Medicine, English, 2015

# GESTATIONAL DIABETES MELLITUS

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## THE FACTS

Every pregnant woman has "temporary and mild(!?!) diabetes."

As pregnancy progress, diabetogenicity rises.

If previously existing, recognized or unrecognized, any tipe od diabetes mellitus increases the problem!

Blood glucose level hormonal regulation is the result of:

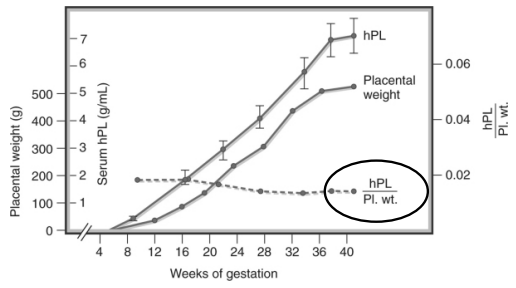
Unrelated to pregnancy:
- insulin
- growth hormone
- glucagon
- glucocorticosteroids
- epinefrin
- norepinefrin
- thyrocsine

During pregnancy only:
- human placental lactogen
- human chorionic gonadotropin
- .....

## HPL

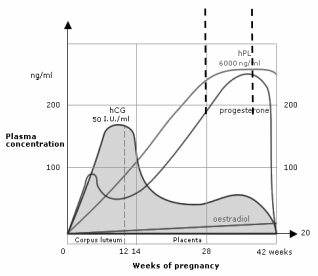
- placenta secretes a hormone called HPL (human placental lactogen)
- no negative (or positive) feedback control
- the amount of excreted HPL is exactly proportional to the size of the placenta
- HPL is built like growth hormone (protein structure)
- HPL increases peripheral tissue insulin resistance !!!

## HPL



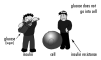

## HPL

HPL plateau due to slowing down of the placenta growth



# HPL

HPL increases peripheral tissue insulin resistance !!!



- slowing down glucose entering into the cells
- glucose stays for much longer time in the mothers blood - to be offered to the fetus
- pregnant women increases insulin secretion trying to push glucose into the cells: hyperinsulinemia = hunger !!!
- offerig to pregnant women ketones (hyperisulinemia = lipogenolysis) as the alternative feed option

# HPL

HPL increases peripheral tissue insulin resistance !!!

leading to hyperinsulinemia

THE RESULT IS:

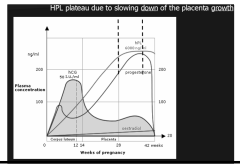
- "Constantly" hungry pregnant women
- increased (prolonged) supply of glucose to the fetus
- mother's "no glucose cell supply"

## THE FACT

A crucial part of pregnancy to identifying GDM as pregnancy disorder is about 25 weeks.

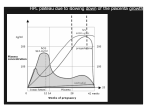

# ANSWER:

- in the first half of pregnancy, placenta is growing significantly faster than fetus (20 weeks ⇨ 3x heavier)
- in the second half of pregnancy, fetus is growing faster, and the term baby is 7x heavier than placenta




# ANSWER:

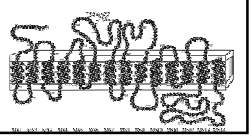
- ~ 26 weeks - fetus begins to secrete its own insulin
  *(the active form - an inactive form is proven in the first quarter)*
- until then, its growth is predominantly genetically determined
- since then, its growth mostly depends on the supply of glucose and insulin dependent metabolism



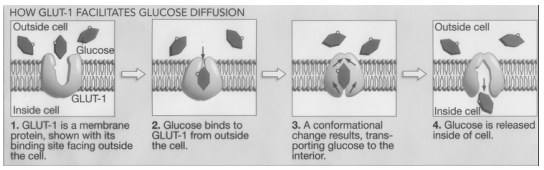
- 22. tjedna = 500g
- 25. tjedna = 800g
- 28. tjedna = 1200g
- 30. tjedna = 1500g
- 32. tjedna = 2000g

