Early recognition of gestational diabetes – how should the routines be?

(Introduction of new guidelines and practice)

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Outline

- 1) Hyperglycemia in pregnancy
  - Classification
  - Its importance and influences on pregnancy outcome

- 2) Diagnosis of hyperglycemia during pregnancy
  - International Association of Diabetes and Pregnancy Study Group (IADPSG) recommendations (Diabetes Care 2010; 33: 676–82.)
    - HAPO study

Diabetes in pregnancy - classification

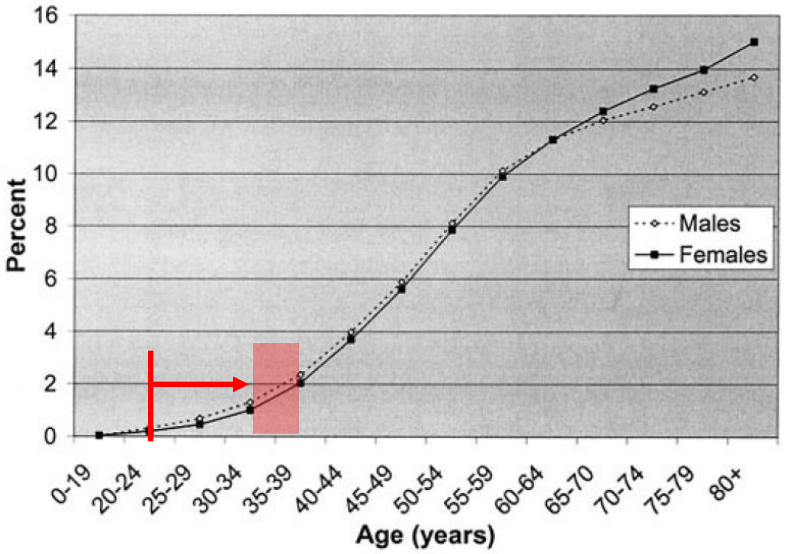
- Pregestational DM (pre-existing)
  - Type 1 (3,5/1000 pregnancies; *Bell et al. BJOG 2008;115:445-52.*)
    - Recognised and treated before pregnancy
  - Type 2 (1,2/1000 pregnancies; *Bell et al. BJOG 2008;115:445-52.*)
    - Recognized and treated before pregnancy
    - Present, but **unrecognized** and consequently not treated, before pregnancy ⇒ great health hazard
  - Other specific types (genetic forms, secondary to other diseases)
    - Recognised and treated before pregnancy
- Gestational DM (~18% of all pregnancies according to HAPO!!!)
  - IADPSG definition: Hyperglycemia that is first recognised during the pregnancy, but not fulfil criteria for „overt" diabetes (hyperglycemia that is lower than diagnostic for type 2 DM).

Why is so important to improve the recognition of type 2 before or at least early in pregnancy

The prevalence of T2DM is increasing with age and is „epidemic" due to increasing prevalence of obesity and „modern way of life".

Women decide for pregnancy at older age.

⇒ The prevalence of pre-pregnancy **unrecognised** T2DM is increasing



Wild S et al. Diabetes Care. 2004 May;27(5):1047-53.

UK data: The Northern Diabetic Pregnancy Survey

1996–1998 → **0.2** per 1000 total births
1999–2001 → **0.4** per 1000 total births
2002–2004 → **1.2** per 1000 total births

⇒ 6x increase *P < 0.0001)*

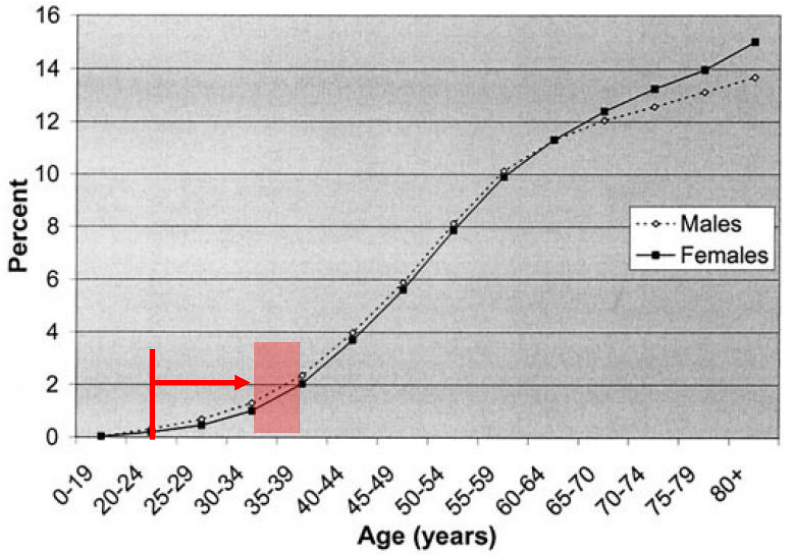
Bell et al. BJOG 2008;115:445-52.

Why is so important to improve the recognition of type 2 before or at least early in pregnancy

Women decide for pregnancy at older age.

