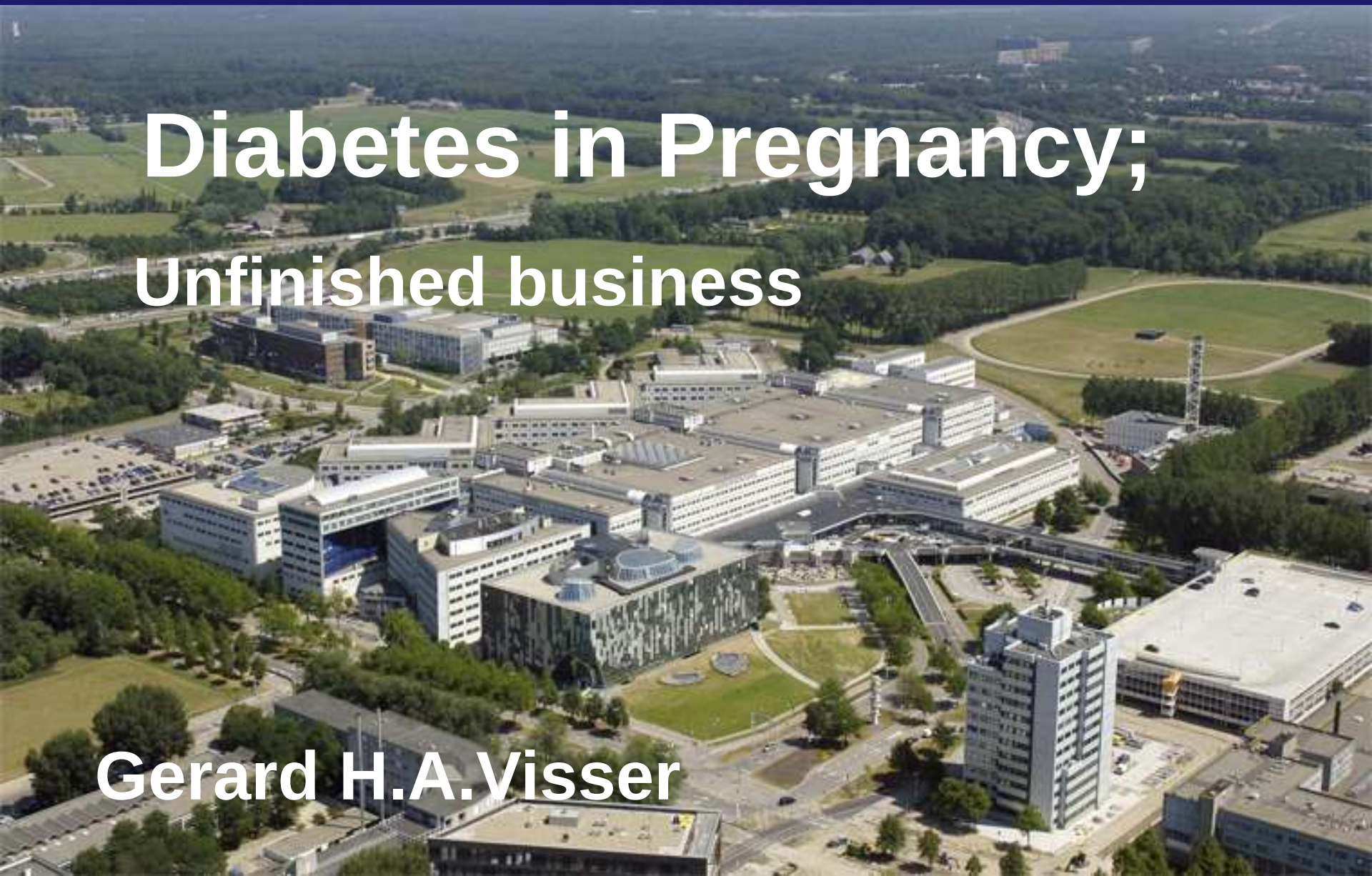
University Medical Center, Utrecht, the NL



Diabetes in Pregnancy;

Unfinished business

Gerard H.A.Visser

Managing Diabetes

Diabetes care has improved

- **various types of insulin**
- **administration (CSII, pen, multiple injections)**
- **self control**

Managing Diabetes

Diabetes care has improved

- **various types of insulin**
- **administration (CSII, pen, multiple injec**
- **self control**

With nowadays the possibility to measure glucose continuously

So,……

However,……..

- Real life does not always follows our logic

- Since ’near-normoglycaemia’ seems difficult to achieve
- And since- strangely enough- fetuses of women with diabetes grow nowadays bigger and bigger, despite……

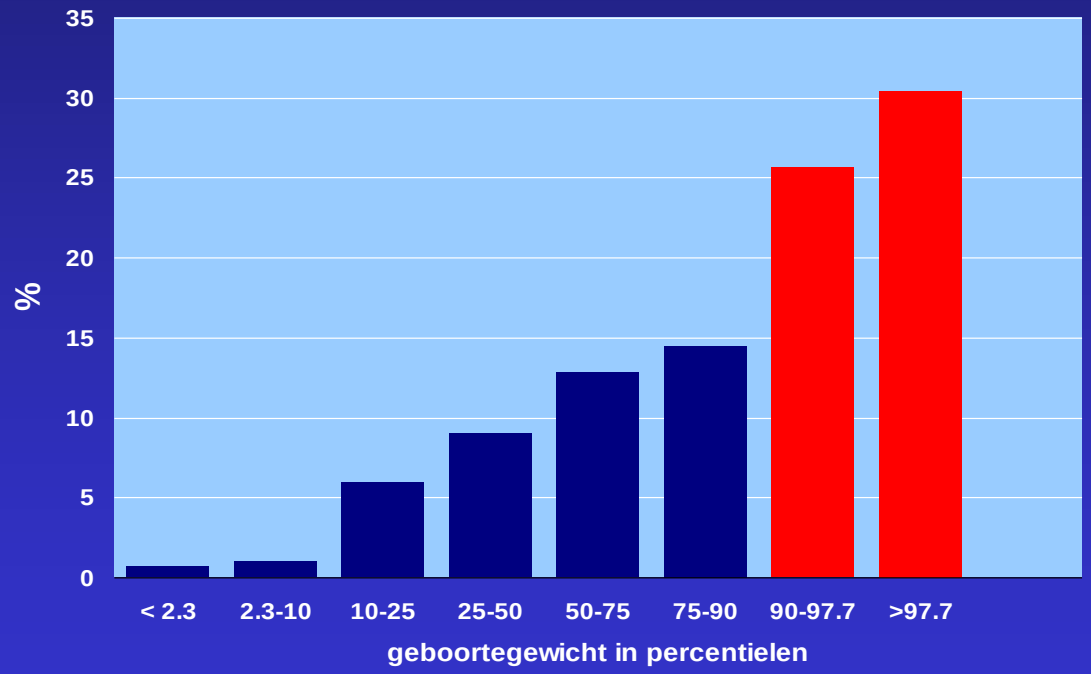

6940 g
3120 g

4480 g

36 weeks

Type-1 diabetes and Pregnancy in the NL

Birth weight centiles



(Evers et al, Diabetologia, 2002)

Birthweight > p 90 in type-1/2 diabetes

country	year	n	%
. UK	02-03	3809	51.7
. Scot.	98-99	289	55
. NL	99-00	323	56.1
. DK	93-99	1218	62.5