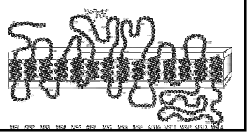
The glucose transfer through the chemochorionic membrane – facilitated diffusion

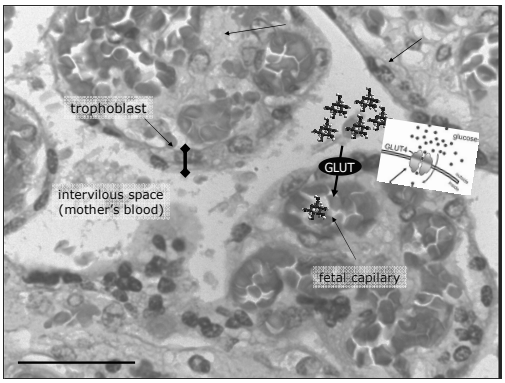
- no energy consumption - concentration gradient
- more correctly: regulated diffusion
- meaning: to "amortize" sudden and extreme changes in the mother's blood glucose concentration values after meals
- GLUT transporters in the membrane

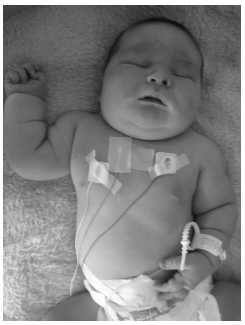


The glucose transfer through the chemochorionic membrane – facilitated diffusion





primiparous, male, ~40 tjedana, CS, 6100g/60cm), DM?

## Placenta - GDM


big, fat, heavy weight, polyhydramnios

## Diagnostic (screening?):

Various threshold values for the diagnosis of GDM

| | Fasting | 1 Hour | 2 Hours | 3 Hours |
|---|---|---|---|---|
| 100 gm OGTT [C&C (24)] | 95 mg/dL or 5.3 mmol/L | 180 mg/dL or 10.0 mmol/L | 155 mg/dL or 8.6 mmol/L | 140 mg/dL or 7.8 mmol/L |
| 100 gm OGTT [NDDG, (22)] | 105 mg/dL or 5.8 mmol/L | 190 mg/dL or 10.6 mmol/L | 165 mg/dL or 9.2 mmol/L | 145 mg/dL or 8.0 mmol/L |
| 75 gm OGTT [WHO, (17)] | 126 mg/dL or 7.0 mmol/L | | 140 mg/dL or 7.8 mmol/L | |
| 75 gm OGTT [ADA, (12)] | 95 mg/dL or 5.3 mmol/L | 180 mg/dL or 10.0 mmol/L | 155 mg/dL or 8.6 mmol/L | |
| 75 gm OGTT [CDA, (85)] | 95 mg/dL or 5.3 mmol/L | 190 mg/dL or 10.6 mmol/L | 160 mg/dL or 8.9 mmol/L | |

Cutoff values for the different diagnostic tests.
Reference numbers appear in parentheses.
C&C indicates Carpenter and Coustan; NDDG, National Diabetes Data Group; WHO, World Health Organisation; ADA, American Diabetes Organisation; CDA: Canadian Diabetes Association.

***Hollander MH, Paarlberg KM, Huisjes AJ. Gestational diabetes: a review of the current literature and guidelines. : Obstet Gynecol Surv. 2007 Feb;62(2):125-36***

## Diagnostic (screening?) – EU & USA differences

Guidelines and recommendations of some major European and North American professional organisations concerning testing for GDM