⇒ The prevalence of pre-pregnancy unrecognised T2DM is increasing

⇒ Unrecognised T2DM carries the **risk of malformation** and spontaneus **abortion,** as well as **risk of development/progression of diabetes chr. complications**



NHANES data from 2005–2008:

US women age 18–44 have:

Known diabetes 2.8%

Undiagnosed diabetes 1.7%

} 4,5%

Prediabetes (IFG, IGT) 26.4%

⇒for a total of **30.9%**

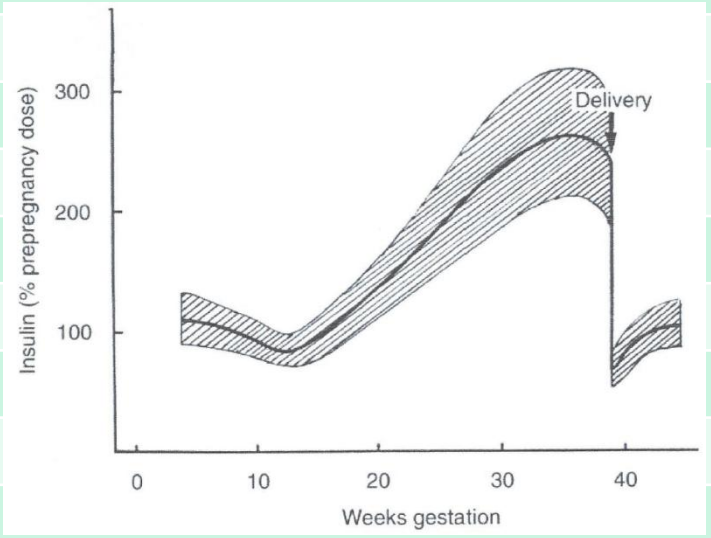
with disorders of glucose metabolism

Wild S et al. Diabetes Care. 2004 May;27(5):1047-53.

Metzger BE et al. J Matern Fetal Neonatal Med 2012;25:2564-9.

Pregnancy is a physiologic pro-diabetogenic event

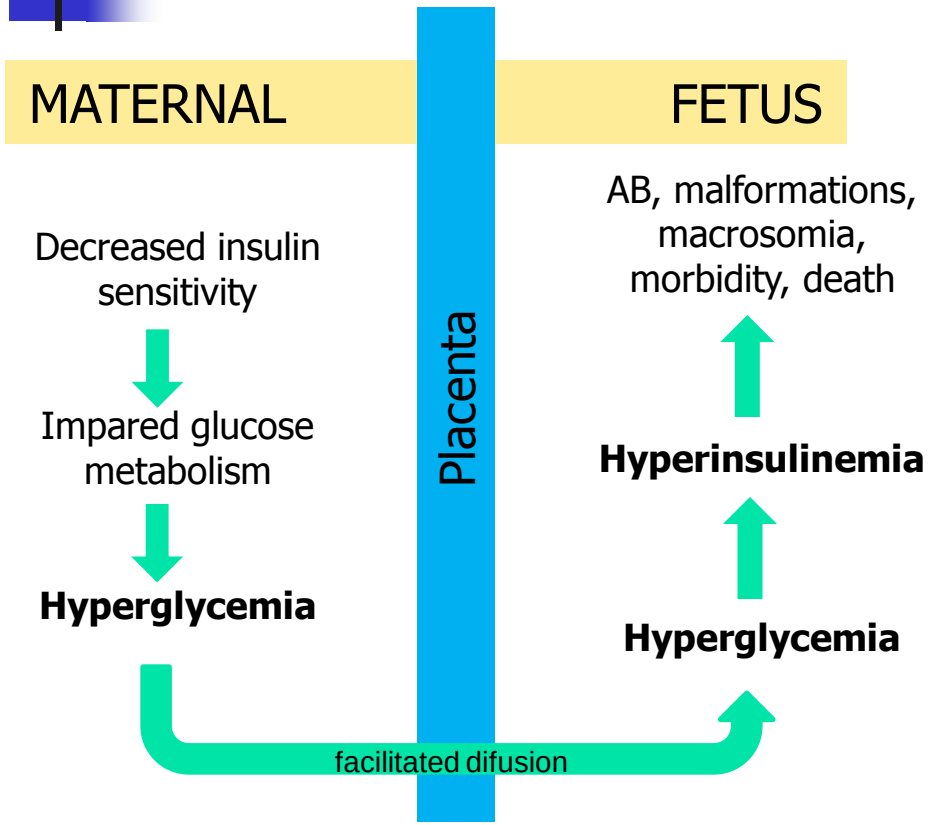
Factors of placental origin that influence maternal insulin sensitivity
Estrogens and progesterone
Human chorionic somatomammotropin (hCS) or placental lactogen (HPL)
Prolactin
Placental growth hormone variant (hGH-V)
Corticotropin-releasing factor (CRF) and corticotropin
Leptin
Tumor necrosis factor α (TNF-α)
Adiponectin
Resistin
Ghrelin
Interleukin 6 (IL-6)



Hyperglycemia in pregnancy is toxic, and may be associated with **fetal** and **maternal** complications as well as with **long-term consequences**.

Metzger BE et al. Diabetes Mellitus and Pregnancy. In: Endocrinology. De Groot LJ. 6th edition.

Hyperglycemia and the **fetus** Pedersenova hypotesis (1952)