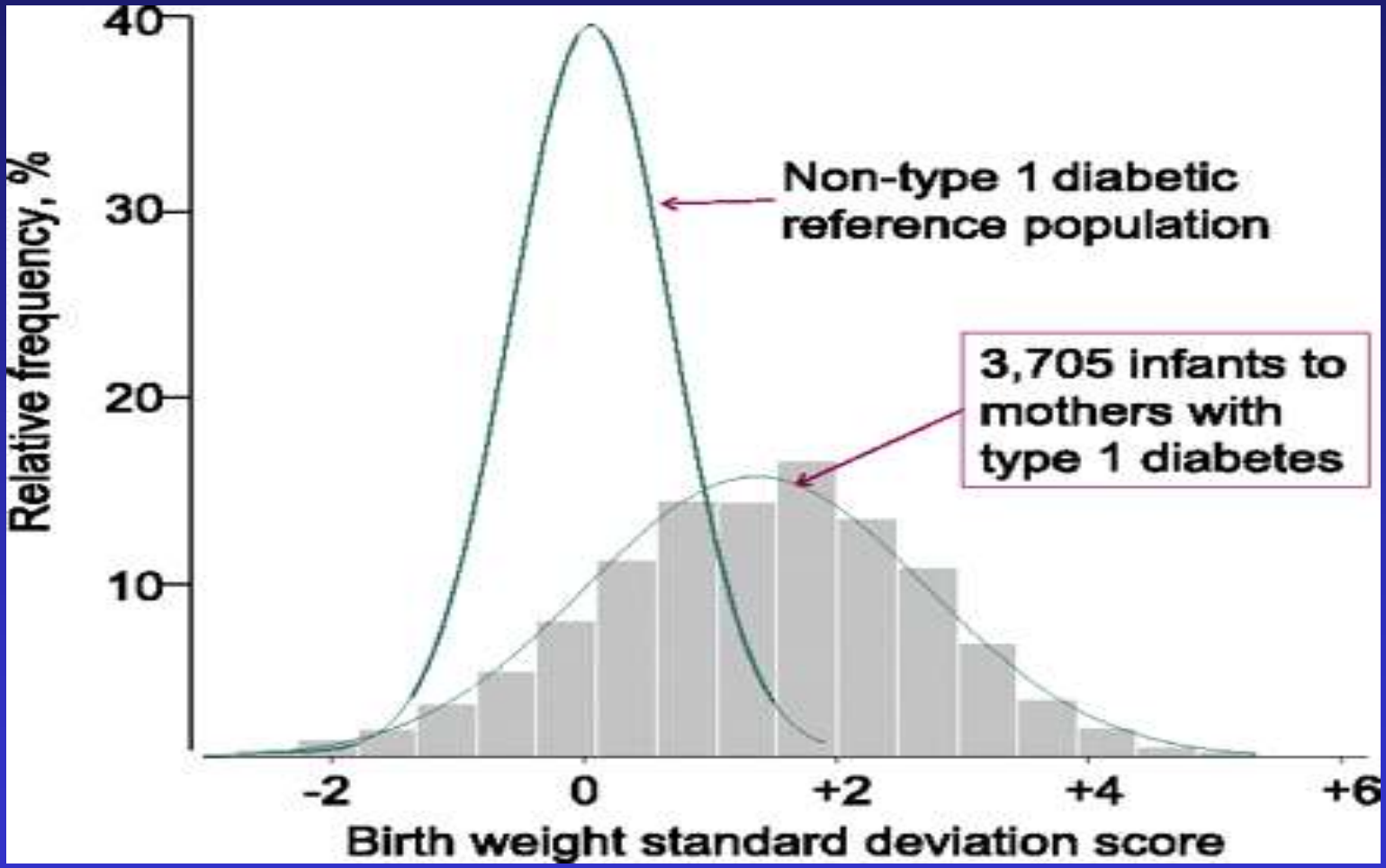
Type-1 diabetes and pregnancy

So, bigger babies with better regulation??

- **Sweden 1982 – 1985 20% > p 97.5**
- **Sweden 1991 – 2003 31% > p 97.5**

(Hanson & Persson, 1993; Persson et al. Diab Care, 2009; n=5.089; Persson et al,Diab Care,2011; n=3.705)

Birth weight distribution



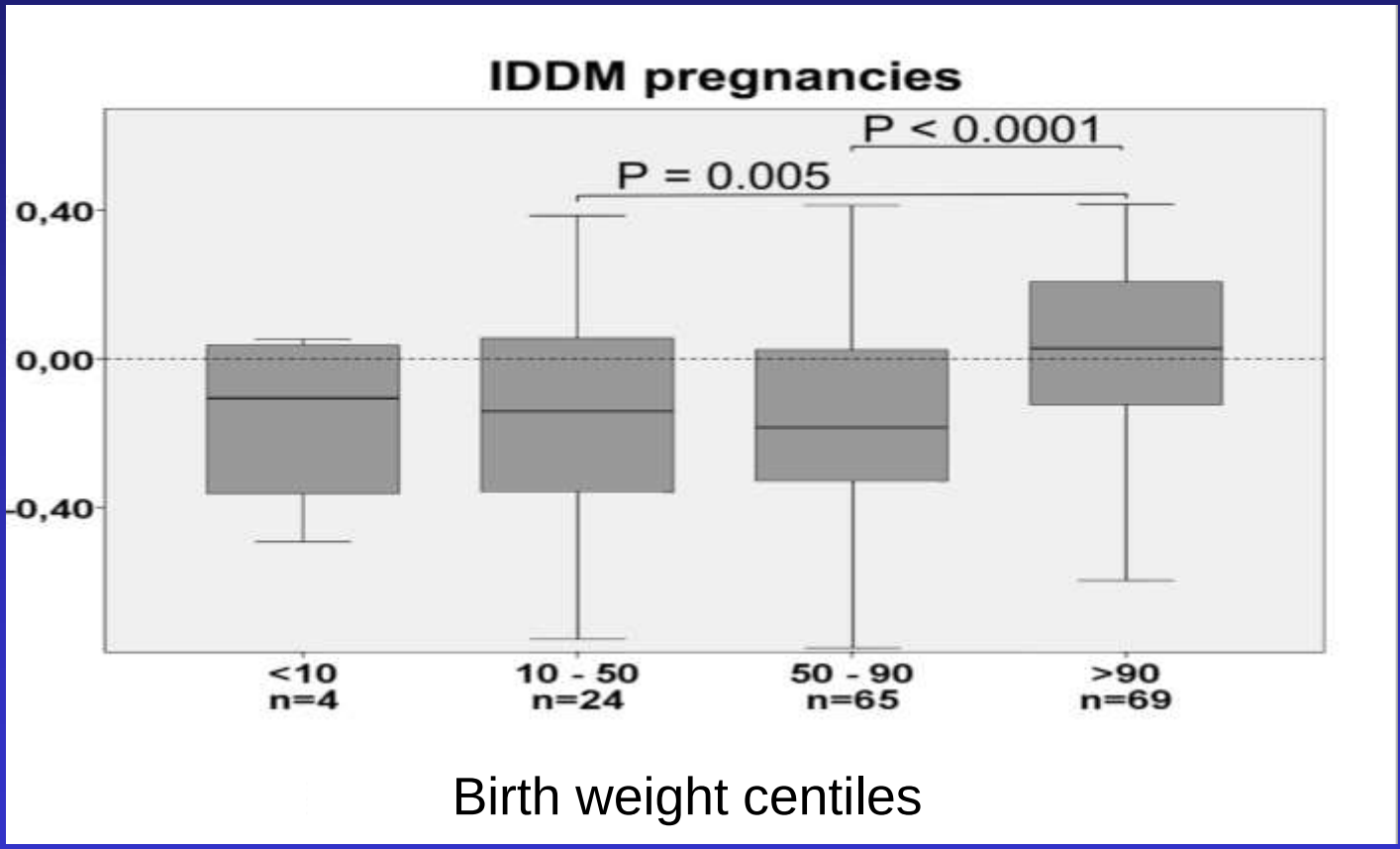
Persson et al. Diab Care 2011;34:1145-1149

Increase in fetal macrosomia

- Increase in maternal obesity
- Better control in early pregnancy, better placentation?
- Lower incidence maternal vascular complications?
- Poorer control, since women are not admitted to hospital anymore?