| Organisation | Year | Screening | Diagnosis | Recommendation |
|---|---|---|---|---|
| Cochrane Database (9) | 2002 | — | — | Not enough data to prove benefit of treatment |
| WHO (17) | 1998 | — | 75 gm OGTT at 24–28 weeks | — |
| ACOG (6) | 2001 | 50 gm GCT | If >130 mg/dL (7.2 mmol/L) or >140 mg/dL (7.8mmol/L) 100 gm OGTT | Test everyone or only in case of risk factors, but 90% have risk factors |
| ADA (12) | 2002 | In case of risk factors 50 gm GCT | Same as ACOG | — |
| USPST (4) | 2003 | — | — | Test everyone or only in case of risk factors, no recommendation on which is preferable |
| Fourth International Workshop-Conference on Gestational Diabetes Mellitus (86) | 1998 | In case of risk factors: 50 gm GCT or 75 gm OGTT for all patients | Same as ACOG | — |
| Canadian Taskforce on the Periodic Health Examination (87) | 1992 | — | — | Insufficient evidence for or against universal screening, no recommendation |
| CDA (85) | 1998 | In case of risk factors 50 gm GCT | 100 gm OGTT | |
| SOGC (5) | 2002 | In case of risk factors 50 gm GCT | 100 gm OGTT if >=110 mg/dL (6.1 mmol/L) 75 gm OGTT | The option not to screen or treat is acceptable |
| Diabetes UK (7) | ? | Random glucose at booking and at 28 weeks | — | Urine for glucose at every visit to check for DMI |
| SIGN (7) | ? | Urine for glucose and random glucose at every visit | — | — |
| Health Technology Assessment UK (7) | 2002 | Risk factors | 50 gm GCT at 24–28 weeks, if >=140 mg/dL (7.8 mmol/L) | Very selective screening based on age, obesity and ethnic origin |
| European Association for the Study of Diabetes (88) | 1991 | 50 gm GCT (>=148 mg/dL or 8.2 mmol/L) and fasting glucose (>=85 mmol/dl or 4.8 mmol/L) | 75 gm OGTT, cut-off fasting 100 mg/dL (5.5 mmol/L) and 2-hours 152 mmol/L (8.0 mmol/L) | |

Reference numbers appear in parentheses.
WHO indicates World Health Organisation; ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Organisation; USPST, United States Preventive Services Taskforce; CDA, Canadian Diabetes Association; SOGC, Society of Obstetricians and Gynecologists of Canada; SIGN, Scottish Intercollegiate Guidance Network.

***Hollander MH, Paarlberg KM, Huisjes AJ. Gestational diabetes: a review of the current literature and guidelines. : Obstet Gynecol Surv. 2007 Feb;62(2):125-36***

## WHO DIAGNOSTIC PROTOCOL:

OGTT (oral) glucose tolerance test (75g glucose):

0 min - blood glucose level (fasting)
0 min - 75g glucose in the glass of water
120 min - bloog glucose level after 120 min

*Alberti KGMM, Zimmet PZ; for the WHO Consultation. Definition, diagnosis et classification of diabetes mellitus and its complications. Diabetes Med 1988;15:534-53.*

## DIJAGNOSTIC (screening):

### GDM:

1. fasting glucose level > 7,0 mmol/l venous blood
   *(> 8,0 mmol/l cypilary blood)*
1. after 120 min > 7,9 mmol/l venous blood
   *(> 8,9 mmol/l capilary blood)*

*In physiological conditions, postprandial hyperglycemia last ~ 45 minutes !!!*

## DIJAGNOSTIC (screening):

- OGTT test :
  1. simple
  2. exact
  3. repeatable
  4. easy to reproduce
  5. harmless
  6. cheap

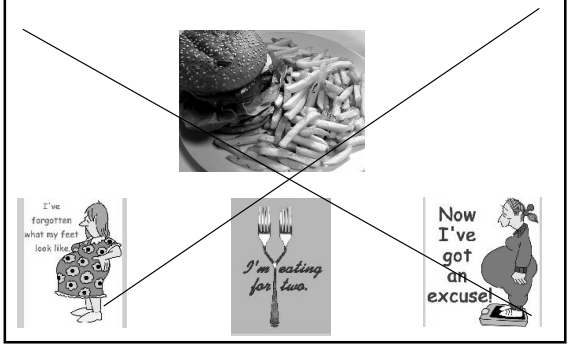
In the case of pathological OGTT test result, pregnant woman is hospitalized (usualy for one day only) to determinate glucose value before and two hours after each meal

glucose profile,
urine culture, cervical smears mycrobiology,
glucose and ketones in urine, US (fetal growth),
weight gain (mother), RR, HgbA1C (only once!!)

