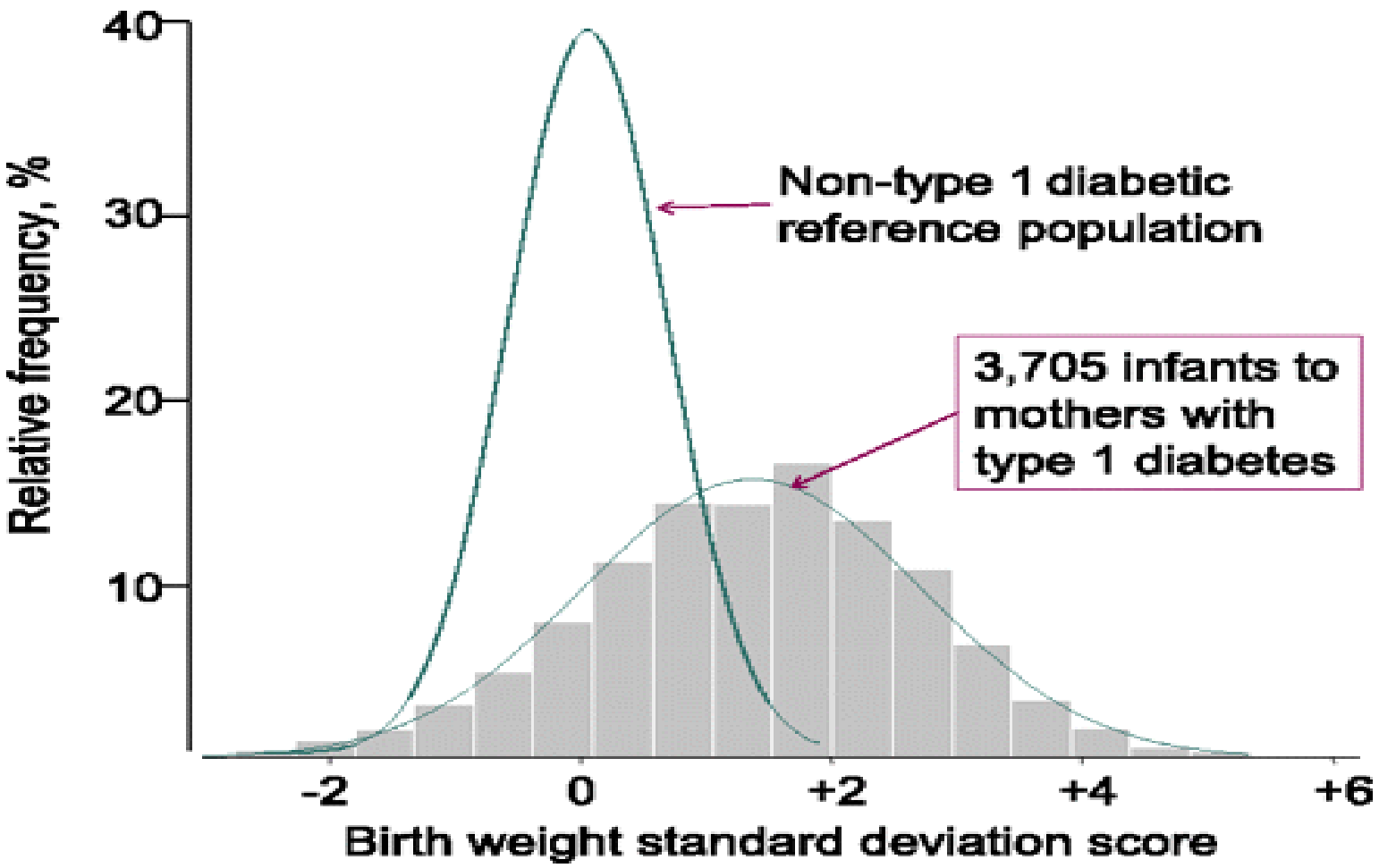
Romero. Am J Obstet Gynecol 2017.

Brett KE. Int. J . Mol. Sci. 2014

Macrosomia e rischio di distocia



Birth weight distribution in diabetic pregnancies



Persson et al. Diab Care 2011;34:1145-1149



"DIABESITY" and MACROSOMIA

Outcome	N	No.	%	Model I OR	95% CI	Model II OR	95% CI
Birth weight >90th percentile[1]							
No GDM, no obesity	17,244	1,339	7.8	1.00		1.00	
GDM, no obesity	2,791	401	14.4	1.99	(1.77–2.25)	2.19	(1.93–2.47)
No GDM, obesity	2,247	278	12.4	1.68	(1.46–1.92)	1.73	(1.50–2.00)
GDM, obesity	935	203	21.7	3.29	(2.79–3.89)	3.62	(3.04–4.32)
Cord C-peptide >90th percentile[2]							
No GDM, no obesity	14,886	916	6.2	1.00		1.00	
GDM, no obesity	2,419	386	16.0	2.90	(2.54–3.30)	2.49	(2.17–2.85)
No GDM, obesity	1,829	201	11.0	1.80	(1.52–2.12)	1.77	(1.49–2.11)
GDM, obesity	751	168	22.4	4.14	(3.43–5.00)	3.61	(2.94–4.42)
Newborn percent body fat >90th percentile[5]							
No GDM, no obesity	14,367	1,143	8.0	1.00		1.00	
GDM, no obesity	2,338	331	14.2	1.91	(1.67–2.18)	1.98	(1.73–2.27)
No GDM, obesity	1,854	233	12.6	1.66	(1.43–1.93)	1.65	(1.41–1.93)
GDM, obesity	768	185	24.1	3.67	(3.08–4.38)	3.69	(3.06–4.44)

CONCLUSIONS—Both maternal GDM and obesity are independently associated with adverse pregnancy outcomes. Their combination has a greater impact than either one alone.