Early placental function and birth weight centiles

Log MOM PAPP-A



Kuc et al, BJOG 2011;118:748-754

data similar for ADAM 12, PP13 and PlGF

So,……. in women with PGDM

poor placentation	normal placentation
↓	↓
normal birthweight	increased birthweight

So,……. in women with PGDM

poor placentation	normal placentation
↓	↓
normal birthweight	increased birthweight

In other words, fetal overgrowth due to overexposure to glucose, in both instances

Type-1 diabetes and PAPP-A

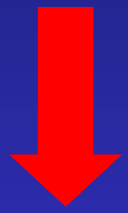
	control	type-1 diabetes
• n	36.415	331
• PAPP-A (Mom)	1.01	0.86
• Free B-hcg	0.99	0.98

Significant inverse relation between HbA1c and PAPP-A

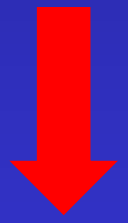
Madsen et al, Acta Ob Gyn Scan 2011, June 15 (Epub ahead of print)

And that closes the circle……

Better periconceptional glucose control,



better placentation,



bigger babies

And that closes the circle……

Better periconceptional glu

Improved care, poorer outcome

bigger babies

Fetal Macrosomia

Correlated to 1st, 2nd and 3rd trimester HbA1c,

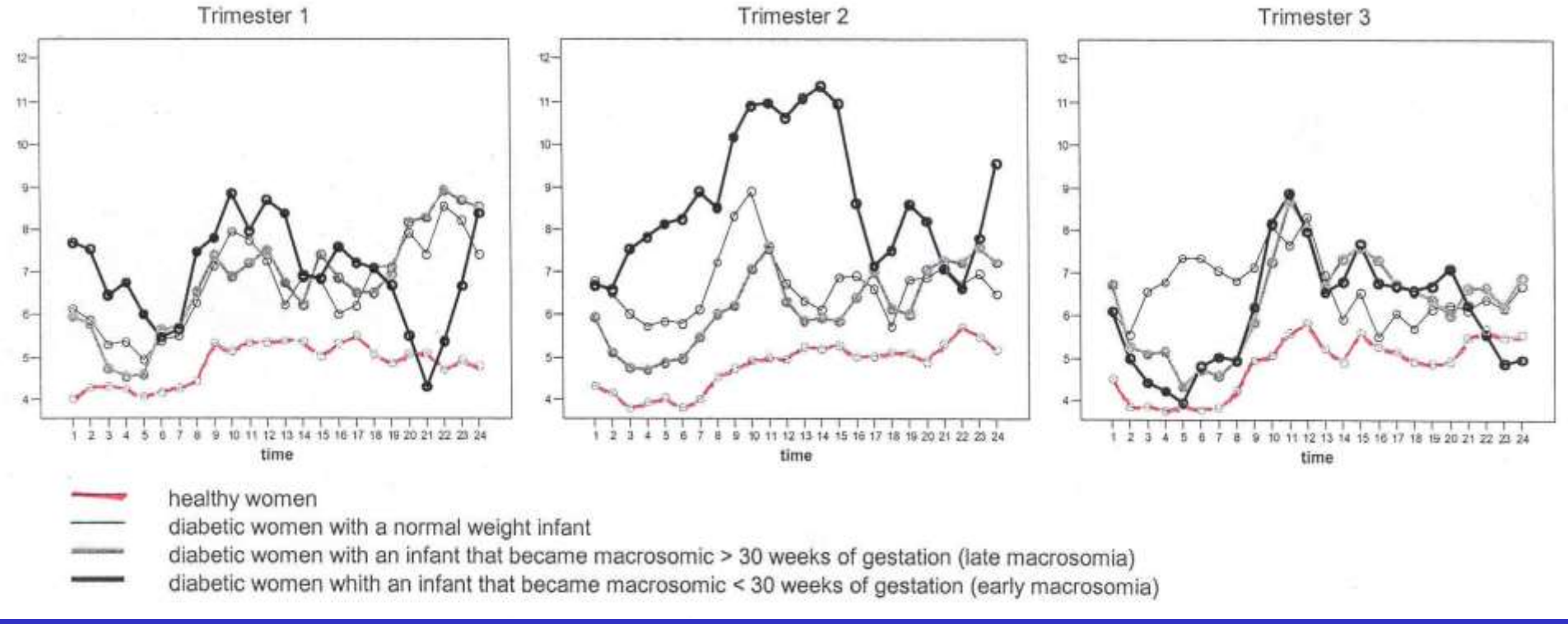
and to overall mean HbA1c (46 versus 42 mmol/l)

But, variance in weight explained by HbA1c & maternal BMI is limited (<10%)

HbA1c is a too insensitive measure of glucose regulation during pregnancy

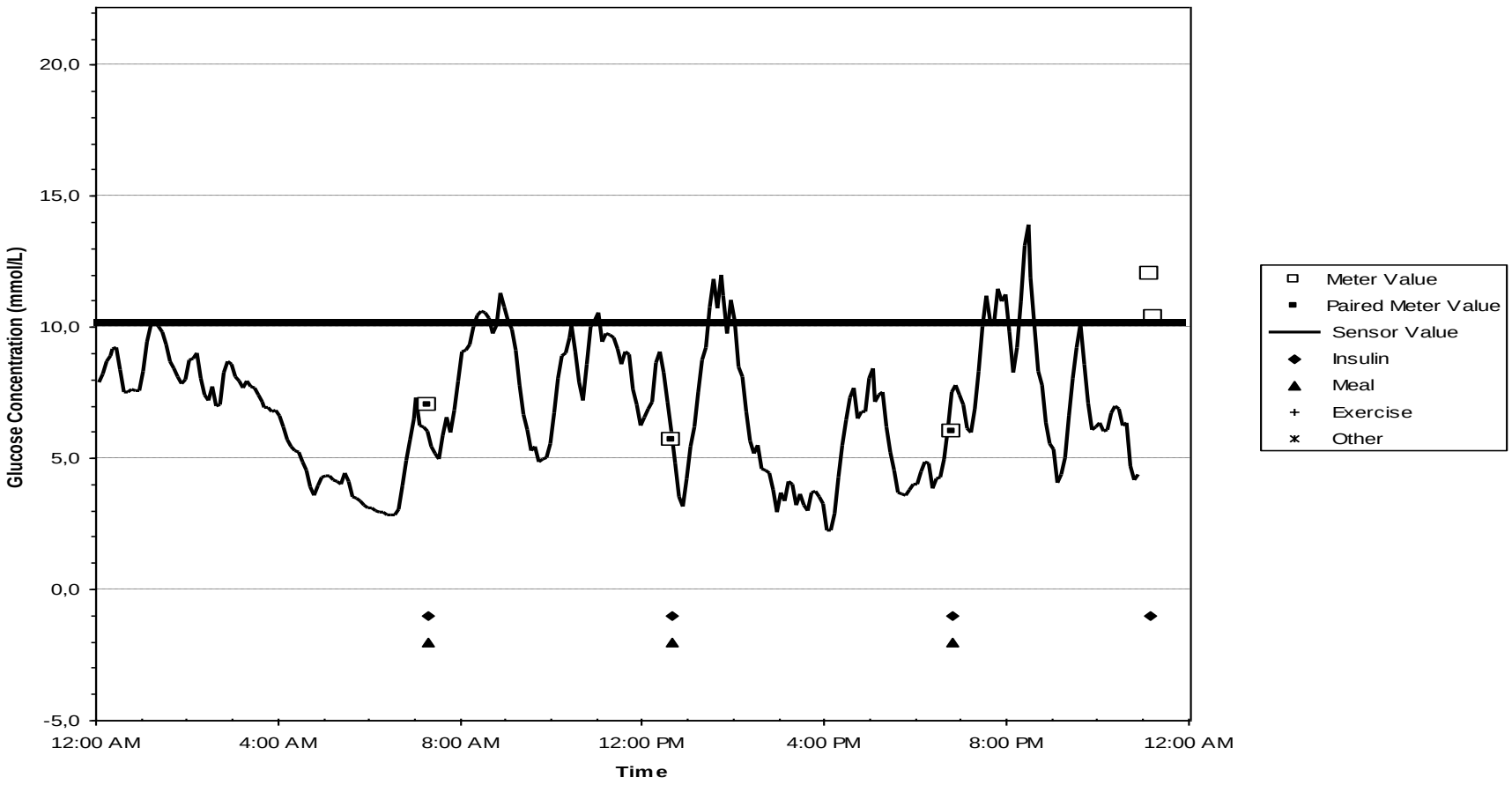
(Evers et al, Diabetologia, 2002)