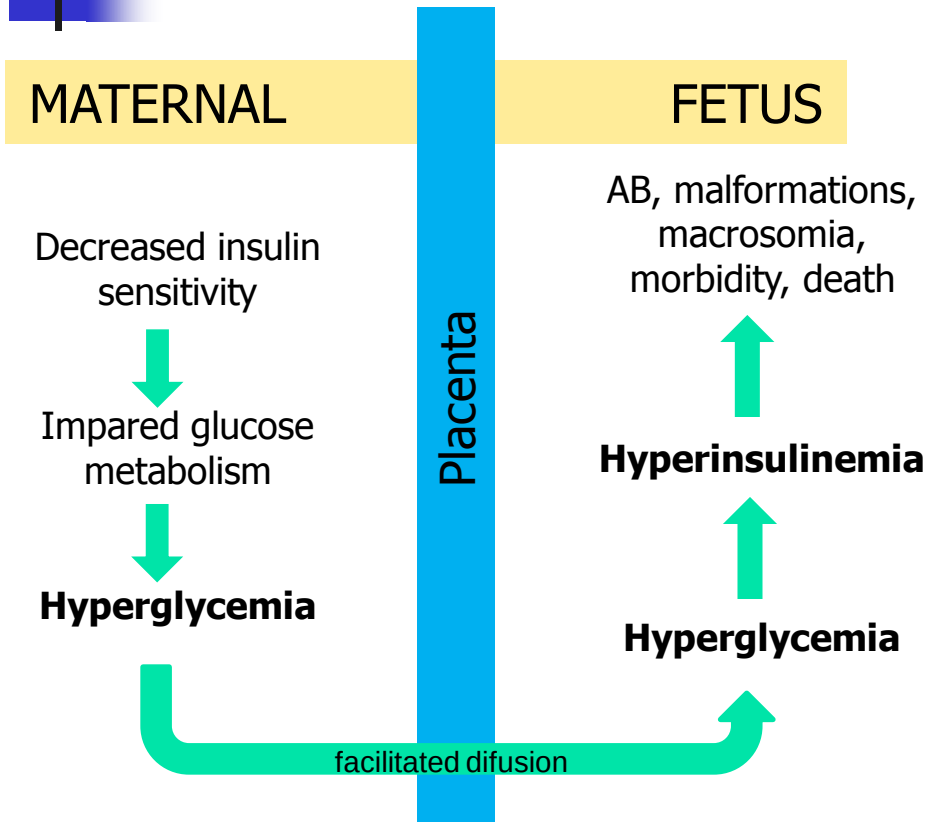
Diabetic embriopathy

Maternal hyperglycemia in early pregnancy

⇒ Malformations

⇒ Spontneous abortion

Hyperglycemia and the **fetus**
Pedersenova hypotesis (1952)



Diabetic embriopathy

Maternal hyperglycemia

⇒ Malformations

⇒ Spontneous abortion

Diabetic fetopathy

Maternal hyperglycemia

⇒ Macrosomia

⇒ Morfological and functional changes in fetus

Morbidity and mortality

ACHOIS – macrosomia is of the greatest concern in **GDM**

Table 4. Secondary Outcomes among the Infants.*

Outcome	Intervention Group (N=506)	Routine-Care Group (N=524)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
Birth weight — g	3335±551	3482±660	−145 (−219 to −70)	<0.001
Large for gestational age — no. (%)‡	68 (13)	115 (22)	0.62 (0.47 to 0.81)	<0.001
Macrosomia (≥4 kg) — no. (%)	49 (10)	110 (21)	0.47 (0.34 to 0.64)	<0.001

In untreated GDM is **macrosomia** 2-3x more prevalent.

Macrosomia per se is risk factor for shoulder dystocia and birth injuries such as bone fractures and nerve palsies.

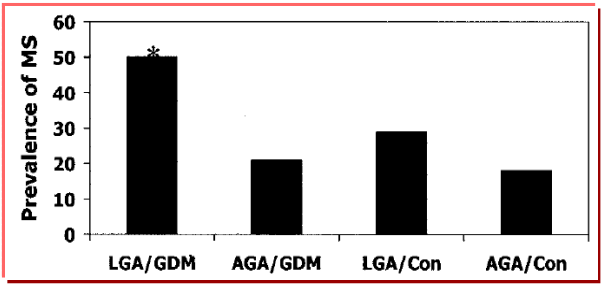
Crowther CA. NEJM 2005. 352;2477-86.

Long-term consequences related to epigenetic modifications of gene expresion

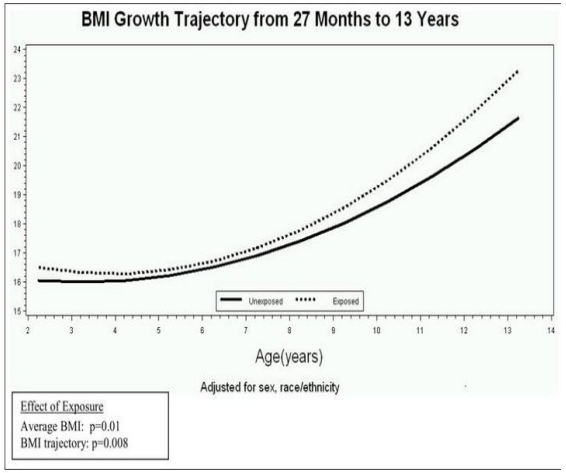
Maternal hyperglycemia

Epigenetic modifications

⇒ MetS
⇒ Obesity
⇒ T2DM



Boney CM et al. Pediatrics. 2005 Mar;115(3):e290-6.



Crume TL et al. J Pediatr. 2011 Jun;158(6):941-6.