PATRICK M. CATALANO, DIABETES CARE, VOLUME 35, APRIL 2012

MACROSOMIA ASIMMETRICA

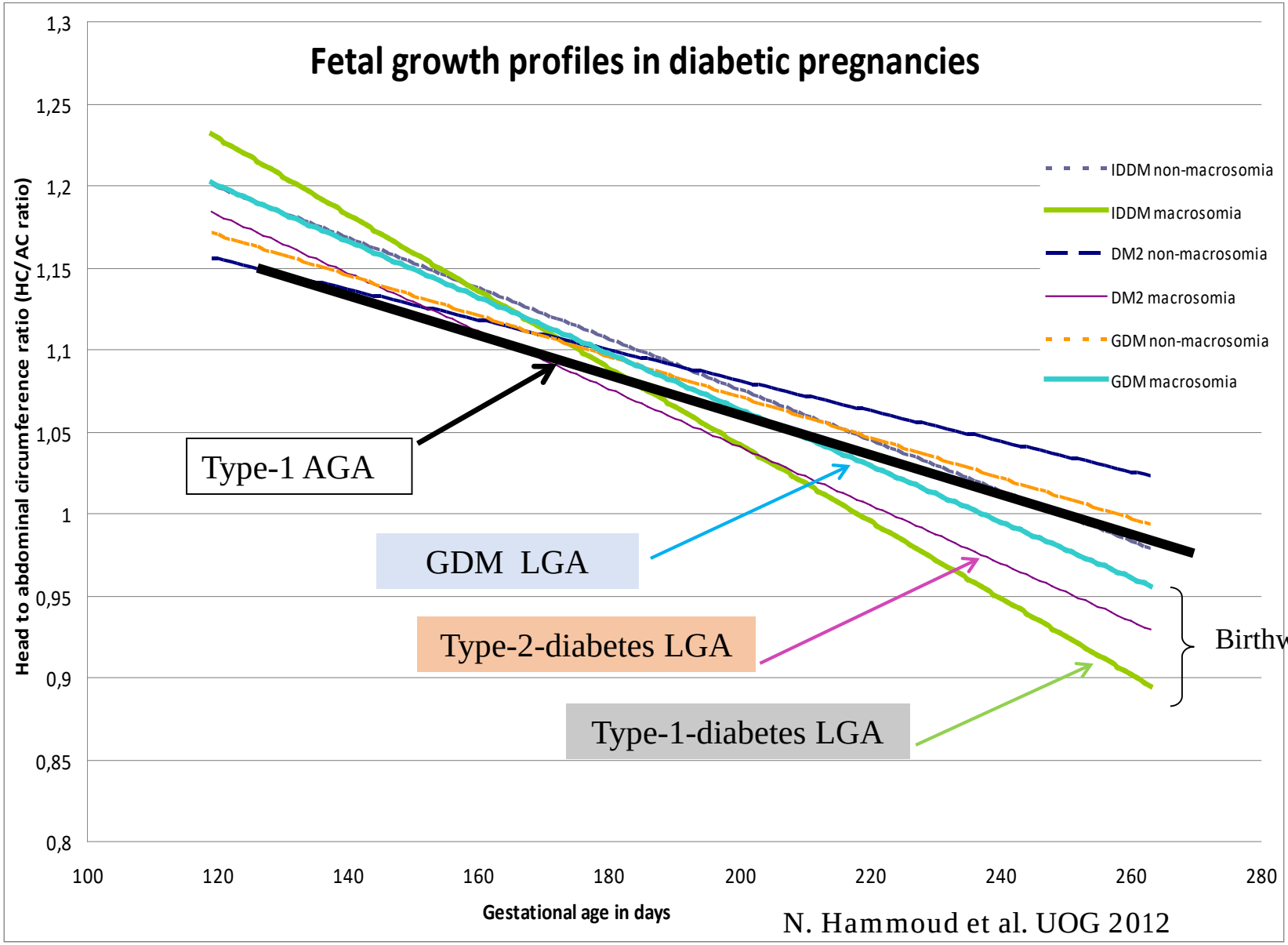


OBESITY IS INDEPENDENTLY ASSOCIATED WITH FETAL HYPERINSULINEMIA, BIRTH WEIGHT, AND NEWBORN ADIPOSITY.

Newborn percent body fat >90th percentile[5]							
No GDM, no obesity	14,367	1,143	8.0	1.00		1.00	
GDM, no obesity	2,338	331	14.2	1.91	(1.67–2.18)	1.98	(1.73–2.27)
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PATRICK M. CATALANO, DIABETES CARE, VOLUME 35, APRIL 2012

Fetal growth profiles in diabetic pregnancies
Head to abdomen circumf. Ratio

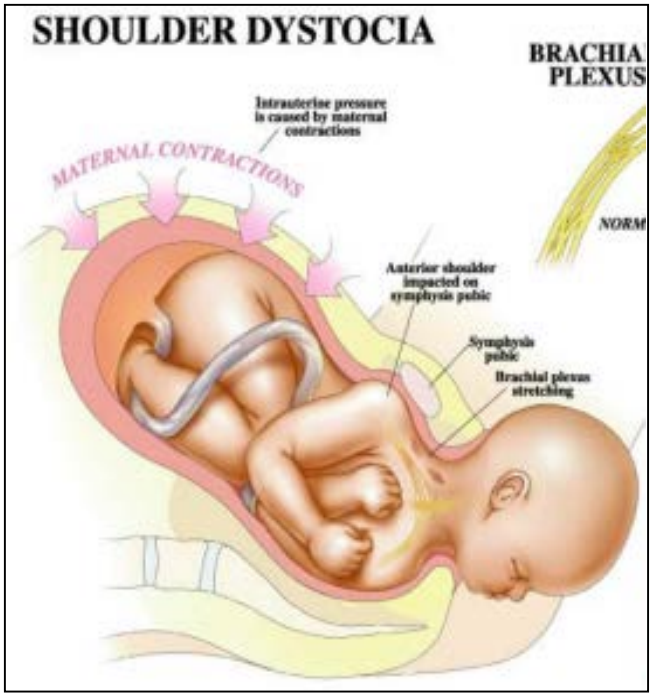




LA MACROSOMIA È UN **IMPORTANTE FATTORE DI RISCHIO** PER DISTOCIA DI SPALLA.

Conseguenze neonatali:

- Paralisi transitoria plesso brachiale (3.0-16.8%)
- Frattura della clavicola (1.7-9.5%)
- Frattura dell' omero (0.1-4.2%)
- Paralisi permanente del plesso brachiale(0.5-1.6%)
- encefalopatia ipossico-ischemica (0.3%)
- morte (0-0.35%)



Hoffman MK, Obstet Gynecol. 2011;117(6):1272.

Gherman RB, Am J Obstet Gynecol. 2006;195(3):657.



Incidence of shoulder dystocia by birth weight in pregnancies with and without maternal diabetes

Birth weight (grams)	Shoulder dystocia in nondiabetic pregnancies (percent)	Shoulder dystocia in diabetic pregnancies (percent)
Less than 4000	0.1 to 1.1	0.6 to 3.7
4000 to 4499	1.1 to 10.0	4.9 to 23.1
4500 or more	2.7 to 22.6	20.0 to 50.0

Data from:

1. *Acker DB, Sachs BP, Friedman EA. Risk factors for shoulder dystocia. Obstet Gynecol 1985; 66:762.*
2. *Nesbitt TS, Gilbert WM, Herrchen B. Shoulder dystocia and associated risk factors with macrosomic infants born in California. Am J Obstet Gynecol 1998; 179:476.*
3. *Sandmire HF, O'Halloin TJ. Shoulder dystocia: its incidence and associated risk factors. Int J Gynaecol Obstet 1988; 26:65.*

UpToDate®

Iperglicemia e rischio di morte fetale a termine di gravidanza

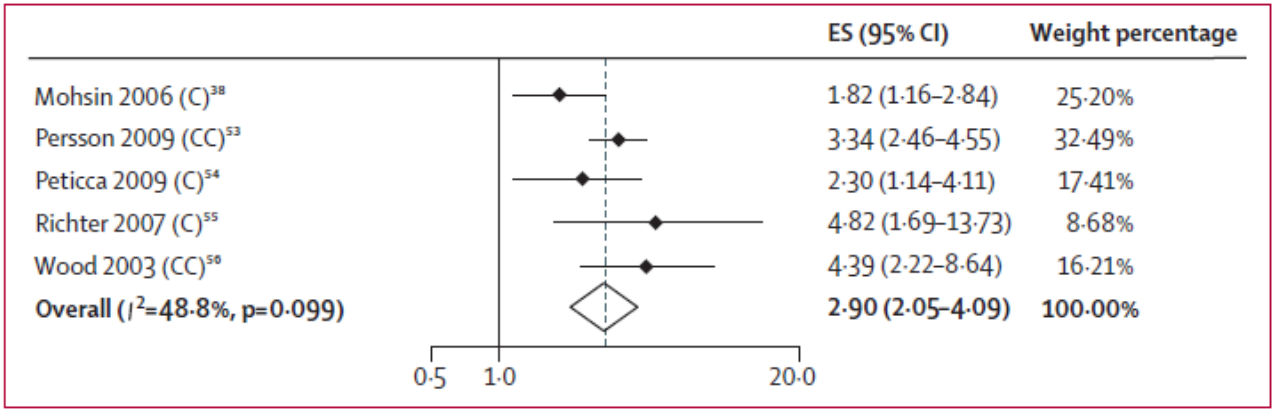


Estimated rate of stillbirth in diabetic women: 1920-2000



4 % of all stillbirths remain attributable to diabetes

Stillbirth rates are higher than in non diabetic pregnancies by **1.5 to 6-folds**