Continuous glucose profiles during pregnancy



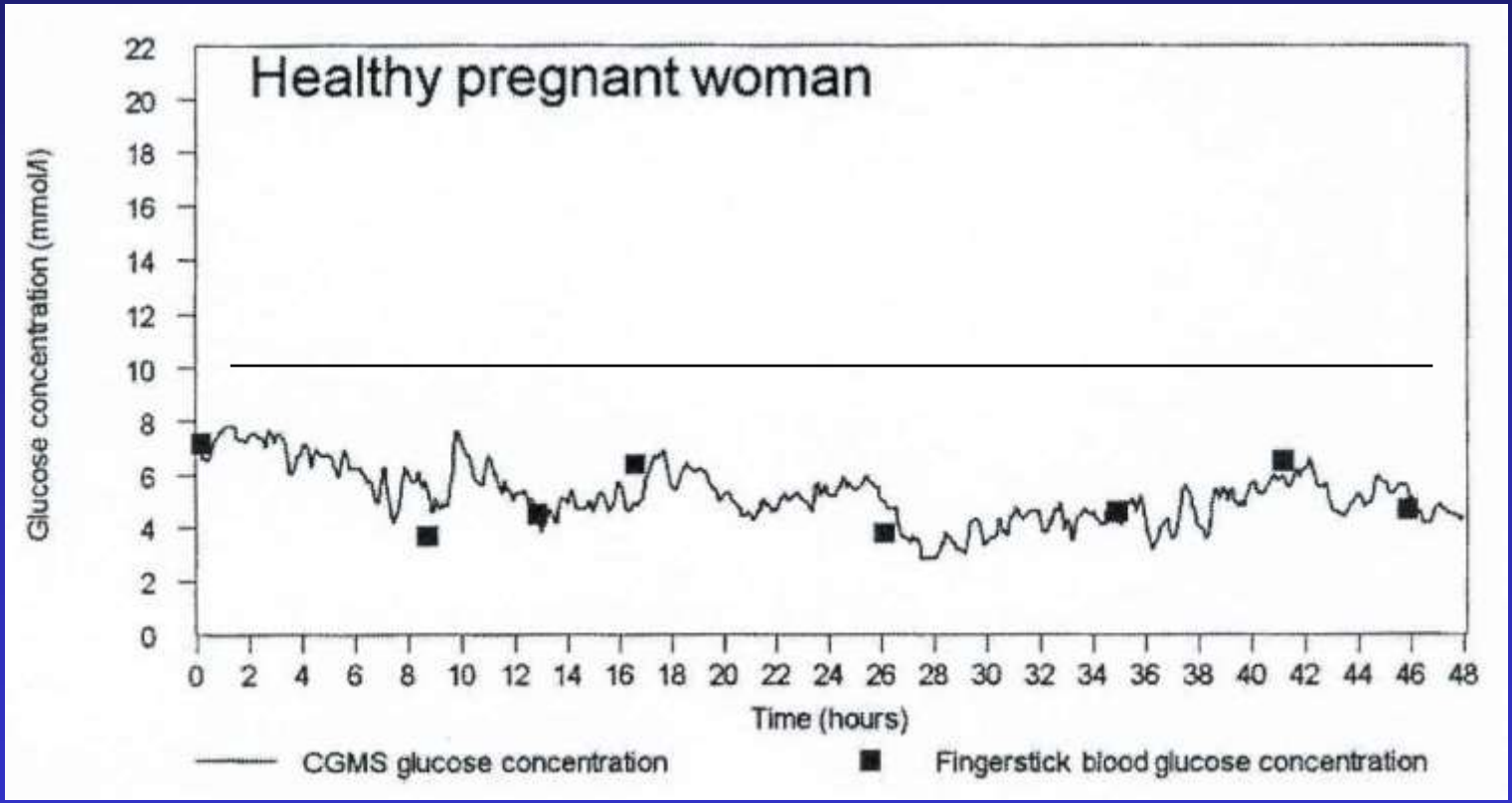
(type-1 diabetes, n = 46; controls n = 12; Kerssen et al. Diab Care,2007)

G_1P_0, 31 y, DM type 1, GA 9 1/7 weeks
HbA_{1c} 42 mmol/l (=6% or 2SD)



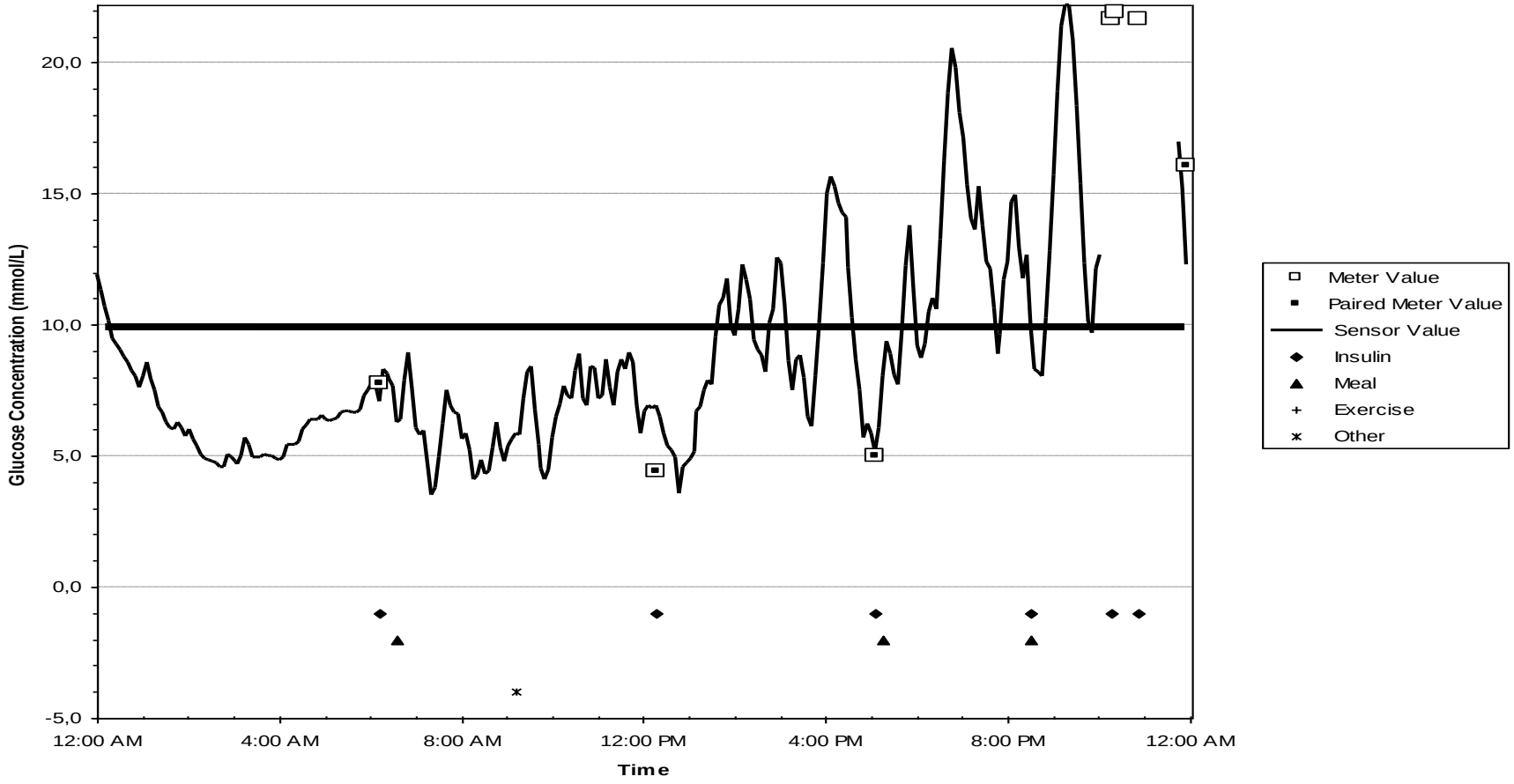
(Kerssen et al, 2003)

