

Diabetes and pregnancy



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Gestational diabetes

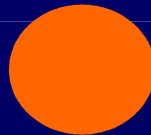
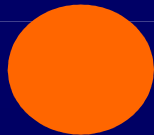
“Carbohydrate intolerance of varying degrees of severity, with onset or first recognition during pregnancy”

Gestational diabetes

Non-pregnant

Insulin
secretion

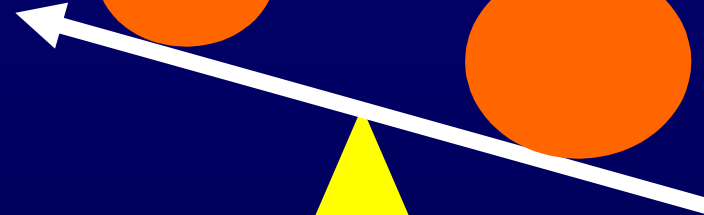
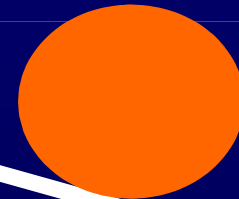
Insulin
resistance



Pregnant

Insulin
secretion

Insulin
resistance



Blood
glucose

Macrosomia and shoulder dystocia



- High sugars induce fetal insulin production
- Extra growth of all tissues
- Extra fat deposition
- Shoulder areas bigger than the head
- Shoulder dystocia

Short-term complications

- Complications in pregnancy
 - Hypertension, pre-eclampsia, preterm delivery
- Complications during labour
 - Shoulder dystocia, C-section, maternal lesions
- Neonatal morbidity
 - Hypoglycaemia, prematurity, jaundice, RDS
- Neonatal mortality - rare

macrosomia

Screening traditions

- Universal testing with OGTT (oral glucose tolerance test)
- Selective testing with OGTT
 - Glucosuria
 - Age
 - BMI
 - Diabetes in first degree relatives
 - Previous GDM

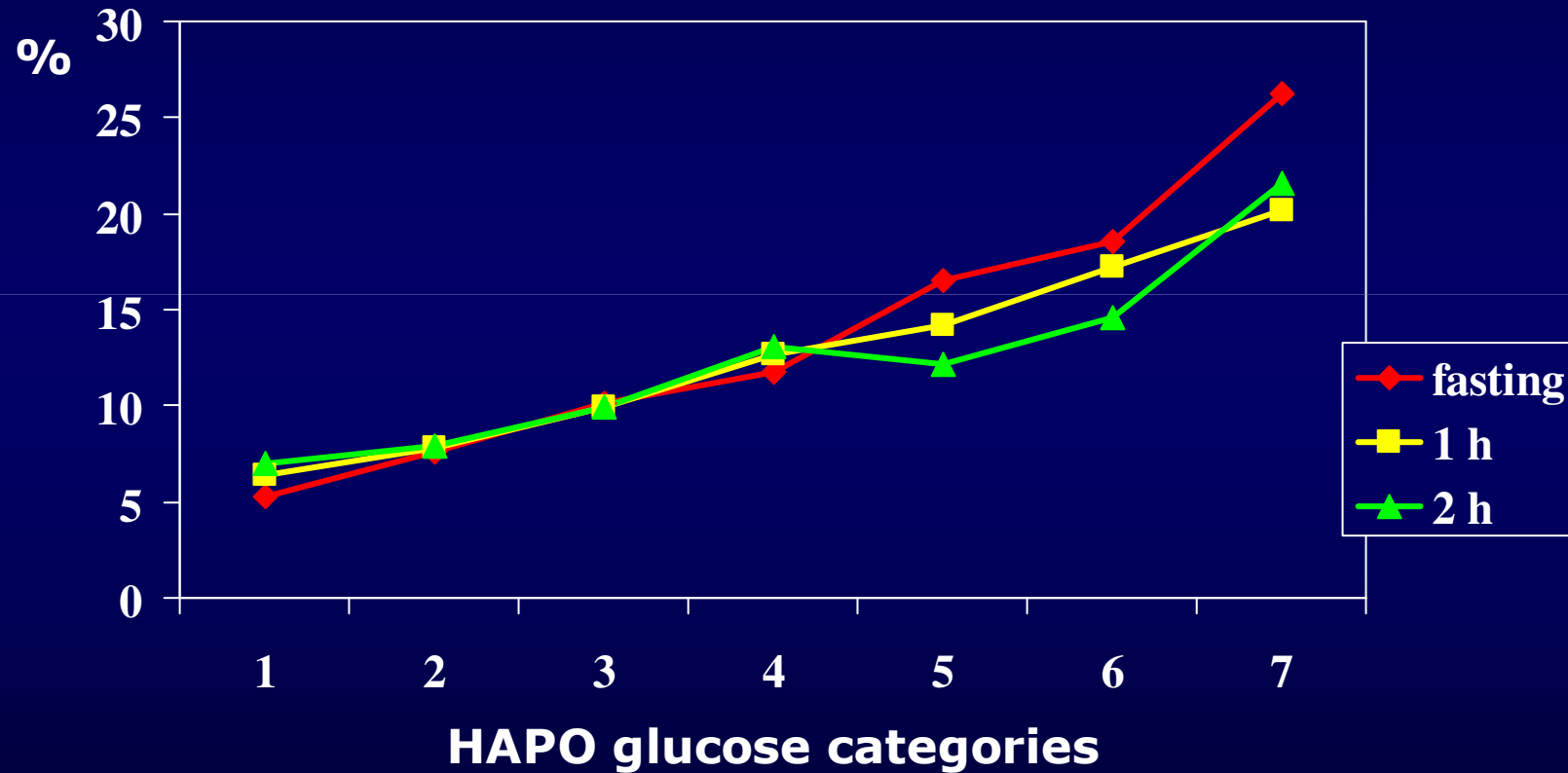
Diagnosis

- ADA
 - 75 g, 3-h OGTT
 - at least 2/3 values \uparrow (5.3, 10.0 and 8.6 mmol/l)
- WHO
 - 75 g, 2-h OGTT
 - 2-h value \geq 7.8 mmol/l (IGT)
- DPSG (Europa)
 - 75 g, 2-h OGTT
 - 2-h value \geq 9.0 mmol/l

HAPO study

- Aim
 - "To clarify unanswered questions on associations of maternal glycemia, less severe than overt diabetes mellitus, with risks of adverse pregnancy outcome"
- Methods
 - Observational multicenter study (N=25.000)
 - Inclusion: FPG<5.8 mmol/l and 2-h PG <11 (75 g OGTT wk 24-32)
 - Blinding of OGTT results