THE LANCET

14 Aprile, 2011 www.thelancet.com

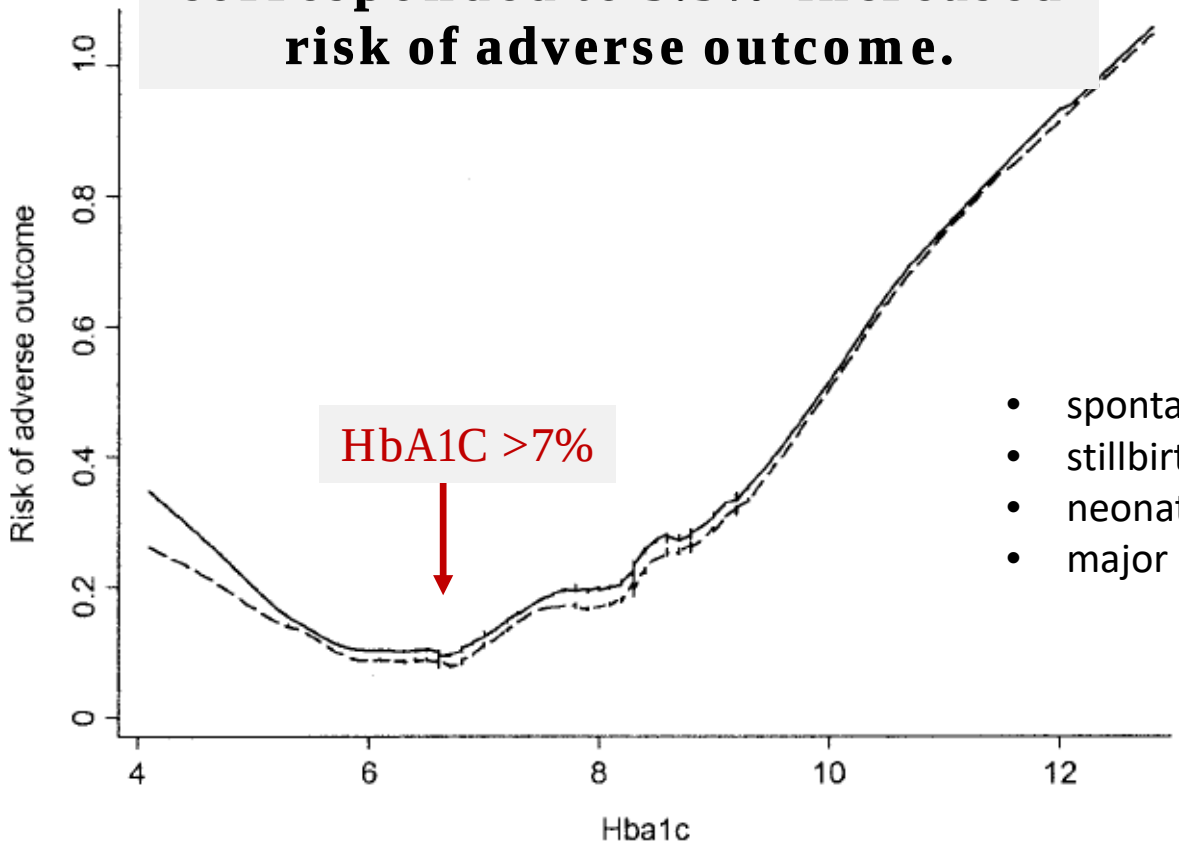
Figure 6: Meta-analysis of pre-existing diabetes and stillbirth risk
ES=effect size. C=cohort study. CC=case-control study.

Diabetic-Associated Stillbirth: Incidence, Pathophysiology, and Prevention
Donald J. Dudley,. Clin Perinatol 34 (2007)

HbA_{1c} in Early Diabetic Pregnancy and Pregnancy Outcomes

Diabetes Care 29:2612–2616, 2006

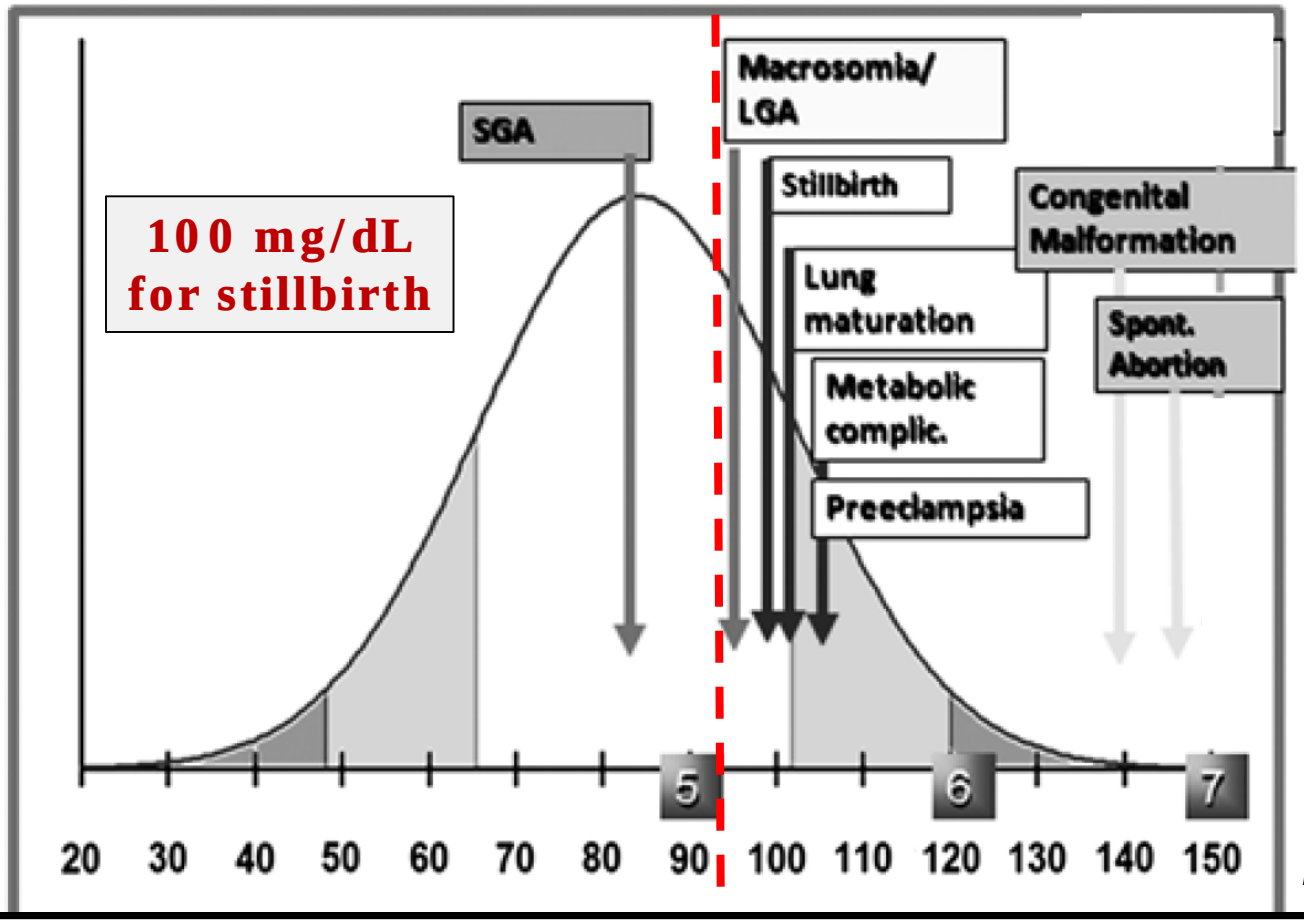
1% increase in A1C corresponded to 5.5% increased risk of adverse outcome.