Continuous glucose profile, 10 weeks' gestation



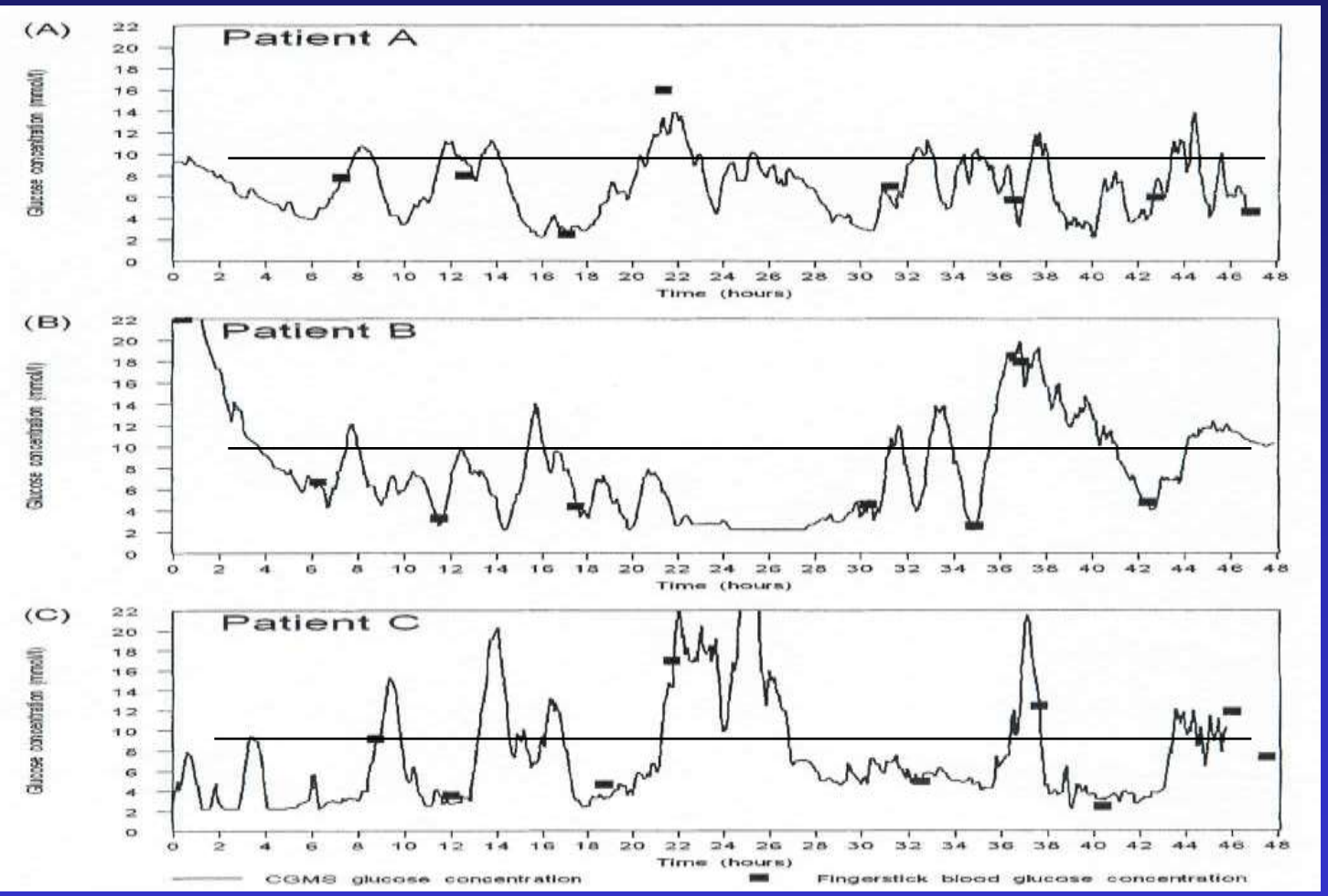
(Kerssen et al, Pren Diagn, 2006)

G_2P_1, 29 y, DM type 1, GA 10 2/7 weeks
HbA_{1c} 50 mmol/l (=6.7%)



(Kerssen et al, 2003)

Continuous glucose profiles; abnormal infants



9 wks,HA1c 42, mild caudal regression,deviated position of hands, extra ear

10 wks,HbA1c 49 bilateral club foot

11 wks,HbA1c 61 unilateral atrophic kidney

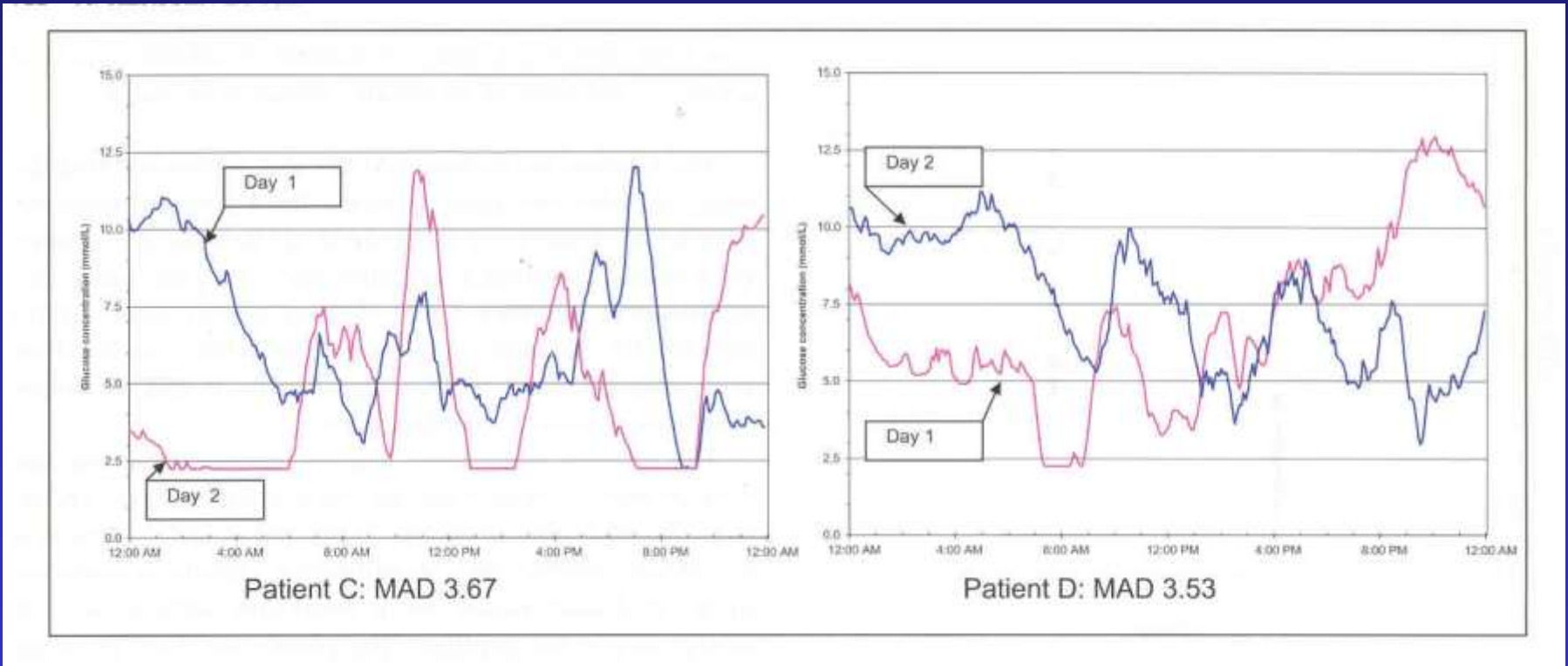
(Kerssen et al, Pren Diagn, 2006)

Near Normoglycaemia???

Near Normoglycaemia???

- **NO……..,** not at all
- The struggle towards adequate glucose control has only just begun