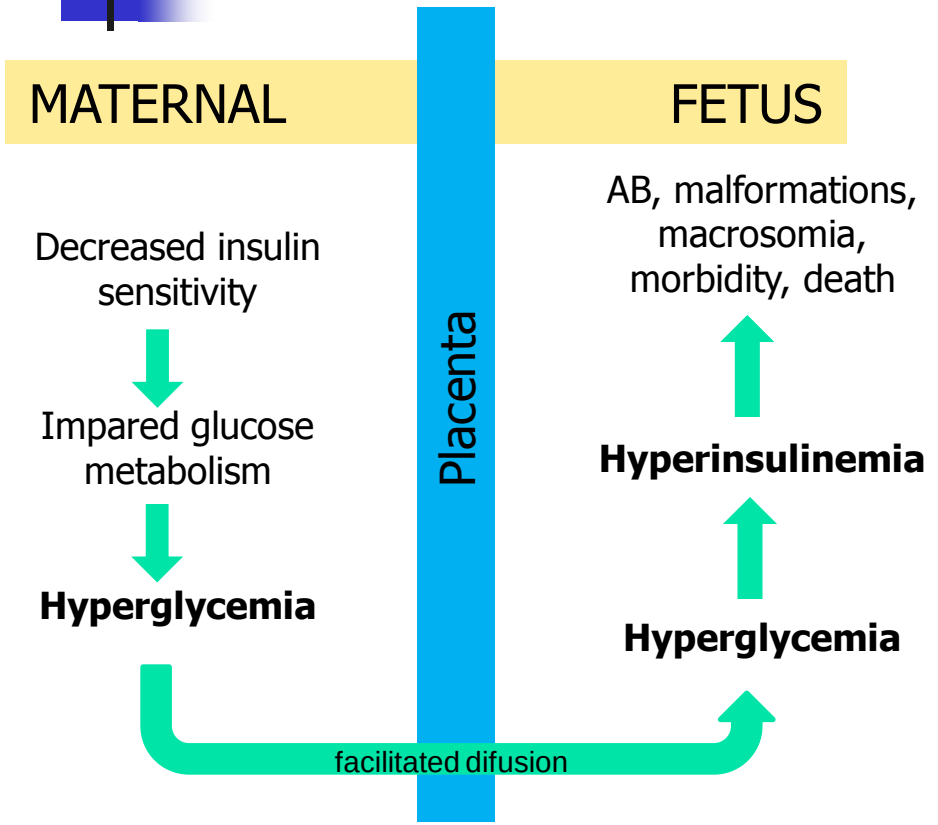
The risk of diabetes was significantly higher **in siblings** born **after the mother developed diabetes** than in those born before the mother's diagnosis of diabetes **(odds ratio 3.7, *P* = 0.02)**

TABLE 3
Number of siblings with diabetes and total number of siblings born before and after mother's diabetes diagnosis, in each family

Family	Number born before/total	Number born after/total
1	0/1	1/1
2	0/1	1/1
3	1/1	0/1
4	0/1	1/1
5	0/1	1/1
6	0/1	1/1
7	0/1	1/1
8	0/1	1/1
9	2/4	1/1
10	1/1	0/1
11	0/1	1/1
12	0/1	2/3
13	0/2	1/1
14	1/3	1/1
15	2/5	1/1
16	3/7	0/1
17	1/2	1/1
18	0/1	1/1
19	1/1	0/2

Dabelea D et al. Diabetes. 2000 Dec;49(12):2208-11.

Hyperglycemia and the **mother**
Pedersen hypotesis (1952)



Maternal consequences

- ⇒ gestational hypertension
- ⇒ preeclampsia, eclampsia
- ⇒ polyhydramnion
- ⇒ premature delivery
- ⇒ Caesarean section
- ⇒ worsening of diabetic chronic complications (DR, DN, IHD)
- ⇒ urinary tract infections
- ⇒ treatment induced hypoglycemia
- ⇒ death of the mother

Outline

- 1) Hyperglycemia in pregnancy
  - Classification
  - Importance and its influences on pregnancy outcome

- 2) Diagnosis of hyperglycemia during pregnancy
  - IADPSG recommendations (Diabetes Care 2010; 33: 676–82.)
    - HAPO study

Various definitions of GDM have been proposed by different diabetes associations

Table 1. Most commonly used guidelines for the diagnosis of GDM

Organisation	Fasting Plasma glucose	Glucose Challenge	1-h plasma glucose	2-h plasma glucose	3-h plasma glucose
WHO 1999[3]*	≥ 7.0	75g OGTT	Not required	≥ 7.8	Not required
American Congress of Obstetricians and Gynecologists[21]**	≥5.3	100g OGTT	≥10.0	≥8.6	≥7.8
Canadian Diabetes Association[22]***	≥5.3	75g OGTT	≥10.6	≥8.9	Not required

Different „cut off" values!!! None were based on fetal or maternal outcomes!!!

*one value is sufficient for diagnosis

** two or more values are required for diagnosis

*** two or more values required for diagnosis

**** one value is sufficient for diagnosis

In 2010 the IADPSG (International Association of Diabetes and Pregnancy Study Group) recommendations have been launched, and are based on HAPO study.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2008 VOL. 358 NO. 19

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*

N Engl J Med 2008;358:1991-2002.

HAPO study objective

To clarify **associations** of levels of **maternal glucose** lower than those diagnostic of diabetes with **fetal and maternal perinatal outcomes.**

Vision:

Formation of **new diagnostic criteria for GDM**, that will:

- Be based on pregnancy outcomes
- Be used globally (be implemented world wide) for classifying glucose metabolism in pregnancy

HAPO

- Observational study
  - Accomplished by performing 75-g OGTT
- Blinded – medical care-givers, pregnant women were blinded to status of glucose tolerance exept when predefined criteria were met:
  - FPG > 5,8 mmol/L and/or 2-h glucose >11,1 mmol/L
- 15 field centers in 9 countries
- **25.505** subjects completed an OGTT in **7 years**:
  - **23.316** were **available for analyses**
  - - 746 (2,9%) unblinded, 1443 (5,7%) dropout

HAPO. NEJM 2008;358:1991-2002.