LGA infants



Diagnose of GDM

- 75g OGTT
- Proposed criterias based on HAPO:
- One of the following:
 - Fasting p-glucose $\geq 5,1$ mmol/l (92 mg%)
 - 1 hour p-glucose $\geq 10,0$ mmol/l (180 mg%)
 - 2 hour p-glucose $\geq 8,5$ mmol/l (153 mg%)

Diagnose of overt diabetes in early pregnancy

- First pregnancy visit:
- Fasting plasma glucose > 7 mmol/l or
- HbA1c $> 6.5\%$ or
- Random plasma glucose > 11 mmol/l + confirmation

Management of GDM

- Diet treatment
- Exercise
- Self monitoring of blood glucose (SMBG)
- Pharmacological treatment
- Intensified obstetric surveillance



SMBG - therapeutic goals

| | ADA American Diabetes Association | | ACHOIS Australian Carbohydrate Intolerance Study in Pregnant Women | | |
|---------|--------------------------------------|-----|--|-----|---------|
| | BG | PG* | BG | PG* | |
| Faste | 5.3 | 5.9 | 5.5 | 6.1 | 108 mg% |
| 1h ppr. | 7.8 | 8.7 | - | - | |
| 2h ppr. | 6.7 | 7.4 | 7.0 (9.0**) | 7.8 | 130 mg% |

Therapeutic goal: Hba1c < 5.6%

Table 1—HbA_{1c} in normal, early, and late pregnancy compared with age-matched nonpregnant women without diabetes

| | Nonpregnant | Early pregnancy | Late pregnancy |
|--------------------------|-------------|-----------------|----------------|
| n | 145 | 100 | 98 |
| Age (years) | 30.0 ± 0 | 30.8 ± 5 | 29.2 ± 3 |
| BMI (kg/m ²) | 24.5 ± 4.6 | 23.0 ± 3.6 | 22.3 ± 2.8* |
| HbA _{1c} (%) | 5.5 ± 0.4 | 5.1 ± 0.3† | 5.0 ± 0.3† |

Data are means ± SD. *Trend test $P < 0.009$. †Trend test $P < 0.0001$; nonpregnant vs. early pregnancy, $P < 0.001$; early vs. late pregnancy, $P < 0.05$; nonpregnant vs. late pregnancy, $P < 0.001$.

Dietary treatment



- Self-management therapy - SMBG
- Secure micronutrients
- Energy restriction of 30% in obese women
 - Reduced glucose and TG with no increase in ketonuria (Franz MJ et al. *Diabetes Care* 17:490–518, 1994)
- Carbohydrate restriction (35-40% of energy)
 - better glycaemic control, reduced rates of macrosomia and CS (Major CA et al. *Obstet Gynecol* 91:600–604, 1998)

Exercise



- Increase insulin sensitivity
- Improve maternal glycaemic control
(Jovanovic-Peterson *AJOG* 1989, Brankston *AJOG* 04)
 - Recent Cochrane review found no effect of exercise alone compared to other regimens (Ceysens G et Al. *Cochrane Database Syst Rev.* 2006 Jul 19;3:CD004225)
- Prevent GDM (Dempsey *Am J Epidemiol* 04)

Obstetric care

- Treatment of hypertension and pre-eclampsia
 - Methyldopa, labetalol, ASA
- Clinical and ultrasonographic surveillance for fetal size and wellbeing
- Timing of delivery 38-40 gestational week

Does treatment of GDM improve outcome?

- Intervention group, N=490
 - informed they had “*glucose intolerance of pregnancy*”
 - SMBG, diet, insulin, intensified obstetric surveillance
- Control group, N=510
 - informed they “*did not have gestational diabetes*”
 - Routine obstetric management

Serious perinatal outcome: Perinatal death and shoulder dystocia

| | Intervention (N 506) | Routine care (N 526) |
|----------------------------------|-------------------------|-------------------------|
| <i>Serious perinatal outcome</i> | 7 (1%) | 23 (4%) NNT =34 |
| <i>Death</i> | 0 | 5 (1%) |

Infant outcome

| | Int. group (N 506) | Rout.Gr. (N 526) | Adj. Treatment effect or RR (95% CI) |
|---------------------|-----------------------|---------------------|--|
| Birth weight (g) | 3335 | 3482 | -145 (-219 to -70) |
| LGA | 13% | 22% | 0.62 (0.47-0.81) |
| 4000g | 10% | 21% | 0.47 (0.34-0.64) |
| SGA | 7% | 7% | 0.88 (0.56-1.39) |
| Apgar 5<7 | 1% | 2% | 0.57 (0.21-1.53) |
| Hypoglyc. | 7% | 5% | 1.42 (0.87-2.32) |
| RDS | 5% | 4% | 1.52 (0.86-2.71) |

Mean±SD, median (IQ range), %

NJEM 2005;352:2477-2486

Summary

Diagnosis and treatment of GDM:

- Reduces the risk of serious perinatal complications by 75%
- Reduces the risk of macrosomia by 50%

Pharmacological treatment

- SAFE
 - Insulin (human and fast acting analogues)
- MAYBE SAFE
 - Glyburide (glibenclamide)
 - Metformin
 - Arcabose
- NOT SAFE
 - Most sulfonylureas (prolonged neonatal hypo)
 - Thiazolidinediones TZD (teratogenicity)

Insulin regimens

- Basal-bolus regimen
 - 4 times daily
- Premixed insulin
 - 2 times daily
- Other regimens

Twice vs. four times daily insulin in gestational diabetes

| | Insulin * 2 | Insulin * 4 |
|--------------------------|-------------|-------------|
| Number | 136 | 138 |
| HbA1c (%) | 5,8 | 5,5* |
| Adequate control (%) | 74 | 91* |
| Macrosomia (>4000 g) | 26 | 22 |
| Neonat- hypoglycaemia | 8 | 1* |
| | | |
| Overall neonat morbidity | 40 | 24* |

Rationale for glyburide

- Potential risk of SU in pregnancy
 - Prolonged neonatal hypoglycemia
 - Teratogenicity
- Placental passage of glyburide minimal in perfusion studies
- Insulin more expensive

Glyburide vs. insulin

| Outcome | Glyburide N=201 | Insulin N=203 | P-value |
|-------------------|--------------------|------------------|---------|
| LGA (%) | 24 (12) | 26(13) | 0.76 |
| Hypoglycaemia (%) | 18 (9) | 12 (6) | 0.25 |
| Stillbirth (%) | 1 (0.5) | 1 (0.5) | 0.99 |
| HbA1c (%) | 5.5 ± 0.7 | 5.4 ± 0.6 | 0.12 |