Adverse outcome

- spontaneous and therapeutic abortion
- stillbirth
- neonatal death
- major congenital abnormalities

fetal and neonatal outcomes are directly correlated with the degree of maternal glycemic control



Langer O. 1995

The risk of stillbirth appears to increase in diabetic pregnancies starting at 34 weeks gestation, particularly in the presence of fetal macrosomia.

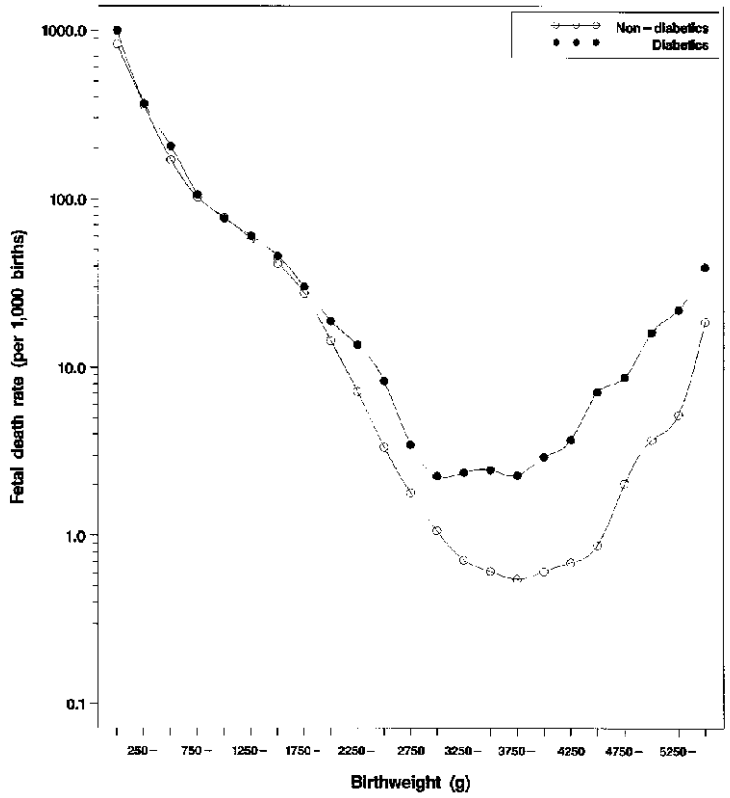
Birth weight and fetal death in the United States: The effect of maternal diabetes during pregnancy

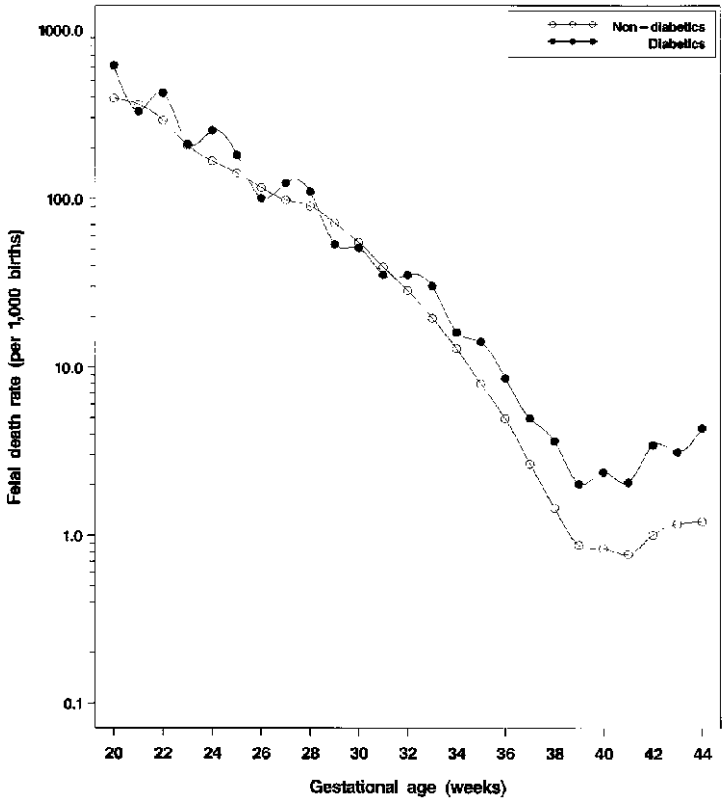
Myriam A. J. Mondestin, MD,[a] Cande V. Ananth, PhD, MPH,[b] John C. Smulian, MD, MPH,[a] and Anthony M. Vintzileos, MD[a]

New Brunswick, NJ

Diabetic patients n = 271,691

Am J Obstet Gynecol 2002





The overall fetal death rates in diabetic women were increased when birth weight was 4000 g (adjusted rela- tive risk of 2.0, 95% [CI]: 1.8–2.2)

Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment

Arianne N. Sweeting[1,2], Glynis P. Ross[1,2], Jon Hyett[3,4], Lynda Molyneaux[1,2], Maria Constantino[1], Anna Jane Harding[1] and Jencia Wong[1,2]

American Diabetes Association. Diabetes Care 2016

4,873 diabetic women

pre-existing diabetes (n = 65)
GDM <12 weeks (n = 68)
GDM 12–23 weeks of gestation (n = 1,247)
GDM ≥24 weeks of gestation (n = 3,493)