HAPO study endpoints

Find relationship between maternal glycemia and:

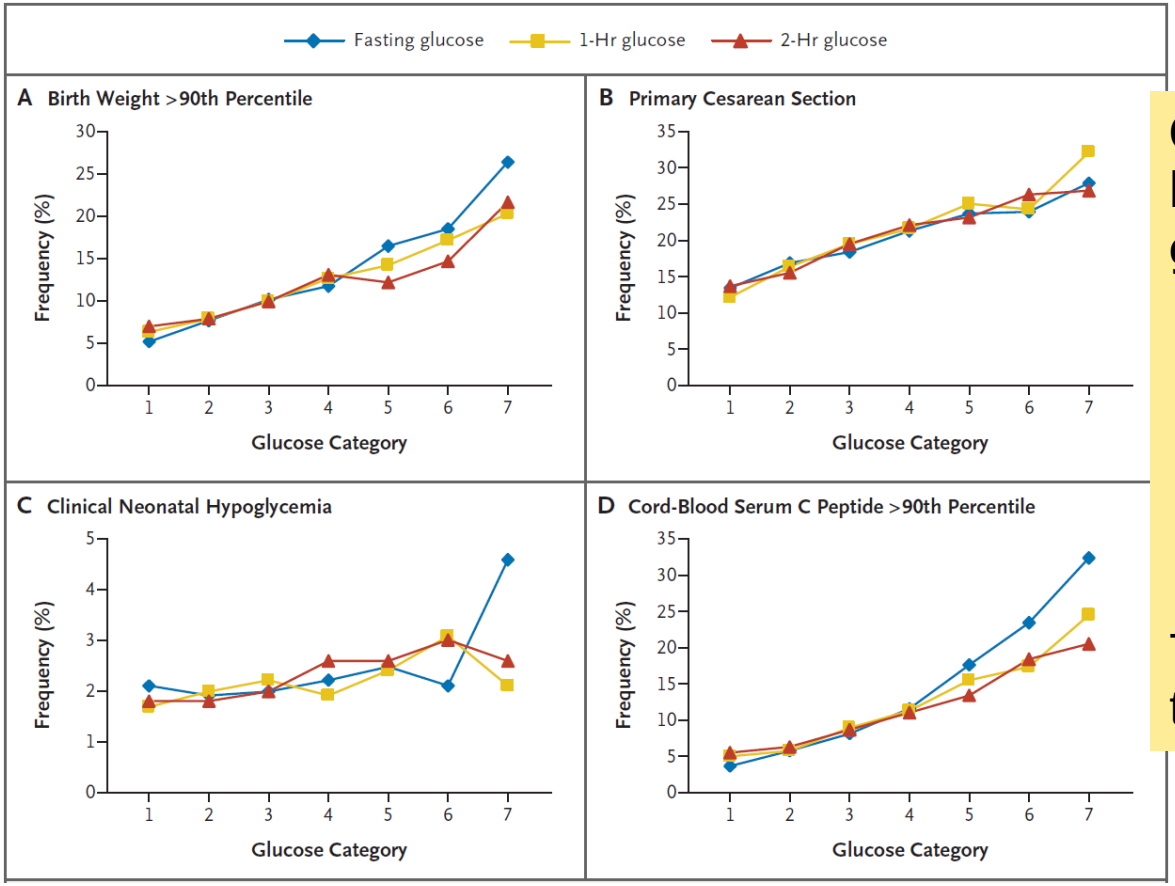
- *Primary outcomes:*
  - Macrosomia rate - LGA (BW >90. percentile for gestational age)
  - Cesarean section rate
  - Neonatal hypoglycemia rate
  - Fetal hyperinsulinemia (**C-peptid** >90. percentile)

- *Secondary outcomes:*
  - Premature delivery (before 37 weeks of gestation)
  - Shoulder dystocia
  - Birth injury
  - Need for intensive neonatal care
  - Hyperbilirubinemia
  - Preeclampsia

„**Cut off point**" or **Continum**?
If „cut off point" – at what glucose concentration?
If continuum – how to define diagnostic values?

HAPO. NEJM 2008;358:1991-2002.

HAPO study results for primary outcomes



Continuous relationship between FPG, 1-hr and 2-hr glucose on 75 g OGTT with

- Macrosomia
- Cesarean section
- Neonatal hypoglycemia
- Cord blood C-peptide (hyperinsulinemia)

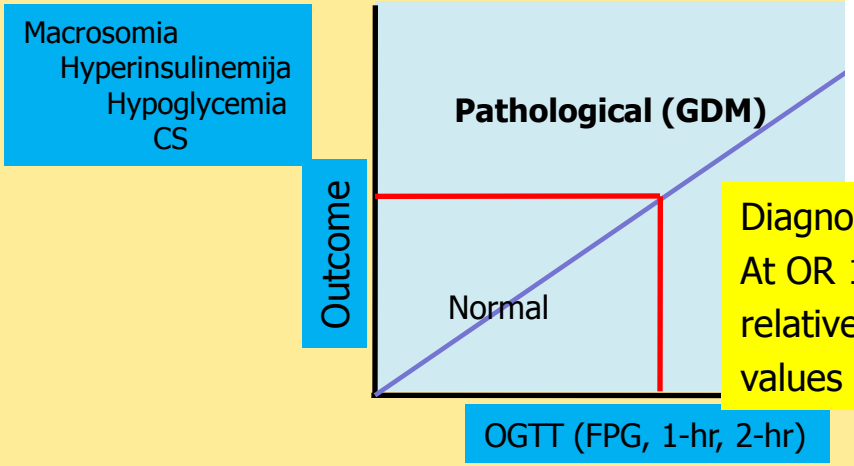
The relationship holds down to the lowest levels of glucose.

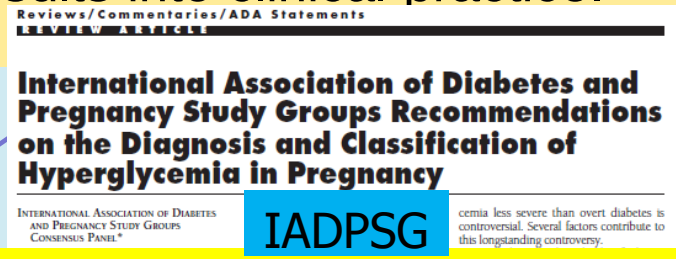
HAPO. NEJM 2008;358:1991-2002.