* Means ± SD

Langer et al. NEJM 2000, 343;1135-38

Metformin in pregnancy

- Potential risks:
 - Teratogenity or less malformations
 - Lactic acidosis
 - Still birth (Helmuth, Diab Med 2000)
 - Neonatal hypoglycemia

Metformin versus insulin in GDM

| | Metformin | Insulin |
|------------------------|-----------|---------|
| Number | 363 | 388 |
| Composite poor outcome | 32 % | 32 % |
| Insulin supplemented | 46% | 100 % |

Women prefer metformin

Rowan, N Engl, J Med 08

Long-term complications

- Mother
 - Diabetes up to 70 %
 - Obesity
 - Cardiovascular disease
- Offspring-importance of the intrauterine milioe
 - Glucose intolerance incl. GDM
 - Other metabolic risk factors
 - Other morbidity

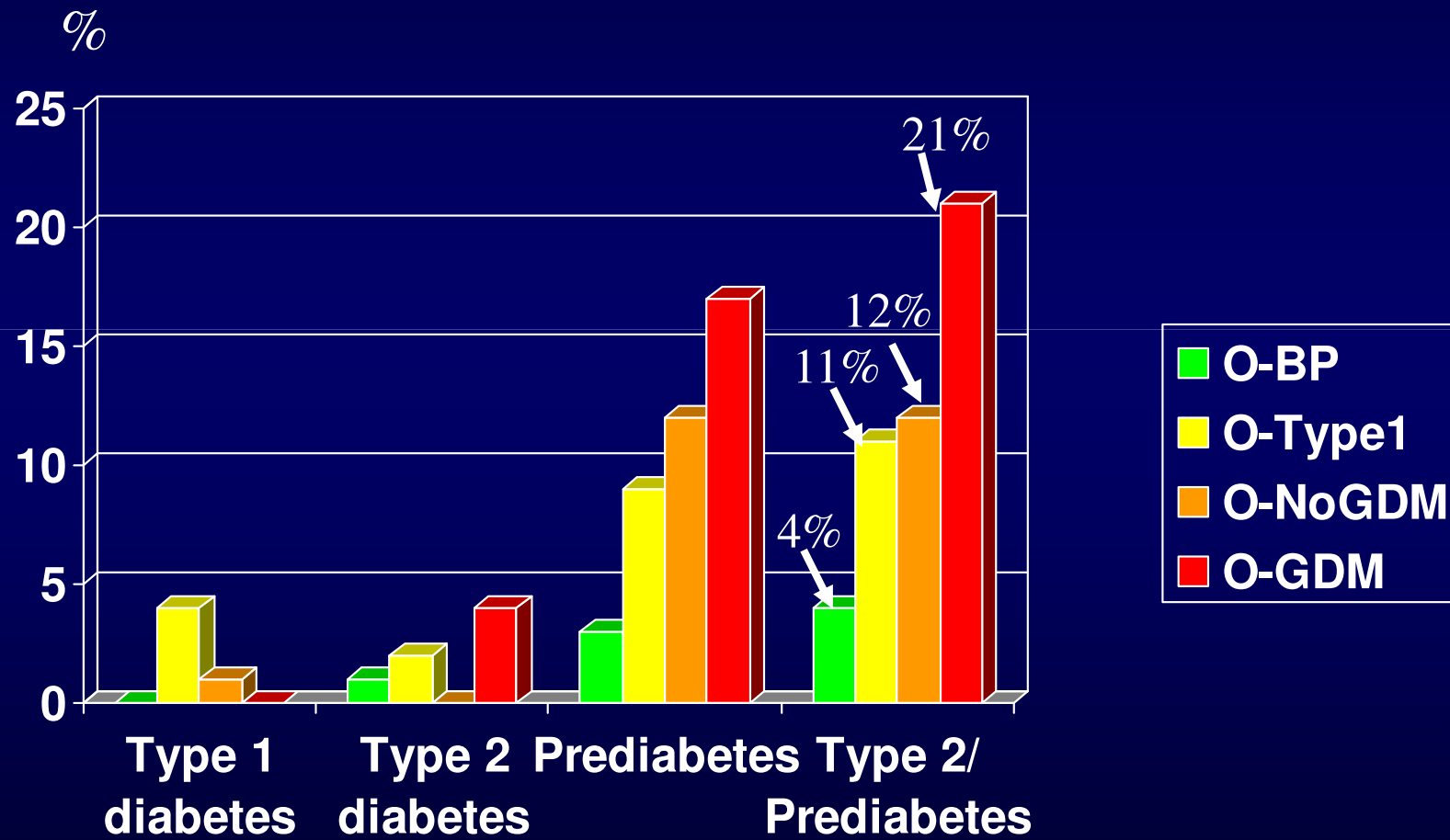
Born big is not necessarily better



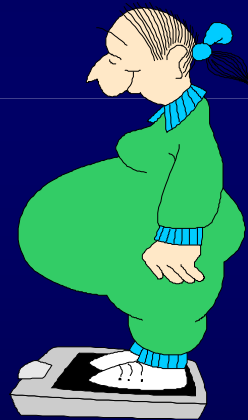
- Intra uterine excess food intake
- Risk of future obesity
- Risk of future diabetes