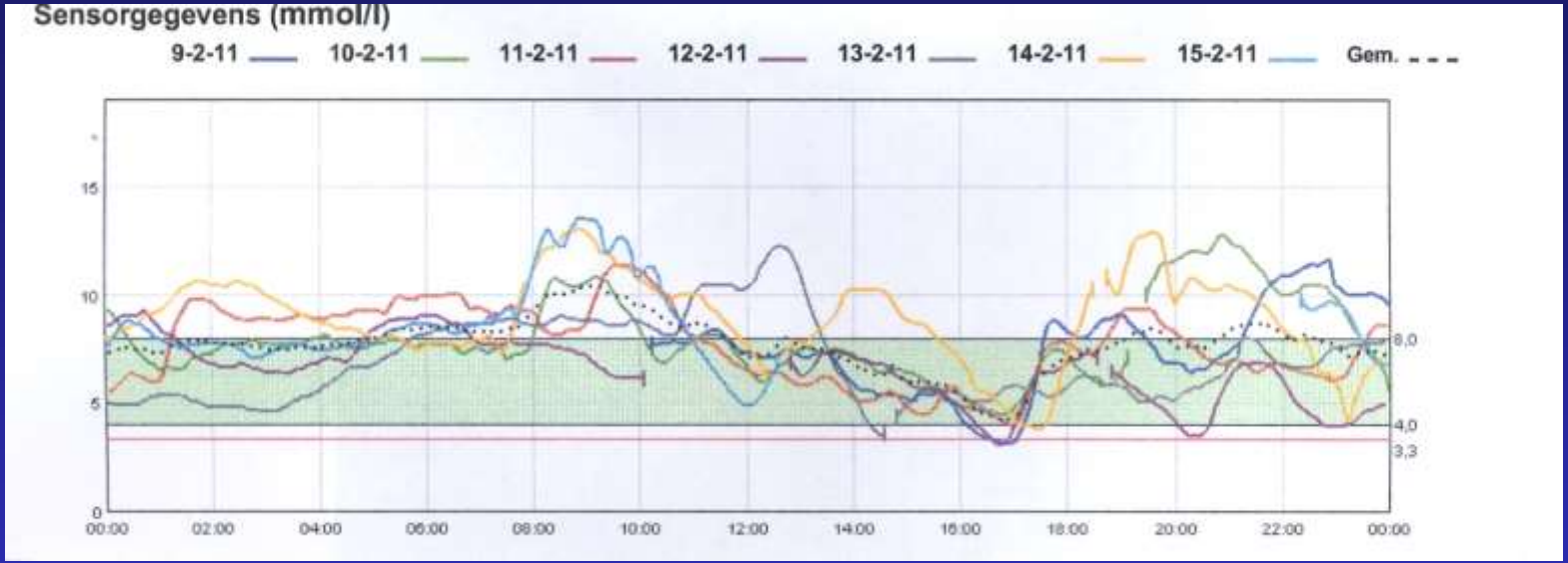
Two-day continuous glucose profiles



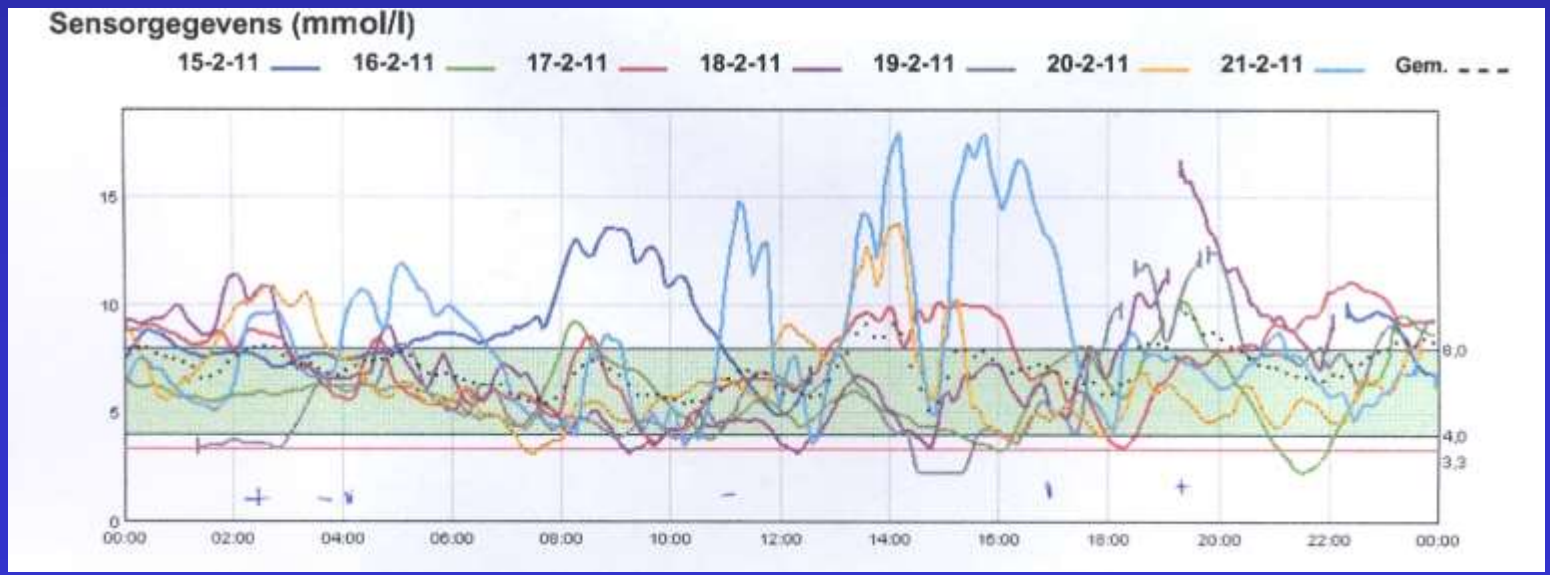
(Kerssen et al, BJOG, 2004)

Type-1 diabetes, 32 y, 1.88 m, 88 kg, CSII, HbA1c 9 wks 56 mmol/l, Continuous glucose sensor since 12 wks

19 wks

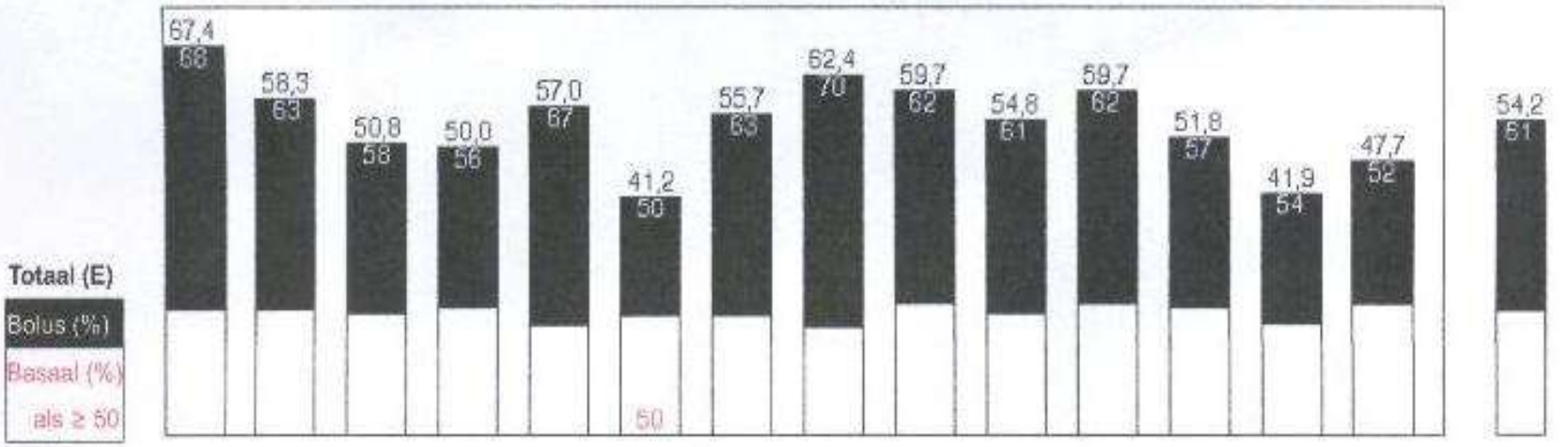


20 wks



Type-1 diabetes, 32 y, 1.88 m, 88 kg, CSII, HbA1c 9 wks 56 mmol/l, Continuous glucose sensor since 12 wks

Insulin (units):



	ma 14-feb	di 15-feb	wo 16-feb	do 17-feb	vr 18-feb	za 19-feb	zo 20-feb	ma 21-feb	di 22-feb	wo 23-feb	do 24-feb	vr 25-feb	za 26-feb	zo 27-feb	Gemiddelde of totaal
Insulinetotaal	67,4	58,3	50,8	50	57	41,2	55,7	62,4	59,7	54,8	59,7	51,8	41,9	47,7	54,2
Basale insuline	21,9	21,8	21,3	22	19	20,7	20,7	18,9	22,7	21,3	22,7	22,3	19,4	22,7	21,3
Bolusinsuline	45,5	36,5	29,5	28	38	20,5	35	43,5	37	33,5	37	29,5	22,5	25	32,9
Aantal bolussen	17	13	11	10	12	5	13	14	12	10	13	8	10	8	11,1
Gem. bolus	2,7	2,8	2,7	2,8	3,2	4,1	2,7	3,1	3,1	3,4	2,8	3,7	2,2	3,1	3
Vulvolume	15,9	0,5			14,3			0,5		14,6					9,2

Near Normoglycaemia???