## First choice (step) therapy:

1. American Diabetic Assotiation (ADA) diet
2. 1800 kcal/day in five meals
3. low glycemic indeks food
4. almost the same diet as for DM ty II.

## Healthy eating pyramid

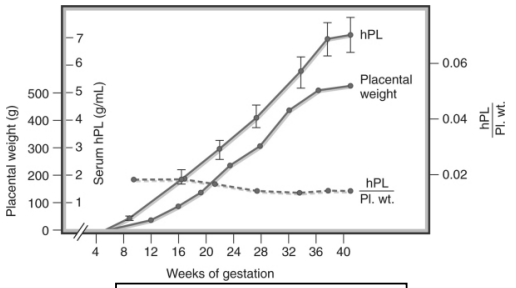

## INSULIN IN THERAPY?

- **at least one value before or after the meal >7,0-8,0 mmol/l**

To every pregnant women with GDM with normal glucouse profile in the case of LGA (US eltimated fetal weight) or polyhydramnios!

Treatment in GDM is due to the fetus, not because of mother!!!

## REPEATED BLOOD GLUCOSE PROFILE IN 2 to 3 WEEKS BECAUSE OF HPL SECRETION DYNAMICS

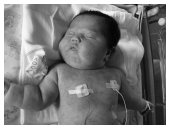



There is no sense in repeating OGTT, except if it want to revise the diagnosis.
OGTT is NOT (and can not be) fix with diet!

## Fetal programming


## LONG TERM OUTCOME:

- Newborns from pregnancies complicated with GDM, as well as with IUGR, later in life more often suffer from chronic diseases (cardiovascular diseases, DM ty. II, ....)



## LONG TERM OUTCOME:

- GDM is not harmfull to women during pregnancy, but they have a greatly increased risk of developing DM ty II. (30% in 10 years after giving birth), DM ty I. (5-10%), hypertension, ...

## THE TRUTH ABOUT GDM:

- screening is performed among pregnant women
- treatment of them (during pregnancy) is almost exclusively the treatment of fetus …
- … and is necessary to prevent short, medium and long term consequences in infant.

- Pregnant women with GDM almost never have a major health problem in pregnancy !!!
- …. But will later in life !!! !!! !!!
- 30% will develop DM ty. II within ten years !!!
- Why not to prepare in time and before the onset of DM ty. II? …. and delaying the onset of disease to delay the possible and unavoidable DM ty. II complications

# AND THEREFORE:

The indication for OGTT test during pregnancy is pregnancy itself !!!

## SIX WEEKS AFTER DELIVERY

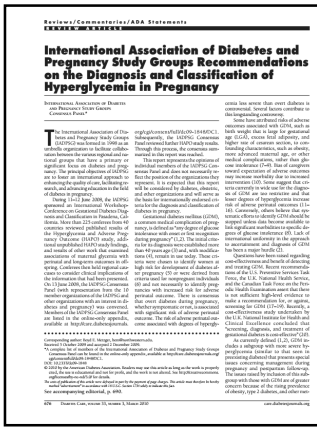
■OGTT should be repaeated

To put the final diagnosis!

To disclose if the woman had diabetes (and) before pregnancy, or it was develope during pregnancy and because of it (due to the hormones of pregnancy )

22% of pregnant women with abnormal OGTT test in pregnancy have the same result six weeks after delivery too!!!