How to define abnormal?

Continuous relationship between glucose on 75-gr OGTT

⇒ Consensus was required to translate HAPO results into clinical practice.




Reviews/Commentaries/ADA Statements

International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy

International Association of Diabetes and Pregnancy Study Groups Consensus Panel*

cemia less severe than overt diabetes is controversial. Several factors contribute to this longstanding controversy.

IADPSG

Diagnostic glucose treshold for intervention:
At OR 1,5 or 1,75 or 2,0 ??? for the outcomes, relative to odds at cohort mean glucose values in HAPO (4,5; 7,4 and 6,2 mmol/L)

Diabetes Care 2010; 33: 676–82.

IADPSG consensus: The tresholds for intervention should be at OR 1,75 for adverse pregnancy outcomes.

75 gr OGTT	S-glucose (mmol/L)*	
FPG	**≥5,1**	(92 mg/dl)
1-hr	**≥10,0**	(180 mg/dl)
2-hr	**≥8,5**	(153 mg/dl)

*One or more of these values must be equaled or exceeded for the diagnosis of GDM.

Will treating GDM defined by IADPSG provide meaningful improvements in clinical outcomes?

75 gr OGTT	S-glucose (mmol/L)*
FPG	≥5,1
1-hr	≥10,0
2-hr	≥8,5

*One or more of these values must be equaled or exceeded for the diagnosis of GDM.

Two major randomised control trials addressing whether controlling glucose in GDM is of value.

1. ACHOIS (The Australian Carbohydrate Intolerance Study in Pregnant Women)

Crowther CA. NEJM 2005. 352;2477-86.

2. MFMU (The Maternal–Fetal Medicine Units network)

Landon MB.NEJM 2009;361:1339-48.

The **expected benefit** of a diagnosis and treatment of gestational diabetes **according to IADPSG criteria**

	All cases	Category 5[a]		
Condition	*n*	Identified (*n*)	Prevented (*n*)[c]	
LGA	2,221	491	221	-55%
Shoulder dystocia	212	108	69	-36%
Birth injury	139	70	50	-29%

Data are based on 23,316 participants in HAPO.
[a]Numbers equate with proposed criteria for gestational diabetes by IADPSG.
Derived from the mean expected benefit from the ACHOIS and MMFU trials.

Ryan EA. Diabetologia 2011;54:480-6.

Reviews/Commentaries/ADA Statements
REVIEW ARTICLE

International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy

INTERNATIONAL ASSOCIATION OF DIABETES AND PREGNANCY STUDY GROUPS CONSENSUS PANEL*

Metzger BE et al. Diabetes Care 2010; 33: 676–82.

Historically, the term "gestational diabetes" was used to define **all** women with **onset or first recognition** of abnormal glucose tolerance during pregnancy.

IADPSG consensus:
it is prudent to distinguish women with probable **pre-existing diabetes** that is first recognised during pregnancy – »overt diabetes« from those with transient hyperglycemia due to pregnancy related insulin resistence – »GDM«.

⇒ measure FPG, HbA1c or random glucose at the first prenatal visit

Why this recomendation??? …To prevent spontaneus abortions, malformations, and chr. complications in undiagnosed T2DM.