Intrauterine milieu and the next generation

- Type 2 diabetes and prediabetes in young adults



Diabetes present before pregnancy



Adverse events in diabetic pregnancy



- Major hypoglycaemia
- Proliferative retinopathy



- Fetal loss
- Malformations
- Preterm delivery
- Macrosomia



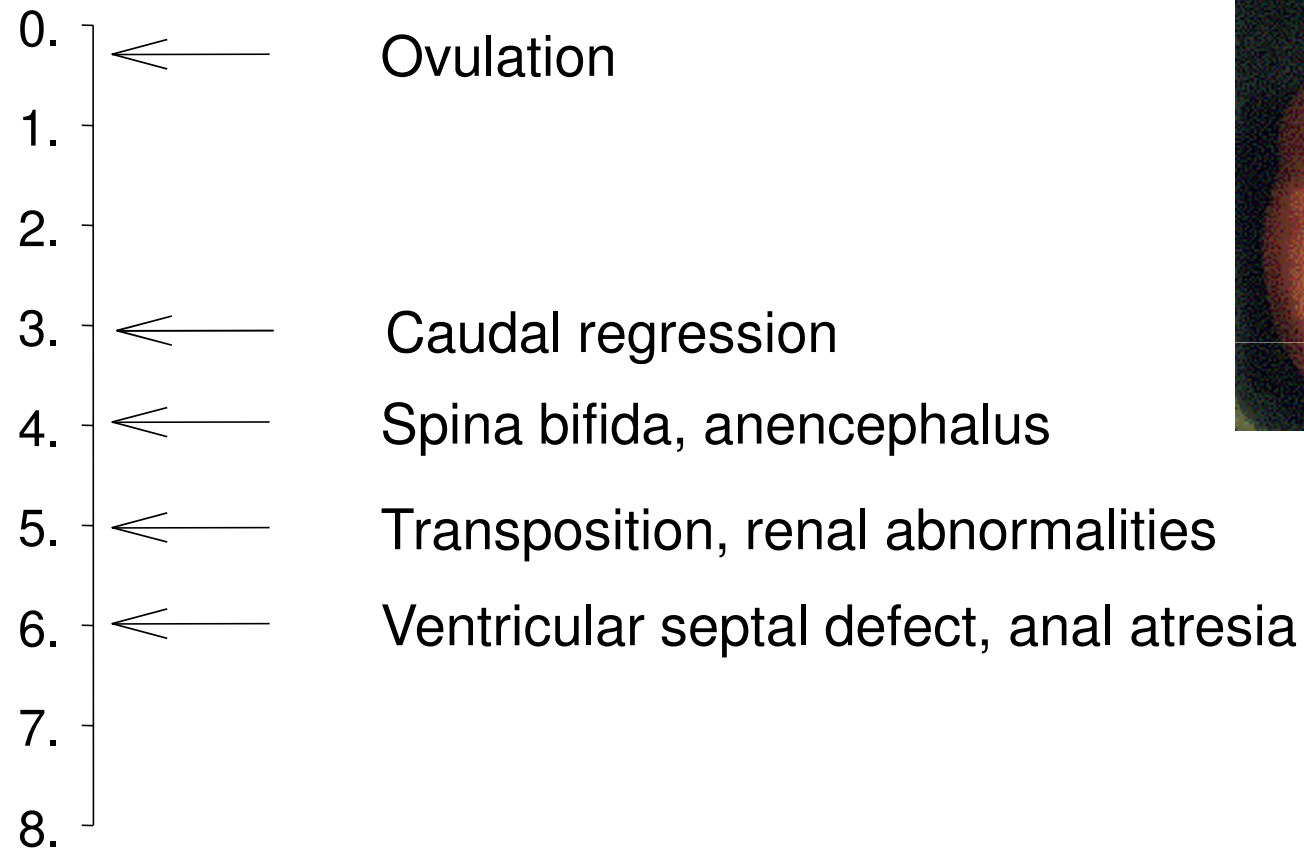
Outcome in Type 2 DM

| | Type 2 | Type 1 | RR |
|------------------------------|--------|--------|----|
| Perinatal mortality (o/1000) | 32 | 32 | 4 |
| Malformations (o/1000) | 43 | 48 | 2 |
| Preterm delivery (%) | 37 | 37 | 5 |
| LGA (>90% percentile,%) | >50 | >50? | 5 |

CEMACH 2005, N=2356

Timing of congenital malformations

Weeks



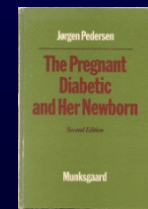
6 weeks after ovulation correspond to gestation week 8

Glycemic control

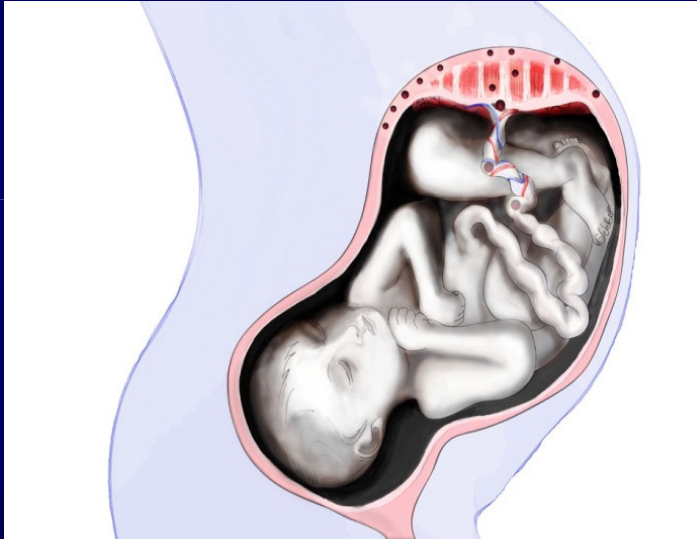


- Elevated plasma glucose in the mother gives
 - High glucose supply to the fetus
 - Increased oxygen need
 - Obese fetus
 - Immature organs
- Insulin does not pass placenta