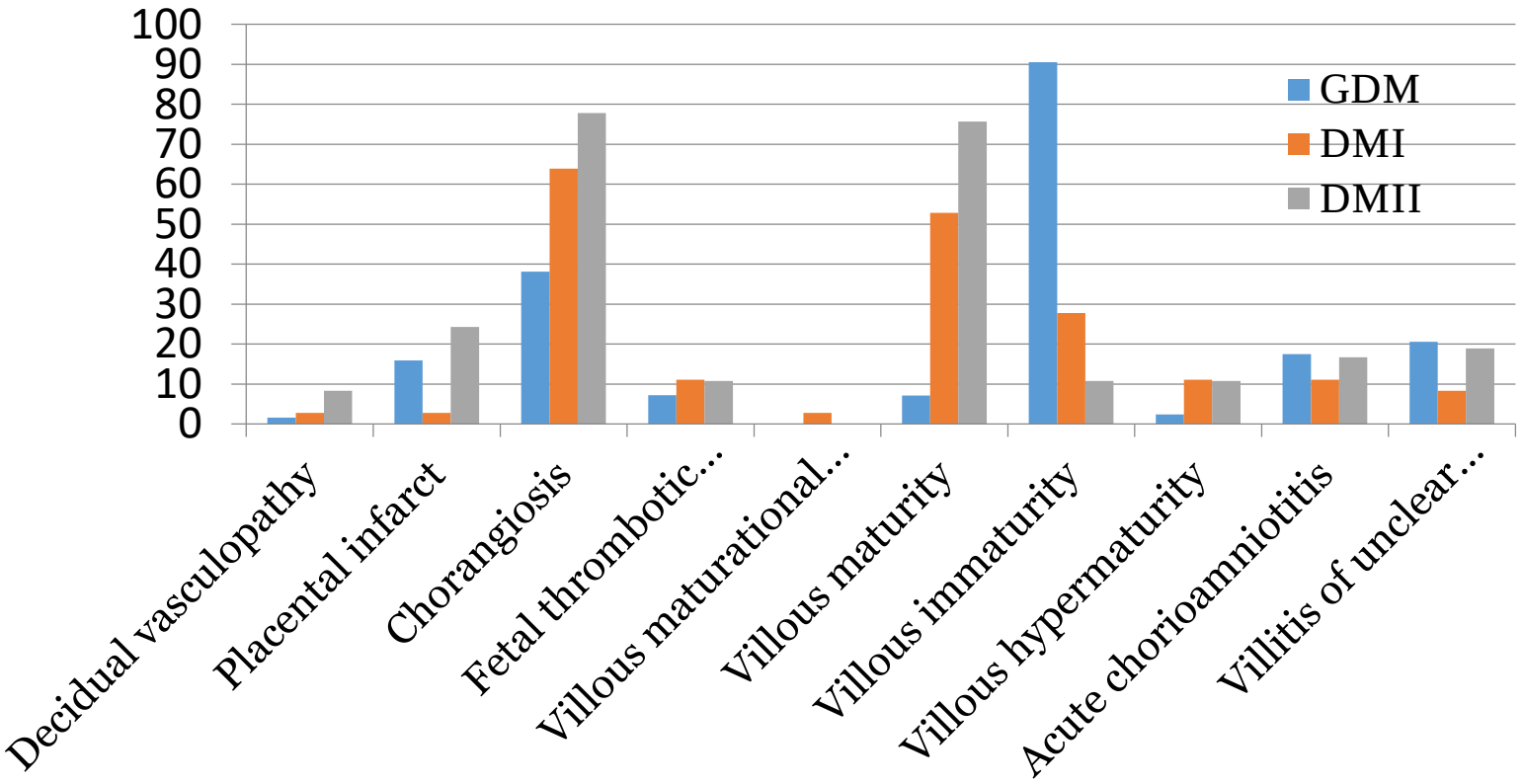
Neonatal outcomes for type 2 diabetes and GDM stratified by timing of diagnosis

Neonatal complications	T2DM (*n* = 65)	GDM			*P* value
		<12 weeks (*n* = 68)	12–23 weeks (*n* = 1,247)	≥24 weeks (*n* = 3,493)	
Macrosomia	21.8*	20.3*	9.0	10.0	<0.0001
LGA	39.6*	32.8	21.5	22.8	0.008
Stillbirth	1.8	3.4	0.8	0.3	0.2
Jaundice	41.7*	28.1*	24.8	19.8	<0.0001
Neonatal intensive care admission	38.5	39.7	38.3*	34.0	0.04
Respiratory distress syndrome	12.3*	7.4*	3.8	4.0	0.005
Hypoglycemia	14.9	20.7	20.2*	17.2	0.1
SGA	0.0	5.2	8.5	7.3	0.2

outcomes in **GDM <12 weeks** are **the worst** of the GDM cohort and approximate those of women with pre-existing diabete

- higher prepregnancy BMI
- greater insulin requirements
- higher rates of hypertensive disorders of pregnancy
- more insulin-resistant phenotype compared with later GDM
- dysglycemia was more difficult to manage.

Differences in placental pathology according to diabetes types



GDM is associated with a greater rate of villous immaturity

Type 1, Type 2 and Gestational Diabetes Mellitus Differentially Impact Placental Pathologic Characteristics of Uteroplacental Malperfusion. Jennifer Huynh et al. Placenta 2016

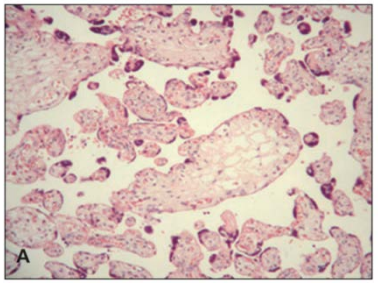
Pediatr Dev Pathol. 2011 Jul-Aug;14(4):273-9. doi: 10.2350/10-07-0872-OA.1. Epub 2011 Feb 17.

Clinical associations with a placental diagnosis of delayed villous maturation: retrospective study.

Higgins M[1], McAuliffe FM, Mooney EE.

Delayed villous maturation (**DVM**)is associated with an increased **risk of stillbirth** in the **late** third trimester

- decreased tertiary villus formation
- reduced vasculosyncytial membrane formation
- increased large bullous villi



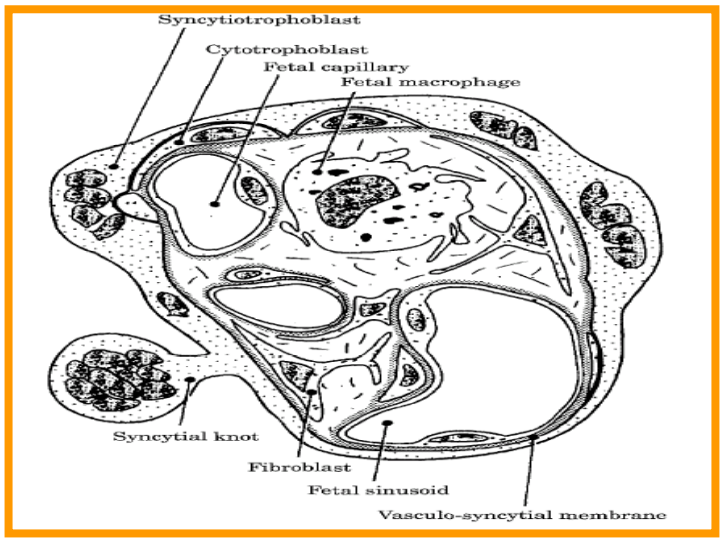
A retrospective study on 175 placentas with DVM vs 175 controls