- The struggle towards adequate glucose control has only just begun
- And……will be difficult

Type 1 & 2 diabetes in the Netherland

Nationwide study	Type 1	type 2
Type-1 yr 2000	UMC Utrecht	7 large clin in NL

- n 323
- Cong malf 8.3%
- CS 44 %
- LGA 56%
- PNM 2.8%

Evers et al BMJ,2004;

Type 1 & 2 diabetes in the Netherlands

	Nationwide study Type-1 yr 2000	Type 1 UMC Utrecht	type 2 7 large clin in NL
• n	323	185	
• Cong malf	8.3%	8.2%	
• CS	44 %	66 %	
• LGA	56%	40 %	
• PNM	2.8%	1.1%	

Evers et al BMJ,2004; Hoeks et al in prep;

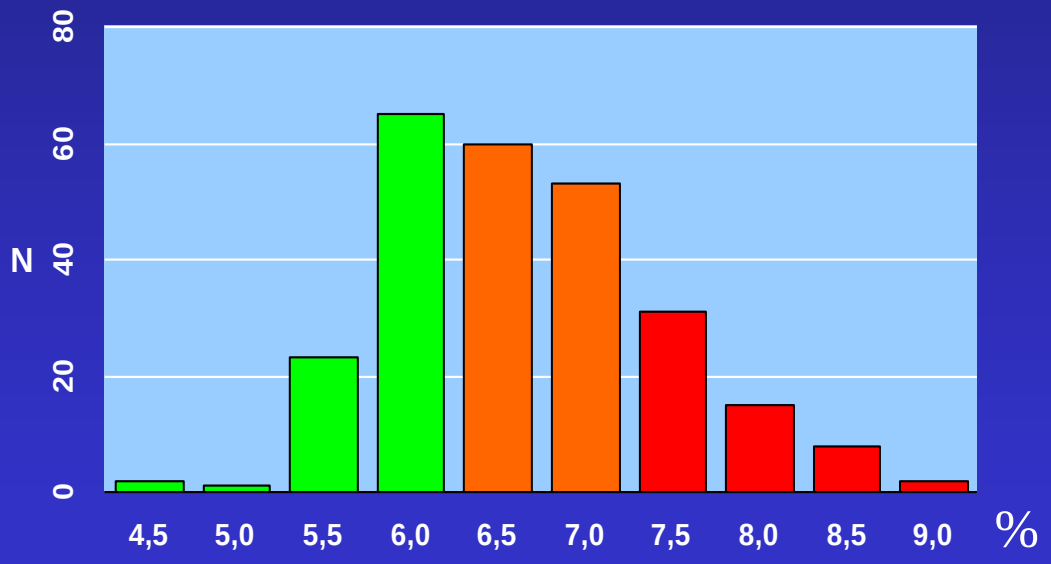
Type 1 & 2 diabetes in the Netherland

	Nationwide study Type-1 yr 2000	Type 1 UMC Utrecht	type 2 7 large clin in NL
• n	323	185	272
• Cong afw	8.3%	8.2%	7.1%
• SC	44 %	66 %	41 %
• LGA	56%	40 %	32 %
• PNM	2.8%	1.1%	4.8%

Evers et al BMJ,2004; Hoeks et al in prep; Groen et al, submitted

Type-1 diabetes and Pregnancy in the NL; n=323

	UK	DK
•84% planned pregnancy	38%	58%
• 70% preconceptional start of folic acid	43%	
• 72% HbA1c < 53 mmol/l (<7% or 4SD)	38%	



(Evers et al, BMJ, 2004)

Type-1 diabetes and Pregnancy in the NL

The price to pay for tight glycemic control:

a two-to threefold increase in severe hypoglycemic epidoses, involving 41% of patients, with hypoglycemic coma in 19% during the first trimester

(based on 278 questionnaires; Evers et al, Diabetes Care 2002;25:554)

Type-1 diabetes and Pregnancy in the NL

The price to pay for tight glycemic control:

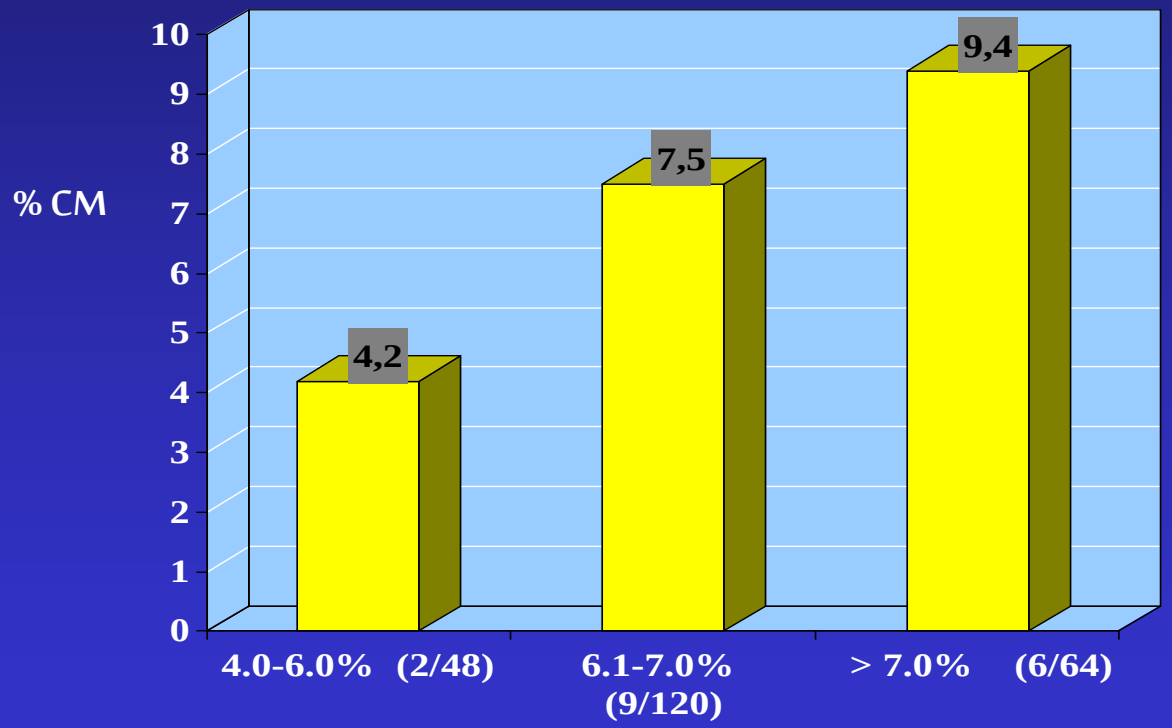
a two-to threefold increase in severe hypoglycemic epidoses, involving 41% of patients, with hypoglycemic coma in 19% during the first trimester

With maternal death in 1 of 200 to 500 pregnancies

(based on 278 questionnaires; Evers et al, Diabetes Care 2002;25:554)

Type-1 diabetes and Pregnancy in the NL

Congenital malformations and HbA1c



(Evers et al, BMJ, 2004)

Type-1 diabetes and Pregnancy in the NL

Congenital malformations and HbA1c

Almost good is not good enough

(Evers et al, BMJ, 2004)

Almost good is not good enough

A HbA1c < 53mmol/l (< 4SD), is too high for the fetus and too low for the mother

Management (=glucose control)

- Preconception: folic acid
- First trimester: prevention hypoglycemia, congenital malformations?
- Second/third: fetal growth assessment
- Delivery: low risk: around 39 weeks

  others: -fetal weight = 4000g

  -poor glucose control

. Caesarean Section: fetal weight > 4-4.5 kg

Shoulder dystocia and birth weight

birth weight (g)	non diabetic (%)	diabetic (%)
2500-3750	0.2	0.5
3750-4000	1.0	1.2
4000-4250	2.6	3.0
4250-4500	5.0	6.9
4500-4750	7.5	21.8
>4750	13.0	37.0

UK 2002-2003

- 4.7%
- 22%
- 25%
- 43%

(Langer et al, 1991: Texas 1970-1985; 74.390 non diab.+ 1589 diabetics)

(UK, CEMACH, n=3423)