Modified after Pedersen hypotesis



Perinatal mortality - Stillbirth

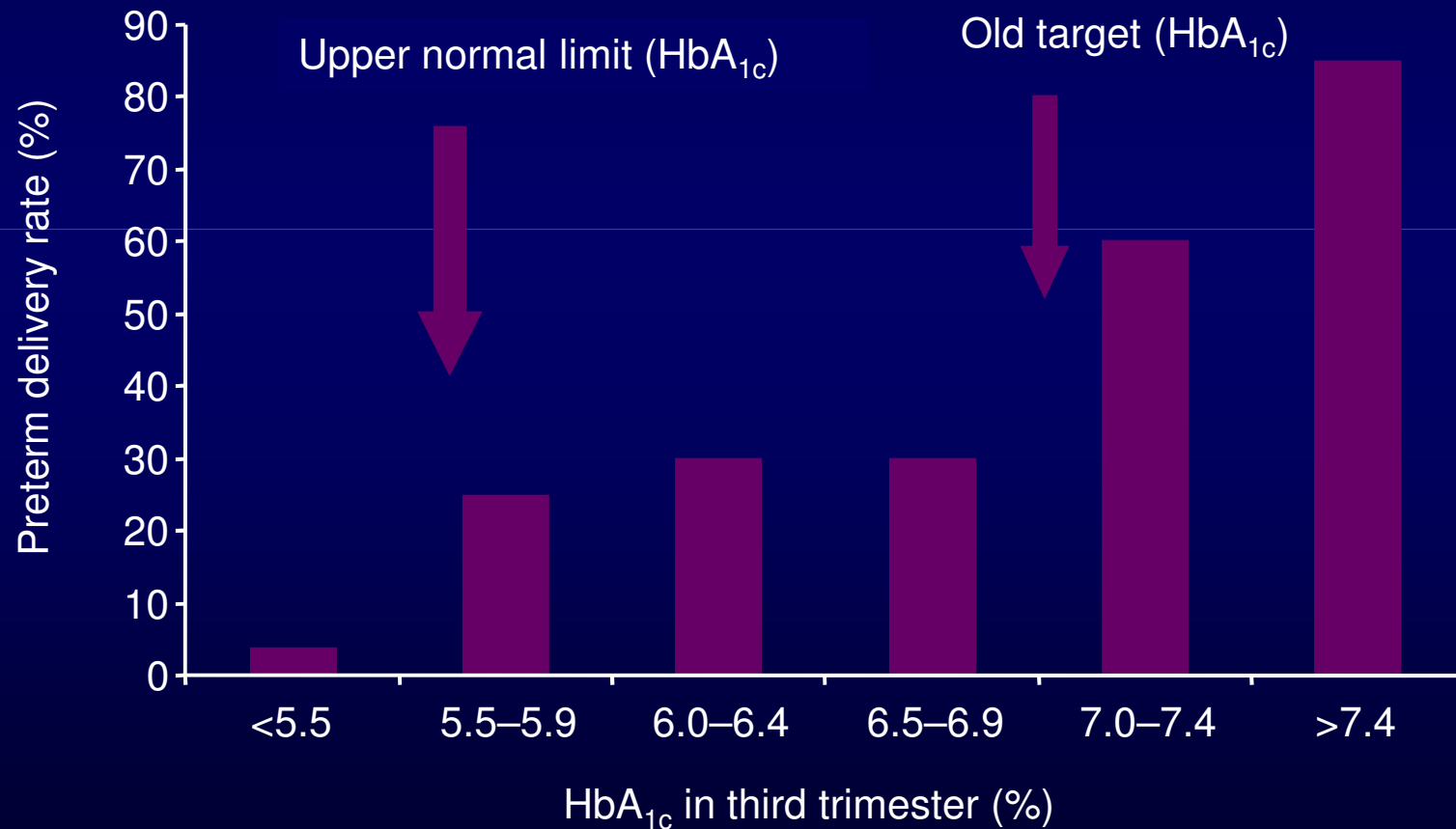


- High glucose
- Increased metabolism
- Increased oxygen need
- Low oxygen
- Lactate acid production
- Stimulation of EPO



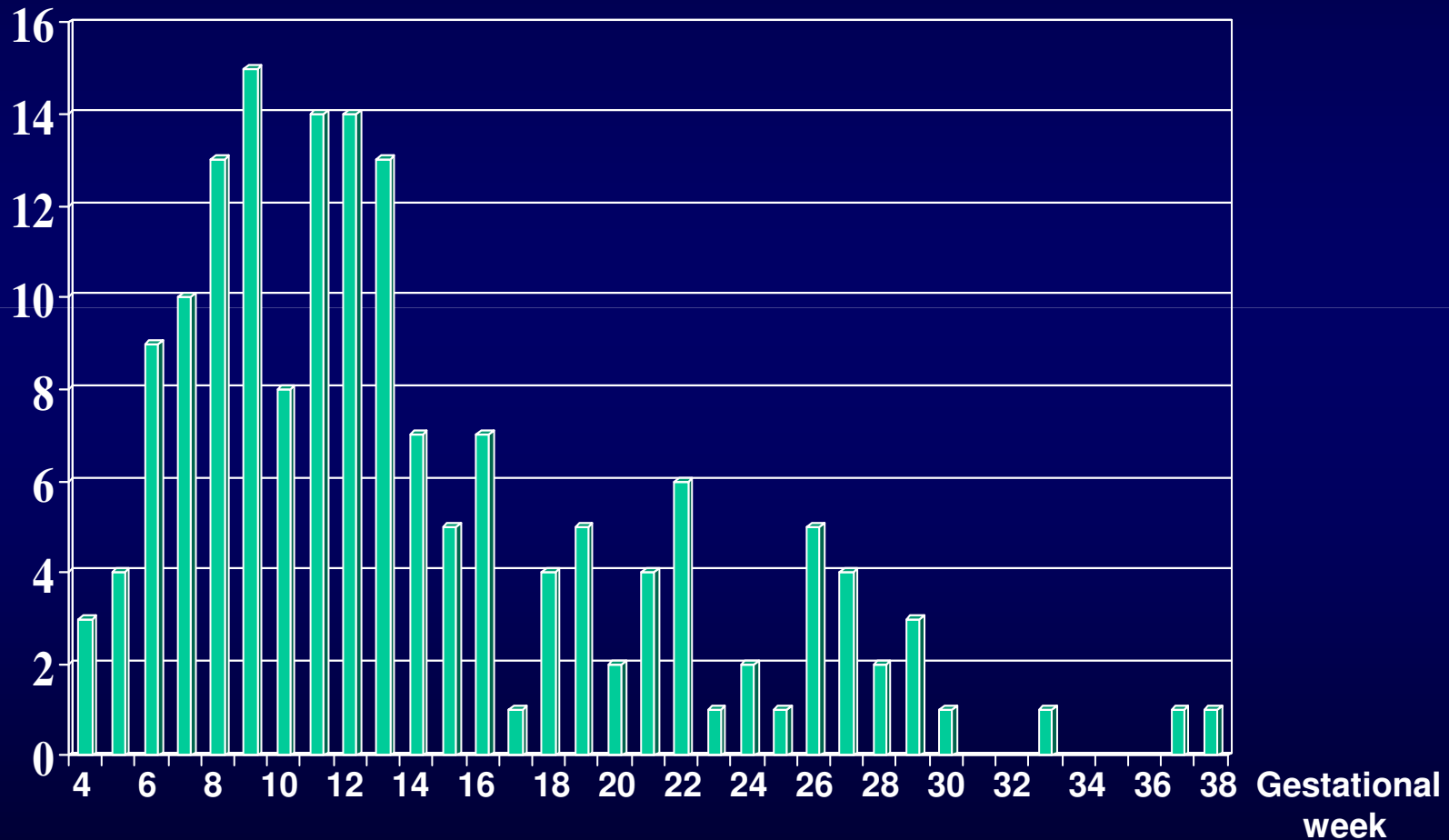
Percentage of preterm delivery vs. third trimester HbA_{1c}