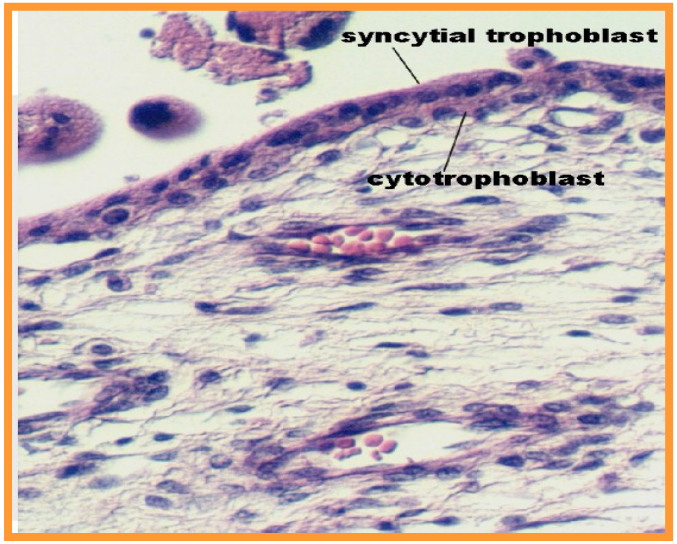
Pregestational diabetes (8% vs 2.8%, $P < 0.05$; relative risk 2.8
Gestational diabetes (8.6% vs 3.4%, $P < 0.05$; relative risk 2.5
Prenatal or intrapartum intrauterine death (8.6% vs 0%, $P < 0.05$)

Pathophysiology of fetal compromise in diabetic pregnancy

- The growth factor-like effect of insulin produces placental overgrowth as well as organomegaly and thus results in changes in vascular tone and haemodynamic

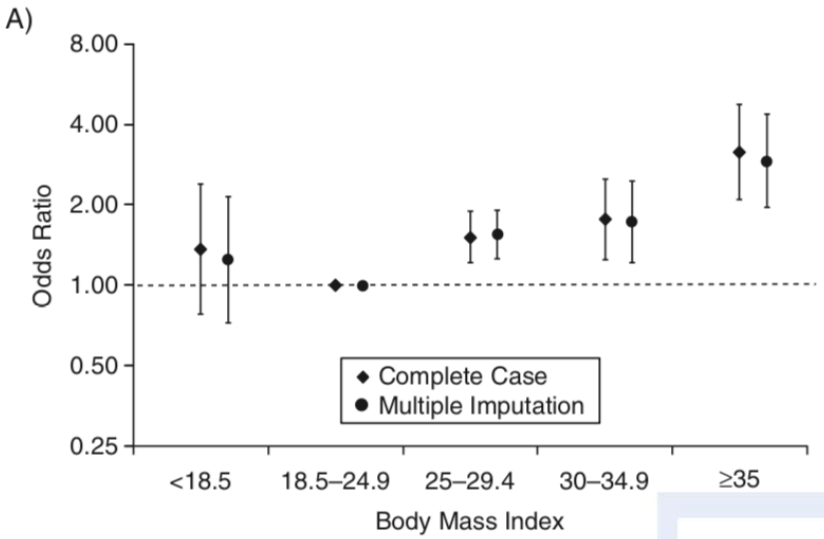
- Thickening of the basement membrane of the chorionic villi in diabetic pregnancies





Bjork 1984
Nylund 1982
Siddiqui 2003

OBESITA' E MORTE FETALE



Tennant P.W.G. Am J Obstet Gynecol 2007

STILLBIRTH RISK

BMI 25-29.9 **OR 1.51** (95% CI 1.21-1.89)
BMI 30-34.9 **OR 1.77** (95% CI 1.24-2.5)
BMI > 35 **OR 3.16** (95% CI 2.10-4.76)

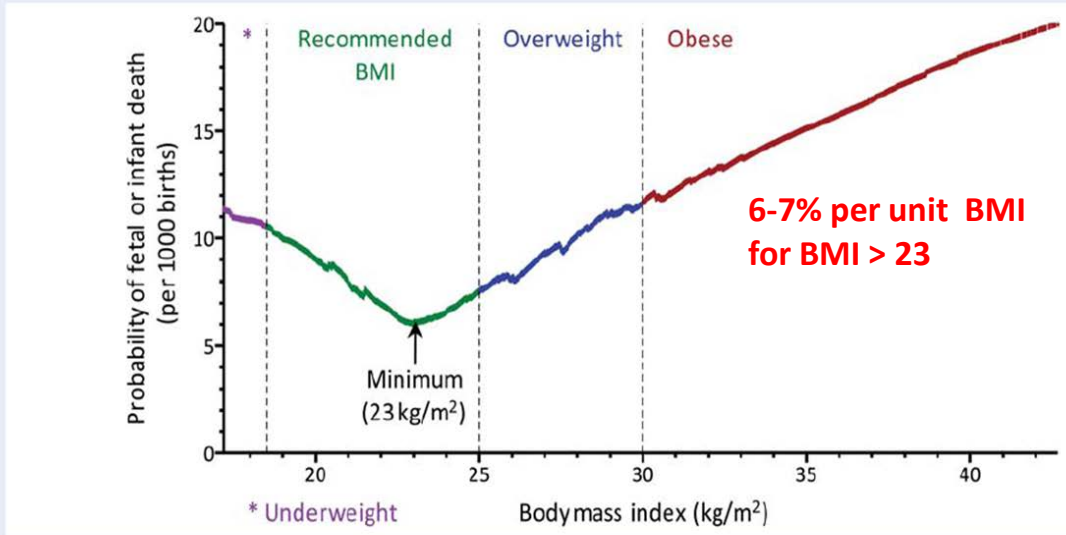


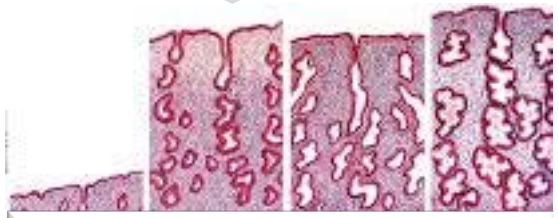
Figure 1 The association between maternal body mass index and the risk of a fetal or infant death, as estimated by locally weighted scatter plot regression.

A Lindam et al. High maternal body mass index in early pregnancy and risks of stillbirth and infant mortality . A population-based Sibling study in Sweden. American Journal of Epidemiology 2016

THE EFFECTS OF OBESITY/METABOLIC SYNDROME

HYPERINSULINISM

HYPERANDROGENISM



Endometrial dysfunction

Impaired decidualization

Impaired trophoblast invasion

↑ Collagenase

Cervical ripening

PRETERM BIRTH



INSULIN RESISTANCE

DYSLIPIDEMIA

LOW GRADE CHRONIC INFLAMMATION

↓ Adiponectina

↑ Insulin, Leptin TNFα ,IL-6

↑ FFA

PLACENTAL ALTERATION IN GENE EXPRESSION

OXIDATIVE STRESS

INFLAMMATION

Leptin
CRH
Urocortin 3
IL-6

IMPAIRED PLACENTATION

PHI/PREECLAMPSIA/STILLBIRTH

Cakmak and Taylor, Hum Reprod Update, 2011

Makieva S, Hum Reprod Update, 2014

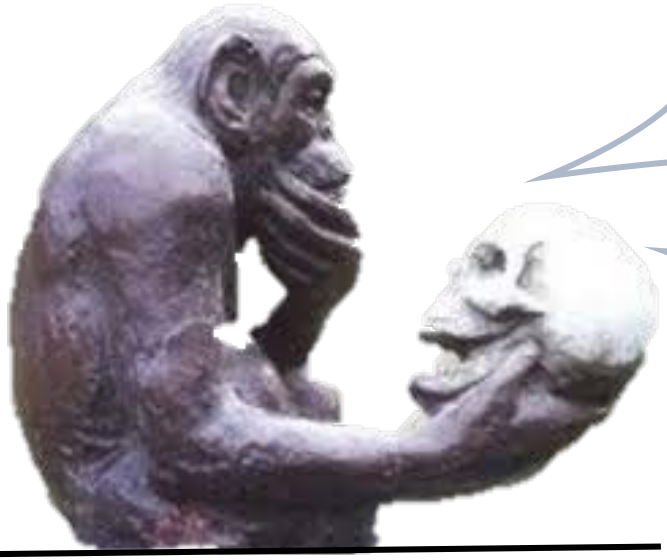
Piltonen TT, Hum Reprod , 2015

Hotamisligil GS, Nature, 2006

Denison FC, Reproduction,2010

Crujeiras and Casanueva, Hum Reprod Update, 2015

TIMING E MODALITA' DEL PARTO



Induzione o attesa??