*Catalano PM et al. J Gynecol Obstet 1991.*



Reviews/Commentaries/ADA Statements

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

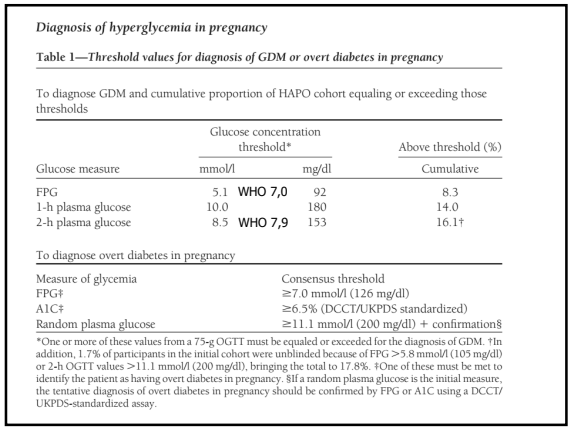
HAPO STUDY

**H**yperglycemia
**A**dverse
**P**regnancy
**O**utcome

## Primary outcomes in the blinded HAPO cohort:

- birth weight 90th percentile
- primary cesarean section delivery
- clinically defined neonatal hypoglycemia,
- cord C-peptide 90th percentile.

- Secondary outcomes were preclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia, and intensive neonatal care.



*Diagnosis of hyperglycemia in pregnancy*

**Table 1—*Threshold values for diagnosis of GDM or overt diabetes in pregnancy***

To diagnose GDM and cumulative proportion of HAPO cohort equaling or exceeding those thresholds

| | Glucose concentration threshold* | | | Above threshold (%) |
|---|---|---|---|---|
| Glucose measure | mmol/l | | mg/dl | Cumulative |
| FPG | 5.1 | WHO 7,0 | 92 | 8.3 |
| 1-h plasma glucose | 10.0 | | 180 | 14.0 |
| 2-h plasma glucose | 8.5 | WHO 7,9 | 153 | 16.1† |

To diagnose overt diabetes in pregnancy

| Measure of glycemia | Consensus threshold |
|---|---|
| FPG‡ | ≥7.0 mmol/l (126 mg/dl) |
| A1C‡ | ≥6.5% (DCCT/UKPDS standardized) |
| Random plasma glucose | ≥11.1 mmol/l (200 mg/dl) + confirmation§ |

*One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM. †In addition, 1.7% of participants in the initial cohort were unblinded because of FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl), bringing the total to 17.8%. ‡One of these must be met to identify the patient as having overt diabetes in pregnancy. §If a random plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or A1C using a DCCT/UKPDS-standardized assay.

*Diagnosis of hyperglycemia in pregnancy*

**Table 2—*Strategy for the detection and diagnosis of hyperglycemic disorders in pregnancy**

| |
|---|
| First prenatal visit |
| Measure FPG, A1C, or random plasma glucose on all or only high-risk women† |
| If results indicate overt diabetes as per Table 1 |
| Treatment and follow-up as for preexisting diabetes |
| If results not diagnostic of overt diabetes |
| and fasting plasma glucose ≥5.1 mmol/l (92 mg/dl) but <7.0 mmol/l (126 mg/dl), diagnose as GDM |
| and fasting plasma glucose <5.1 mmol/l (92 mg/dl), test for GDM from 24 to 28 weeks' gestation with a 75-g OGTT† |
| 24–28 weeks' gestation: diagnosis of GDM |
| 2-h 75-g OGTT: perform after overnight fast on all women not previously found to have overt diabetes or GDM during testing earlier in this pregnancy |
| Overt diabetes if fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) |
| GDM if one or more values equals or exceeds thresholds indicated in Table 1 |
| Normal if all values on OGTT less than thresholds indicated in Table 1 |

*To be applied to women without known diabetes antedating pregnancy. Postpartum glucose testing should be performed for all women diagnosed with overt diabetes during pregnancy or GDM. †Decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is to be made on the basis of the background frequency of abnormal glucose metabolism in the population and on local circumstances. ‡The panel concluded that there have been insufficient studies performed to know whether there is a benefit of generalized testing to diagnose and treat GDM before the usual window of 24–28 weeks' gestation.

# WHO *vs.* HAPO

| **WHO** | **HAPO** |
|---|---|
| ■ not for pregnant women only | ■ for pregnant womne only |
| ■ ~ 4% positive | ■ ~16% positive |

# TO CONSIDER ONLY


A healthy diet for all pregnant women (especially after 24 weeks) ?

# WOULD YOU?
# IT IS HEALTHY TO YOU TOO!


A healthy diet for all pregnant women (especially after 24 weeks) ?

# WHY NOT?