- 213 women with type 1 diabetes



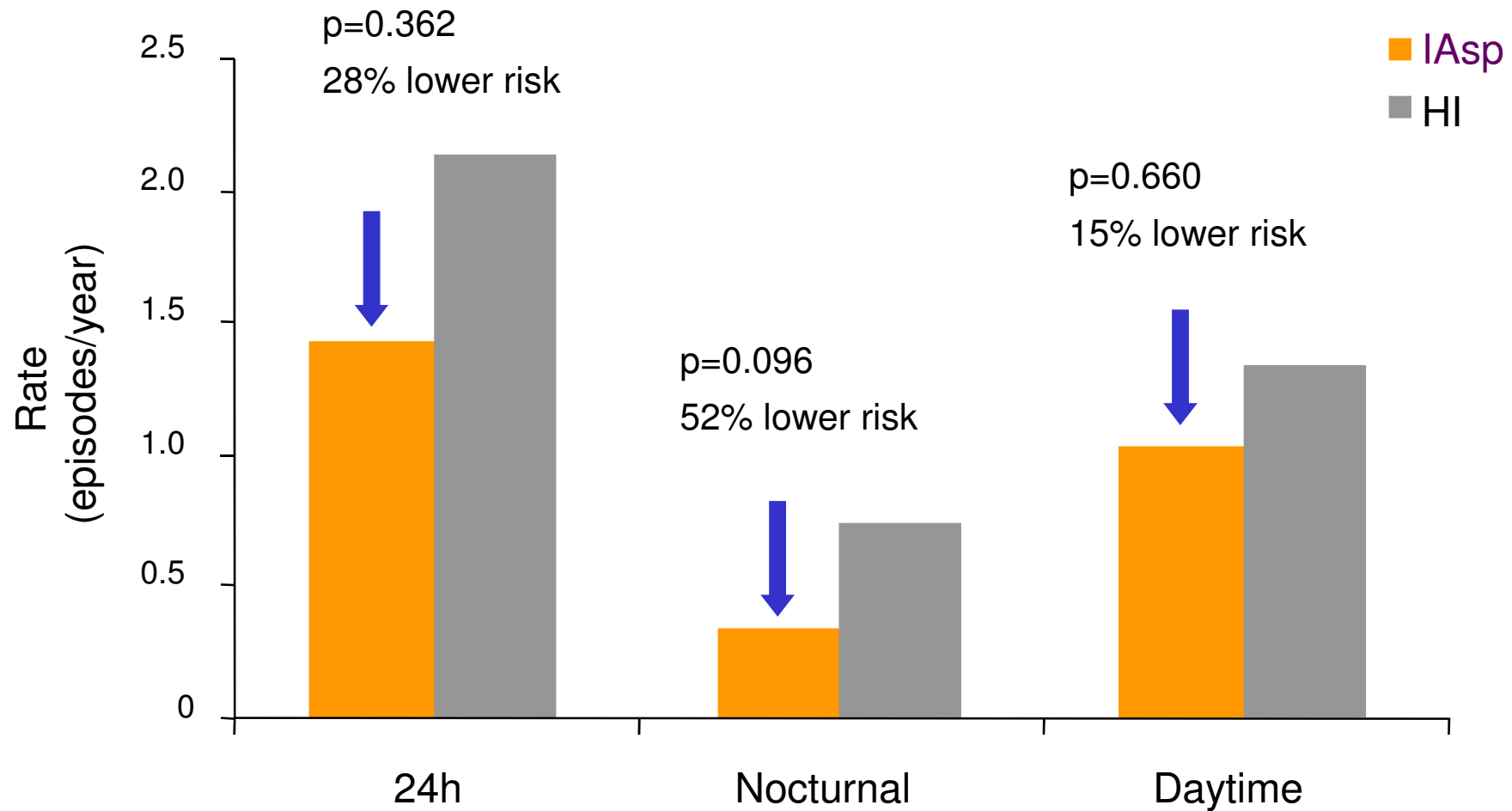
167 events of severe hypoglycaemia in 108 pregnant women with type 1 diabetes