Quando fare un TC elettivo?

> 4000 gr
> 4500 gr
> 5000 gr

?

INDUZIONE DEL TRAVAGLIO

PREVENZIONE STILLBIRTH

PREVENZIONE COMPLICANZE INTRAPARTUM DEL FETO MACROSOMA



AUMENTO INCIDENZA TC

COMPLICANZE TRAVAGLIO INDOTTO

MORBIDITÀ NEONATALE



ESISTONO RCT SUL TIMING E MODALITÀ DEL PARTO NELLE GRAVIDANZE COMPLICATE DA DIABETE?



RCT: INDUZIONE VS ATTESA in GDM

Insulin-requiring diabetes in pregnancy: A randomized trial of active induction of labor and expectant management

Siri L. Kjos, MD, Olivia A. Henry, MPH, MB, BCh, Martin Montoro, MD, Thomas A. Buchanan, MD, and Jorge H. Mestman, MD
Los Angeles, California

September 1993
Am J Obstet Gynecol

200 donne, diabete insulino trattato (13 diabete preesistente)
Induzione a 38 vs attesa fino a 42
No differenza in TC, > % di LGA e peso medio nel gruppo di attesa

Immediate delivery or expectant management in gestational diabetes at term: the GINEXMAL randomised controlled trial

S Alberico,[a] A Erenbourg,[a] M Hod,[b] Y Yogev,[b] E Hadar,[b] F Neri,[c] L Ronfani,[d] G Maso,[b] the GINEXMAL Group

BJOG 2017

425 donne con DMG, escluse se PFS > 4000
Induzione tra 38+0 e 39+0 vs attesa fino a 41
No differenza in TC e outcome perinatale

RACCOMANDAZIONI DELLE LINEE GUIDA INTERNAZIONALI



German Diabetes Associaton: Clinical Practice Guidelines 2014

Gestational Diabetes Mellitus (GDM) Diagnosis, Therapy and Follow-Up Care

1. **Diet controlled** GDM's may deliver **post-dates** if the fetal parameters are normal

2. Patients **well controlled on insulin** should probably be delivered by the **due date**

3. **Poorly controlled** GDM's using insulin require **individual judgment**

Estimated weight at birth **≥4500 g** ,there is a significant increase in the risk of shoulder dystocia, so a **primary section** must be considered.
When estimated weight at birth is **4000–4999g**, an **informed consent** about increased **shoulder dystocia risk**

NICE

National Institute for Health and Care Excellence

Published: 25 February 2015

nice.org.uk/guidance/ng3

1.4.4 Advise women with gestational diabetes to give birth no later than 40^{+6} weeks, and offer elective birth (by induction of labour, or by caesarean section if indicated) to women who have not given birth by this time. **[new 2015]**

1.4.5 Consider elective birth before 40^{+6} weeks for women with gestational diabetes if there are maternal or fetal complications. **[new 2015]**

1.4.6 Diabetes should not in itself be considered a contraindication to attempting vaginal birth after a previous caesarean section. **[2008]**

Induction of labour at term can reduce the incidence of shoulder dystocia in women with gestational diabetes. **B**

Royal College of Obstetricians & Gynaecologists

Shoulder Dystocia March 2012

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 190, FEBRUARY 2018 *(Replaces Practice Bulletin Number 180, July 2017)*

Gestational Diabetes Mellitus

- ***What are delivery considerations in pregnancies complicated by gestational diabetes mellitus?***

1. the timing of delivery in women with GDM that is controlled with only **diet and exercise (A1GDM)** should **not** be **before 39 weeks** of gestation, unless otherwise indicated. **Expectant management up to 40 6/7 weeks** of gestation in the setting of indicated antepartum testing is generally appropriate

2. For women with GDM that is well **controlled by medications (A2GDM**), delivery is recommended **from 39 0/7 weeks to 39 6/7 weeks** of gestation.

3. Earlier delivery for women with **poorly controlled GDM** : delivery **between 37 0/7 weeks and 38 6/7 weeks** of gestation may be justified, but delivery in the late preterm period from 34 0/7 weeks to 36 6/7 weeks of gestation should be reserved for those women who fail in-hospital attempts to improve glycemic control or who have abnormal antepartum fetal testing