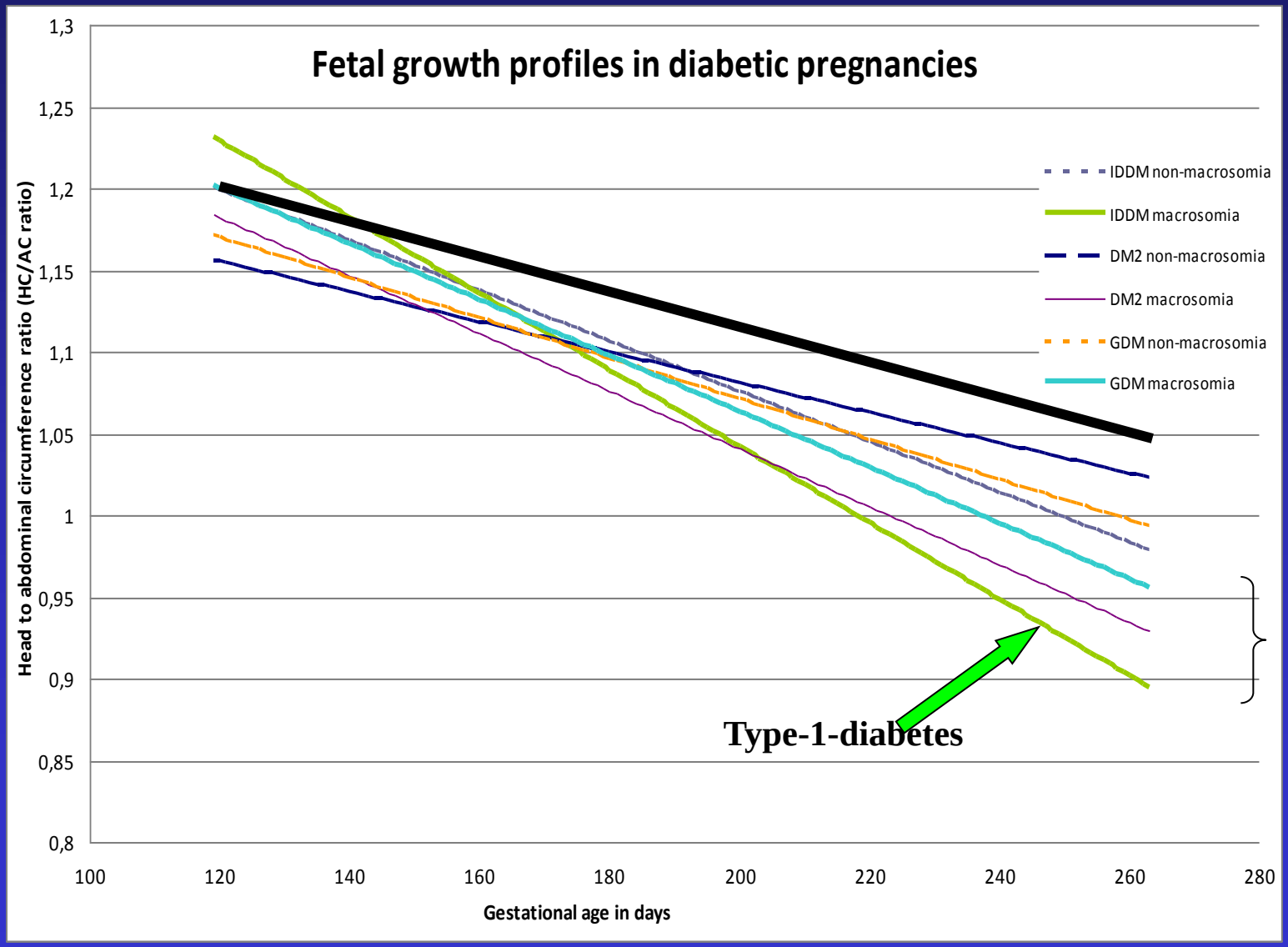
Shoulder dystocia and birth weight; NL

birth weight	N	Vag.(n)	Shoulder dystocia	Clavicle fracture	Erb's palsy	%
< 3000	69	32	-	-	-	0
3000-3500	79	52	2	-	-	4
3500-4000	96	56	8	1	-	14
4000-4500	58	30	9	1	-	30
≥ 4500	22	9	6	2	1	66
total	324	179(56%)	25(14%)	4	1	

(Evers, 2002)


they have a large head,
but the shoulders are even bigger

Fetal growth profiles in diabetic pregnancies Head to abdomen circumf. ratio(N. Hammoud et al, UOG 2012 inpress)



Birthweight>90th cent

Shoulder dystocia

- Overall perinatal mortality 1.2%, which may increase to up to 6.2% if the mother has diabetes (population study, Christoffersson & Rydhstroem,2002)
- 56 cases of stillbirth as a direct consequence of shoulder dystocia (mean interval delivery head-rest of the body only 5 min; UK Conf Enq into Stillbirths and Deaths 1994-6)

So,

- Consider to do a CS in case fetal weight > 4.000-4.250 g, depending on maternal size and wish

And what about fetal weight estimation?

Ultrasound fetal weight estimation

- **Less accurate for large fetuses**
- **Less accurate at term than at 34-37 wks**

(Best, 2002; Ben-Haroush, 2004; Mongelli, 2005)

Birth weight prediction at 34-37 weeks

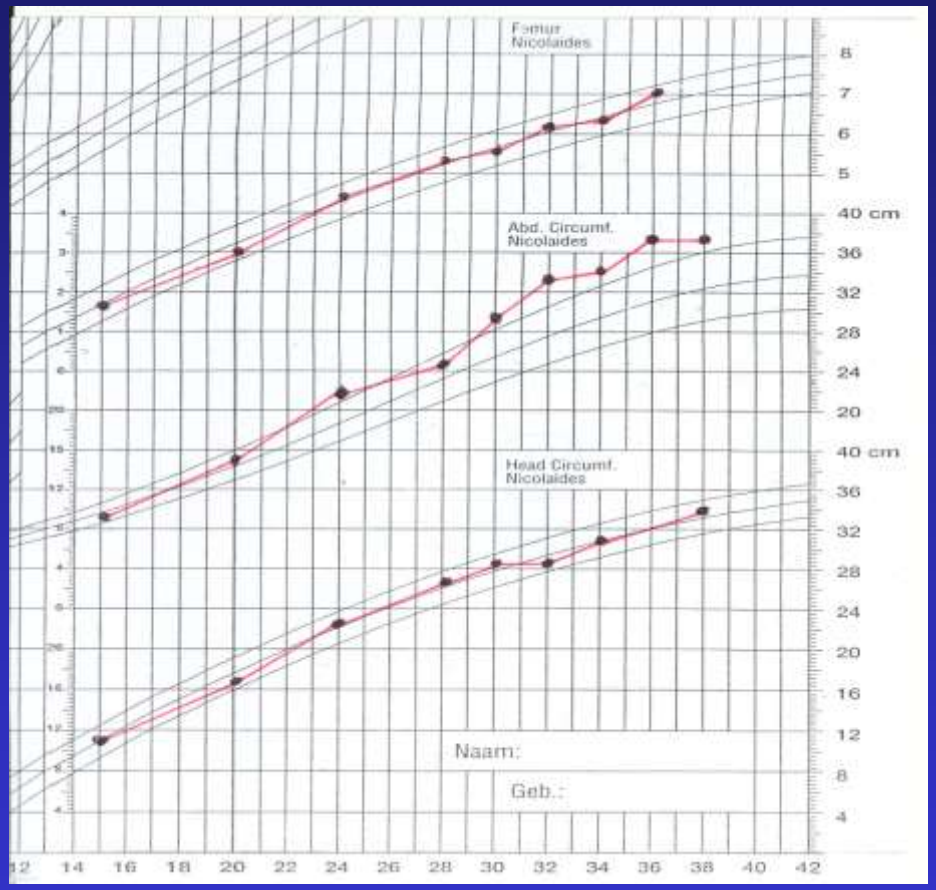
ERROR (%)	Diabetes (n=133)	Control (n=1690)
± 5	47%	42%
± 10	71%	70%
± 15	91%	87%
(mean absolute error	6.8%	10.1%)

(Best & Pressman, 2002)

Moreover……..

- Big babies have an early growth acceleration from 18 weeks onwards
  (Wong et al, Diab Care,2002)
- And all infants with a birth weight> p 97.7 can be identified before 30 wks gestation, by longitudinal growth assessment
  (Kerssen et al, Diab Care, 2007)

So, monitor growth longitudinally



to assess fetal weight reliably

So,

- Consider to do a CS in case fetal weight > 4.000-4.250 g, depending on maternal size and wish
- Preterm CS, determine fetal lung maturation or give steroids (beware of glucose dysregulation)

So,

- Consider to do a CS in case fetal weight > 4.000-4.250 g, depending on maternal size and wish
- Preterm CS, determine fetal lung maturation or give steroids (beware of glucose disregulation)
- And induce all the others at 38 wks?

Diabetes
RCT induction (38 wks)-expectant management

n=200: **- Insulin dependent (pre) gestational diabetes (Low risk)**

	Induction	Expectant
CS	25%	31%
LGA (>4000g)	10%	23%
Shoulder dystocia	0%	3%

(Kjos et al, Am J O&G, 1993. Induction at 38 weeks)


Thank you