Number of events



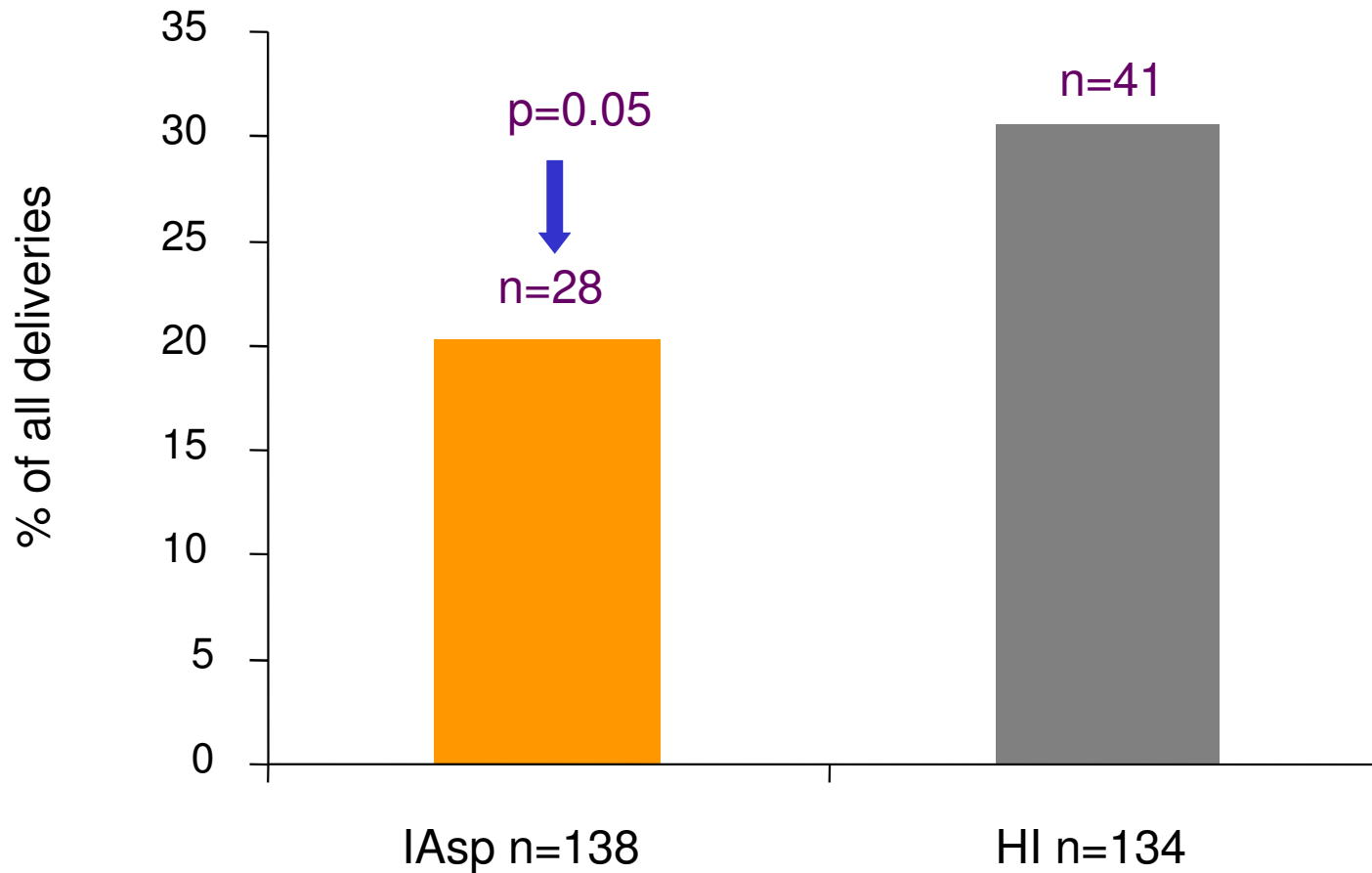
LR Nielsen, unpublished

Major hypoglycemia during pregnancy



N=322

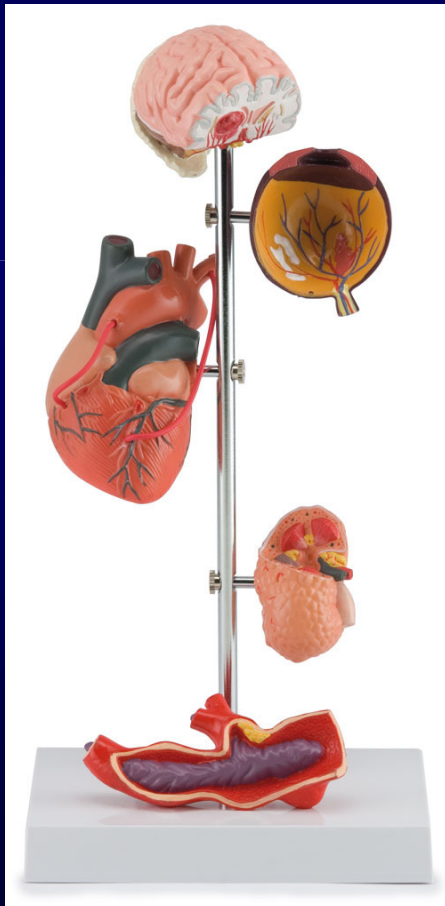
Frequency of preterm delivery



Clinical experience of insulin analogues in pregnancy 2010

- Insulin Lispro (1996)
 - Several observational trials
 - Approved for use in pregnancy
- Insulin Aspart (1999)
 - One large randomized trial
 - Approved for use in pregnancy
- Insulin Glargine (2000)
 - Several observational studies – no concerns
- Insulin Detemir (2004)
 - Ongoing large randomized trial – no concerns

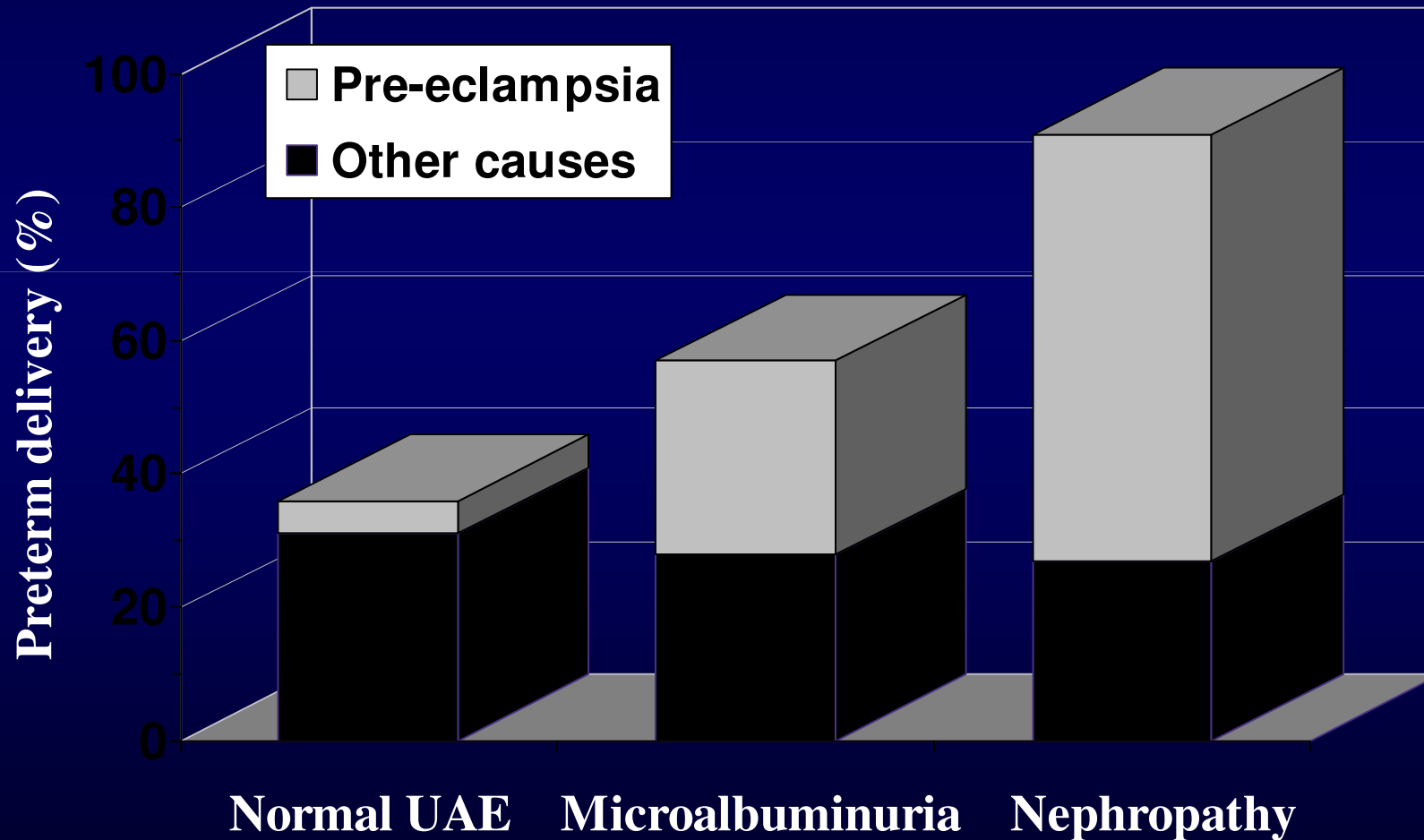
Hypertension-diabetes- preeclampsia



- Brain
- Eye
- Heart

- Kidney
- Arteries

Preterm delivery in relation to urinary albumin excretion



Effect of early antihypertensive treatment in pregnant women with microalbuminuria

| | | | |
|---|-----------------------|--|--|
| Cohort- year | 1995-99 | | |
| AH- treatment protocol Methyldopa first choice | BP>140/95 AH-pause | | |
| Number | 26 | | |
| HbA1c at 28 wks (%) | 6.3 | | |
| Preeclampsia (%) | 42% | | |
| Delivery < 34 wks | 23% | | |
| Delivery < 37 wks | 62% | | |