- **cesarean** delivery when the estimated fetal weight is **≥ 4,500 g**

MATERNAL DIABETES + ESTIMATED FETAL WEIGHT

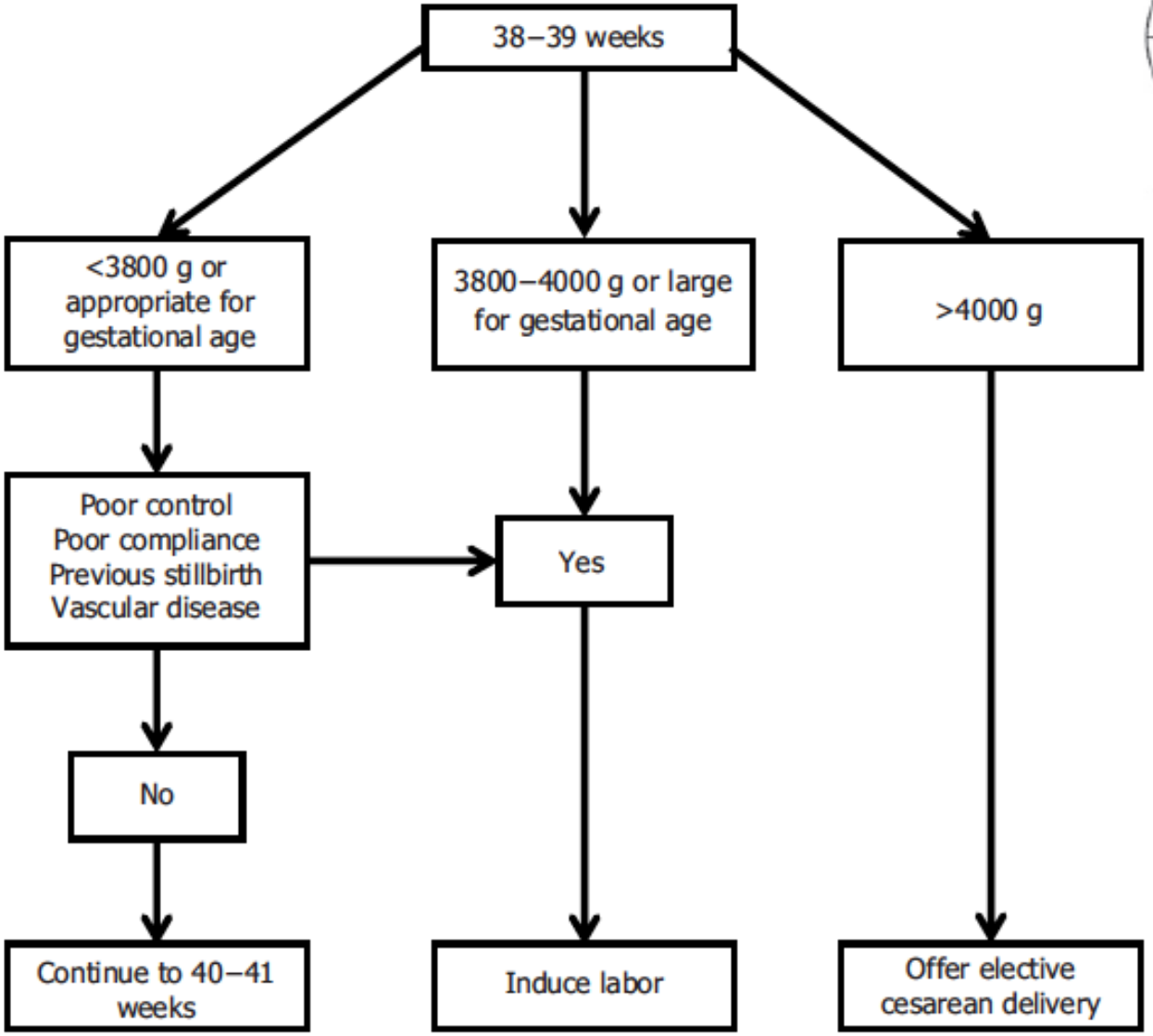


Figure 4 Timing of delivery in women with gestational diabetes mellitus and diabetes in pregnancy.

International Journal of Gynecology and Obstetrics 131 S3 (2015) S173–S211

www.figo.org

MODALITÀ E TIMING DEL PARTO nel GDM

GDM in terapia nutrizionale
con profili glicemici ottimali
+
Feto AGA

MANAGEMENT DI ATTESA
FINO ALLA 41 SETTIMANA

Condotta di attesa: ↑ probabilità di travaglio spontaneo → minor rischio di parto cesareo per fallita induzione

GMD in terapia insulinica
Ben controllato
+
Condizioni fetali rassicuranti

MANAGEMENT DI ATTESA
NON OLTRE LA 40 SETTIMANA
IN ASSENZA DI COMORBIDITÀ

MODALITÀ E TIMING DEL PARTO nel GDM

IN BASE AL PESO FETALE STIMATO

EFW < 4000g / LGA
Controllo metabolico non ottimale

Parto vaginale indotto a 38-39 sett.

4000g < EFW > 4500g

Parto vaginale o TC
Considerare:
-caratteristiche materne (statura, BMI pregravidico, pelvi,, bishop..)
-anamnesi ostetrica (pregressi parti macrosomici o con distocia)

EFW ≥ 4500g

Programmare TC elettivo

Pregestational Diabetes Mellitus

ACOG PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS
NUMBER 60, MARCH 2005

▶ ***When and how should delivery occur?***

- Patients with **well-controlled** diabetes may be allowed to progress to **their expected date of delivery** as long as antenatal testing remains reassuring .
- Expectant management **beyond the estimated due date** generally **is not recommended.**

- Early delivery may be indicated in some patients with vasculopathy, nephropathy, poor glucose control, or a prior stillbirth

- **Cesarean delivery** may be considered if the estimated fetal weight is greater than **4,500 g**

ANTENATAL CORTICOSTEROIDS FOR IMPROVING PRETERM BIRTH OUTCOMES WITH MATERNAL DIABETES MELLITUS



If corticosteroids are administered to accelerate lung maturation, an increased insulin requirement over the next 5 days should be anticipated *(ACOG)*

Betamethasone should be prescribed for inducing fetal lung maturity (beforeWeek34) only if strictly indicated because this will also cause the blood glucose levels to rise *(GERMAN DIABETES ASSOCIATION)*

- ✓ The presence of maternal diabetes in pregnancy is not a reason to withhold antenatal corticosteroids where there is an imminent **RISK OF PRETERM BIRTH**
- ✓ A **HYPERGLYCAEMIC EFFECT** of corticosteroids in pregnant women: close monitoring and treatment for glycaemic control essential at all stage

Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women atRisk of Imminent PretermBirth: A Systematic Review and Meta-Analysis. RachelM.Amiya et al. Plos One 2016

GDM and the Use of Betamethaso ■ JOGC ■ 2016

Society of Obstetricians and Gynaecologists of Canada



The administration of **betamethasone** to pregnant women with **GDM** should be restricted to the routine obstetric indications related to the risk of preterm and late preterm delivery between **24 to 36 weeks'** gestation



- administration of betamethasone in the late preterm period should be limited to women with ***GDM only***
- ***ketoacidosis*** in the pregnant diabetic individual is a potential cause of fetal demise
- it is recommended to closely ***monitor maternal glycaemia*** after betamethasone administration in women with poorly controlled diabetes, particularly during the **first 12 hours**

ASSISTENZA IN TRAVAGLIO

GDM

Maternal plasma glucose mg/dL (mmol/L)	Glucose management using subcutaneous rapid-acting insulin (units) *
≤120 (6.6)	0
121 to 140 (6.7 to 7.7)	1.0
141 to 160 (7.8 to 8.8)	2.0
161 to 180 (8.9 to 9.9)	3.0
181 to 200* (10.0 to 11.1)	4.0
≥200 (11.1)	4.0 units subcutaneously plus a short acting or regular insulin by intravenous push starting at 2 units

- **MONITORAGGIO FETALE CONTINUO**
- **Monitoraggio glicemie plasmatiche materne nelle pz in terapia insulinica ogni ora**

MANTENERE GLICEMIA >70 E < 126

(Endocrine Society Clinical Practice Guidelines 2013 ACOG 2005)

UpToDate

Modified from: Kitzmiller JL, Gavin L. Preexisting diabetes and pregnancy. In: Manual of Endocrinology and Metabolism, 3rd ed, Lavin N (Ed), Lippincott Williams & Wilkins, 2002.

ASSISTENZA IN TRAVAGLIO

DIABETE PREGESTAZIONALE

Insulin Management During Labor and Delivery

- Usual dose of intermediate-acting insulin is given at bedtime.
- Morning dose of insulin is withheld.
- Intravenous infusion of normal saline is begun.
- Once active labor begins or glucose levels decrease to less than 70 mg/dL, the infusion is changed from saline to 5% dextrose and delivered at a rate of 100–150 cc/h (2.5 mg/kg/min) to achieve a glucose level of approximately 100 mg/dL.
- Glucose levels are checked hourly using a bedside meter allowing for adjustment in the insulin or glucose infusion rate.
- Regular (short-acting) insulin is administered by intravenous infusion at a rate of 1.25 U/h if glucose levels exceed 100 mg/dL.

- Intravenous infusion of regular insulin titrated and glucose

- Maintain hourly readings of **BLOOD GLUCOSE LEVELS LESS THAN 110 MG/DL**

(ACOG 2005)



Venere di Willendorf

Thank you for your attention

Pathophysiology of fetal compromise in diabetic pregnancy

Islet cell hyperplasia common in stillborn IDMs

There is a significant association between fetal plasma insulin concentration and the degree of fetal acidemia

Hyperglycemia (chronic), when accompanied by minimal hypoxemia may result in lactic acidosis

Salvesen 1993
Hay 1989
Chukwuma 2001