IADPSG – first phase of hyperglycemia diagnostics

Purpose: to identifie the prepregnancy unrecognised DM

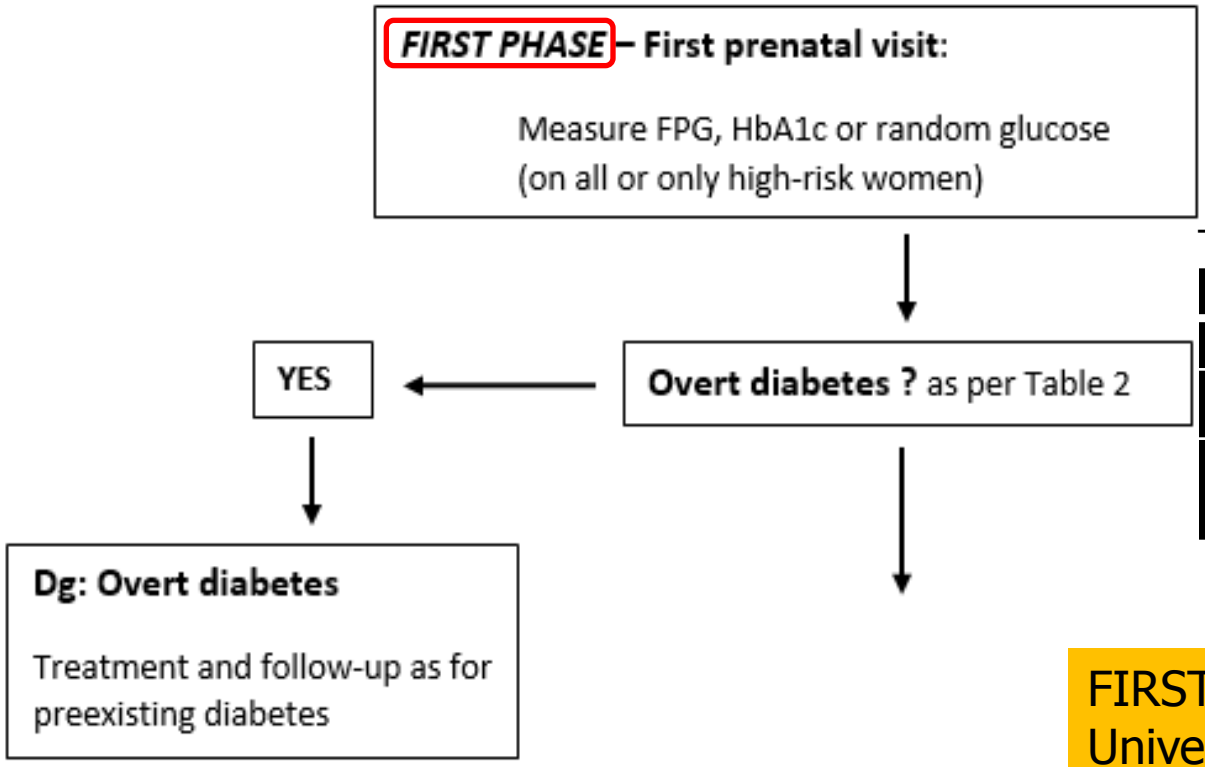


TABLE 2

Measure of glycemia	Consensus threshold
FPG	≥**7.0** mmol/l (126 mg/dl)
HbA1c	≥**6.5%** (DCCT/UKPDS standardized)
Random plasma glucose	≥**11.1** mmol/l (200 mg/dl) + confirmation

FIRST PHASE can be performed:
Universal (in all pregnant women)
In high-risk women

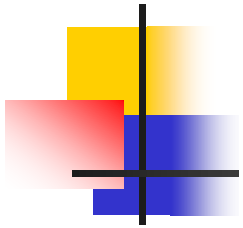
Metzger BE et al. Diabetes Care 2010; 33: 676–82.

Risk factors for diabetes mellitus

Testing should be considered in all women who are overweight (BMI ≥25 kg/m2) and have additional risk factors:

- **physical inactivity**
- **first-degree relative with diabetes**
- **high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)**
- **women who delivered a baby weighing 4,1 kg or were diagnosed with GDM**
- **hypertension (140/90 mmHg or on therapy for hypertension)**
- **HDL cholesterol level <0.90 mmol/L and/or a triglyceride level >2.82 mmol/L**
- **women with polycystic ovarian syndrome**
- **A1C ≥5.7%, IGT, or IFG on previous testing**
- **other clinical conditions associated with insulin resistance (e.g., severe obesity,**
- **acanthosis nigricans)**
- **history of CVD**

ADA recomendations. Diabetes Care 2014; 37 Suppl 1:S81-90.