Effect of early antihypertensive treatment in pregnant women with microalbuminuria

| Cohort- year | 1995-99 | 2000-2003 | |
|---|-----------------------|-------------------------------------|--|
| AH- treatment protocol Methyldopa first choice | BP>140/95 AH-pause | U-alb>2000 BP>140/90 AH-shift | |
| Number | 26 | 20 | |
| HbA1c at 28 wks (%) | 6.3 | | |
| Preeclampsia (%) | 42% | | |
| Delivery < 34 wks | 23% | | |
| Delivery < 37 wks | 62% | | |

Effect of early antihypertensive treatment in pregnant women with microalbuminuria

| Cohort- year | 1995-99 | 2000-2003 | 2004-2006 |
|---|-----------------------|-------------------------------------|------------------------------------|
| AH- treatment protocol Methyldopa first choice | BP>140/95 AH-pause | U-alb>2000 BP>140/90 AH-shift | AH-shift U-alb>300 BP>135/85 |
| Number | 26 | 20 | |
| HbA1c at 28 wks (%) | 6.3 | | |
| Preeclampsia (%) | 42% | 20% | |
| Delivery < 34 wks | 23% | 0 | |
| Delivery < 37 wks | 62% | 40% | |

Effect of early antihypertensive treatment in pregnant women with microalbuminuria

| Cohort- year | 1995-99 | 2000-2003 | 2004-2006 |
|---|-----------------------|-------------------------------------|------------------------------------|
| AH- treatment protocol Methyldopa first choice | BP>140/95 AH-pause | U-alb>2000 BP>140/90 AH-shift | AH-shift U-alb>300 BP>135/85 |
| Number | 26 | 20 | 10 |
| HbA1c at 28 wks (%) | 6.3 | | 5.6 |
| Preeclampsia (%) | 42% | 20% | 0 |
| Delivery < 34 wks | 23% | 0 | 0 |
| Delivery < 37 wks | 62% | 40% | 20% |

Drugs compatible with breast-feeding



- Insulin
- Metformin
- Glyburide
- Glipizide
- Methyldopa
- Labetalol
- Dihydropyridine
- Aspirin
- Captopril, enalapril

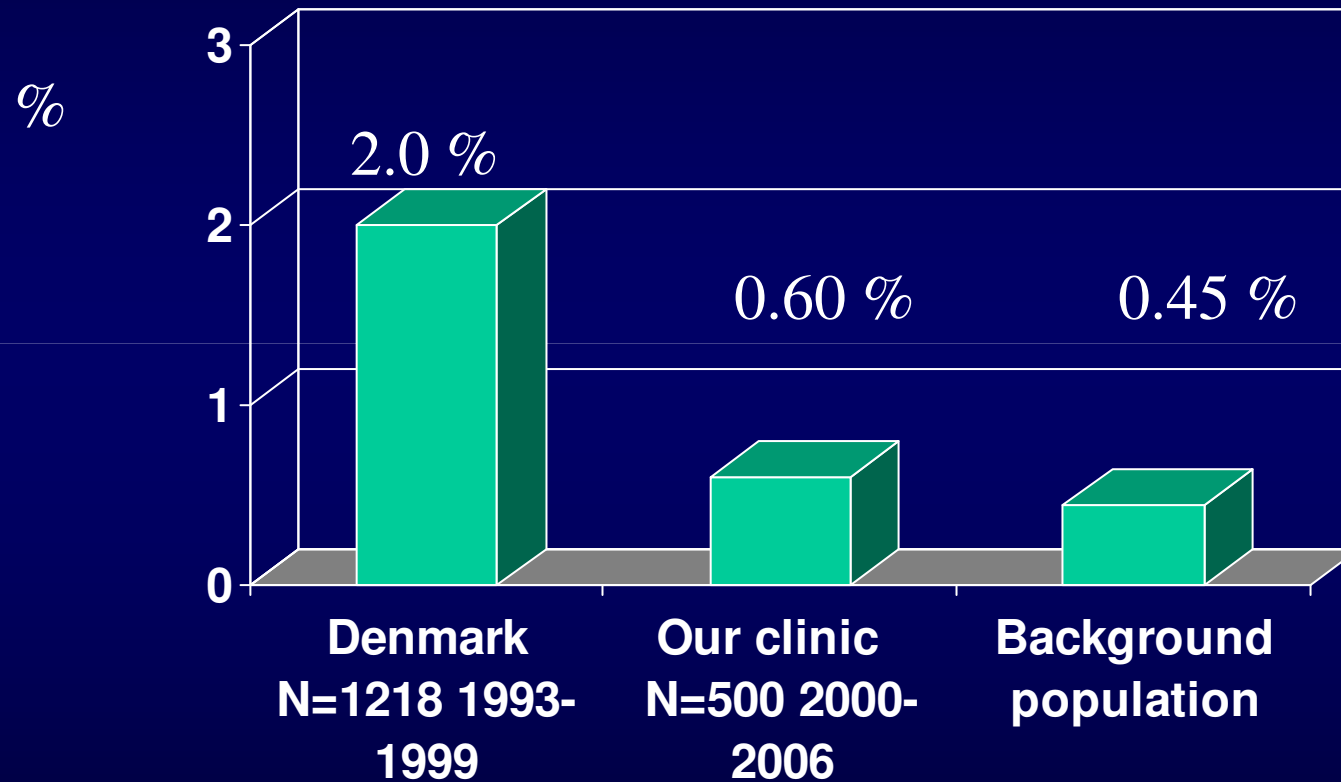


Prevention of poor outcome in diabetic pregnancy

- Strict metabolic control
 - Aim for
 - blood glucose 4-6 mmol/l preprandially and 4-8 mmol/l postprandially measured 7-8 times daily
 - HbA1c <5,6 % measured 1-2 times monthly
 - avoid severe hypoglycaemia.
 - self-adjustment of insulin treatment and frequent clinic visits.
 - Modern insulin treatment focusing on pre and postprandial blood glucose
- Early and strict treatment of micro- and macro-albuminuria with antihypertensive drugs.



Stillbirth in type 1 diabetes





Preterm delivery in type 1 DM



HbA1c: 6,3%

HbA1c: 5,9%

HbA1c: 5.0%

It is possible to obtain better outcome
within a short time period

We have to strive for better outcome
in diabetic pregnancies

Extra slides