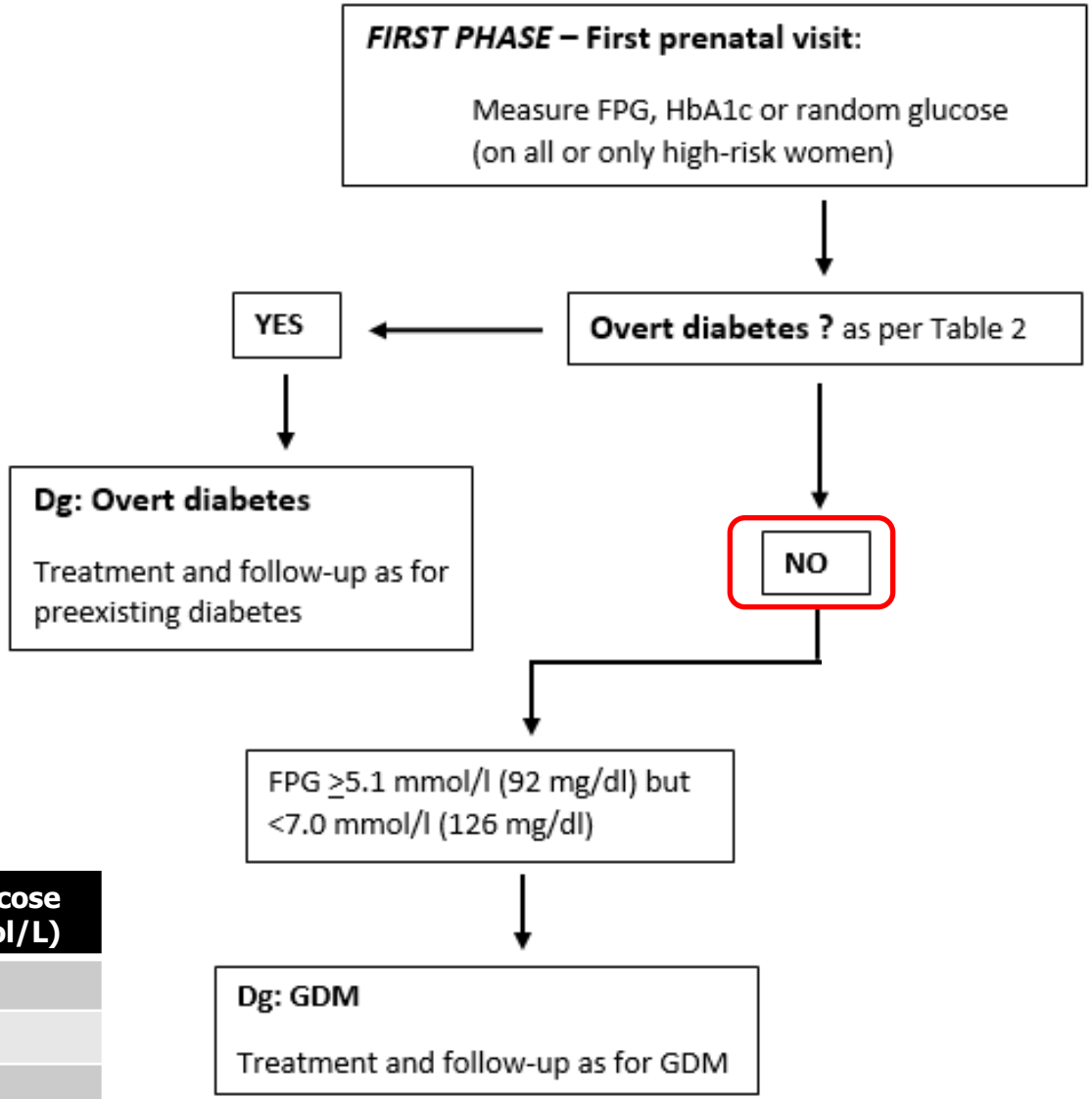


TABLE 3

75 gr OGTT	S-glucose (mmol/L)
FPG	≥5,1
1-hr	≥10,0
2-hr	≥8,5

SECOND PHASE is **mandatory**
in **all** previously „normal" **at 24-28 GW**

Metzger BE et al. Diabetes Care 2010; 33: 676–82.

Are IADPSG recommendations cost effective?

Concerns at IADPSG recomandations:

Significantly increase the prevalence of GDM

from 5-6% to ~18%

Due to:

1) cut-off values for GDM are lower than those recommended by earlier guidelines
2) only one abnormal value, not two, is sufficient to make the diagnosis

Significant impact on:

1) the costs
2) medical infrastructure capacity
3) potential for increased “medicalisation” of pregnancies previously (by older criteria) categorised as normal

Are IADPSG recommendations cost effective – USA data?

Treating mild gestational diabetes mellitus: a cost-effectiveness analysis

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Abstract

OBJECTIVE—This study investigated the cost-effectiveness of treating mild gestational diabetes mellitus (GDM).

STUDY DESIGN—A decision analytic model was built to compare treating vs not treating mild GDM. The primary outcome was the incremental cost per quality-adjusted life year (QALY). All probabilities, costs, and benefits were derived from the literature. Base case, sensitivity analyses, and a Monte Carlo simulation were performed.

RESULTS—Treating mild GDM was more expensive, more effective, and cost-effective at $20,412 per QALY. Treatment remained cost-effective when the incremental cost to treat GDM was less than $3555 or if treatment met at least 49% of its reported efficacy at the baseline cost to treat of $1786.

CONCLUSION—Treating mild GDM is cost-effective in terms of improving maternal and neonatal outcomes including decreased rates of preeclampsia, cesarean sections, macrosomia, shoulder dystocia, permanent and transient brachial plexus injury, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal intensive care unit admissions.

Treating mild GDM is cost-effective

Parameter	Probabilities		Utilities	Costs	Reference
GDM treatment				$1786	16
Maternal outcomes	**Without treatment**	**With treatment**			
Preeclampsia	0.136	0.086		$19,184	6,12
Cesarean delivery	0.338	0.269	0.99	$11,979	6,13,19,22
Vaginal delivery			1	$7790	13,21
Maternal death					
Cesarean	0.000022	0.000022	0	$100,000	10,17
Vaginal	0.000002	0.000002	0	$100,000	10,17
Shoulder dystocia					
With macrosomia	0.105	0.03885			6,8
Without macrosomia	0.016	0.00592			6,8
Neonatal outcomes					
Macrosomia	0.143	0.059			6
Brachial plexus injury	Please see Table 2 for the probabilities of brachial plexus injury				
Permanent	0.067	0.067	0.6	$15,699	6,9,18
Transient			0.99	$1757	6,9,18
Hypoglycemia			1	$2419	6,8,14
With macrosomia	0.053	0.05618			
Without macrosomia	0.026	0.02756			
Hyperbilirubinemia			1	$2006	6,8,26
With macrosomia	0.132	0.0977			
Without macrosomia	0.104	0.077			
NICU admission	0.116	0.09	1	$15,065	6,14,21
Neonatal death	0	0		$82,361	6,15,21,22
Maternal perspective			0.92		
Neonatal perspective			0		

Ohno MS et al. Am J Obstet Gynecol 2011; 205: 282.e1–282.e7.

Are IADPSG recommendations cost effective – USA data?

Variable	Costs	QALYs	$/QALY
Treatment	$12,623	56.891002	$20,412
No treatment	$12,167	56.868753	Baseline
	Treatment is more expensive	Treatment has higher QALYs	
Cost threshold in which treatment is more expensive vs no treatment: $1330			
Cost threshold in which treatment is no longer cost-effective: $3555			

GDM, gestational diabetes mellitus; *QALY*, quality-adjusted life year.

Ohno MS et al. Am J Obstet Gynecol 2011; 205: 282.e1–282.e7.

Benefits of treating GDM in terms of the NNT analysis

Perinatal outcome	NNT*
Macrosomia	12
Shoulder dystocia	75
Transient brachial plexus injury	320
Cesarean section	14

***NNT analysis**: to calculate the number of women who would need to be treated to decrease the incidence of a complication by 1.

Ohno MS et al. Am J Obstet Gynecol 2011; 205: 282.e1–282.e7.

Conclusions

- There is a direct causal relationship between maternal glycaemia and adverse pregnancy outcomes.
- Recomended aproach to diagnose hyperglycemia in pregnancy
  - **First phase testing** early in pregnancy is important to detect overt diabetes – in all or only in high risk women
  - **Second phase testing** is mandatory at 24–28 weeks' of gestation in all pregnancies not already diagnosed with overt diabetes or GDM by early testing
- Detection of hyperglycemic disorders in pregnancy based on IADPSG criteria will substantially increase the frequency of hyperglycemic disorders in pregnancy but is cost-effective.