UNIVERSITY OF CAMBRIDGE

What's New in the Management of Diabetes in Pregnancy

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First EARDIP Audit 1999-04

n = 535 pregnancies

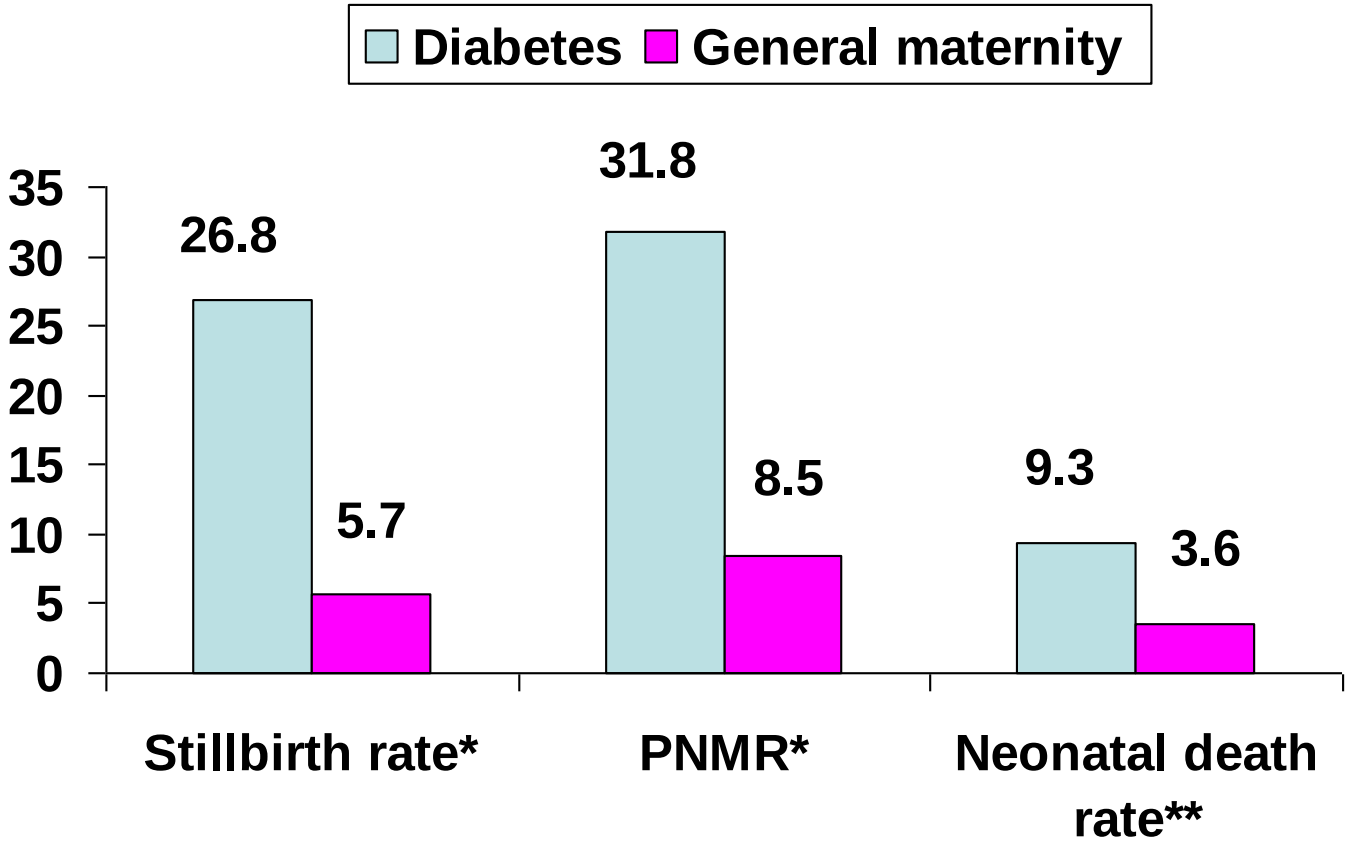
	T1DM (n=389)	T2DM (n=146)	p value
Age – mean	29.8	33.9	<0.0001
Ethnic origin			
Caucasian	96%	59%	
Asian	2%	29%	<0.0001
Other	0.5%	11%	
BMI	26.4	34.2	<0.0001
Smoker	21%	15%	0.13
“Preconception care”	41%	29%	0.02
Folic acid	36%	22%	0.001

EARDIP 1999-2004 pregnancy outcomes

	T1DM (n=389)	T2DM (n=146)	p value
Congenital malform	17 (4.4%)	18 (12.3%)	<0.02
Perinatal mortality	11 (2.8%)	9 (6.2%)	NS
Serious adverse outcome	25 (6.4%)	24 (16.4%)	0.002
Birth weight			
SGA < 10th	3.6%	9.6%	<0.02
LGA 90th	46.5%	46.9%	NS

Roland J et al, 2005

CEMACH adverse outcomes 2002-2003 n=2,359 pregnancies

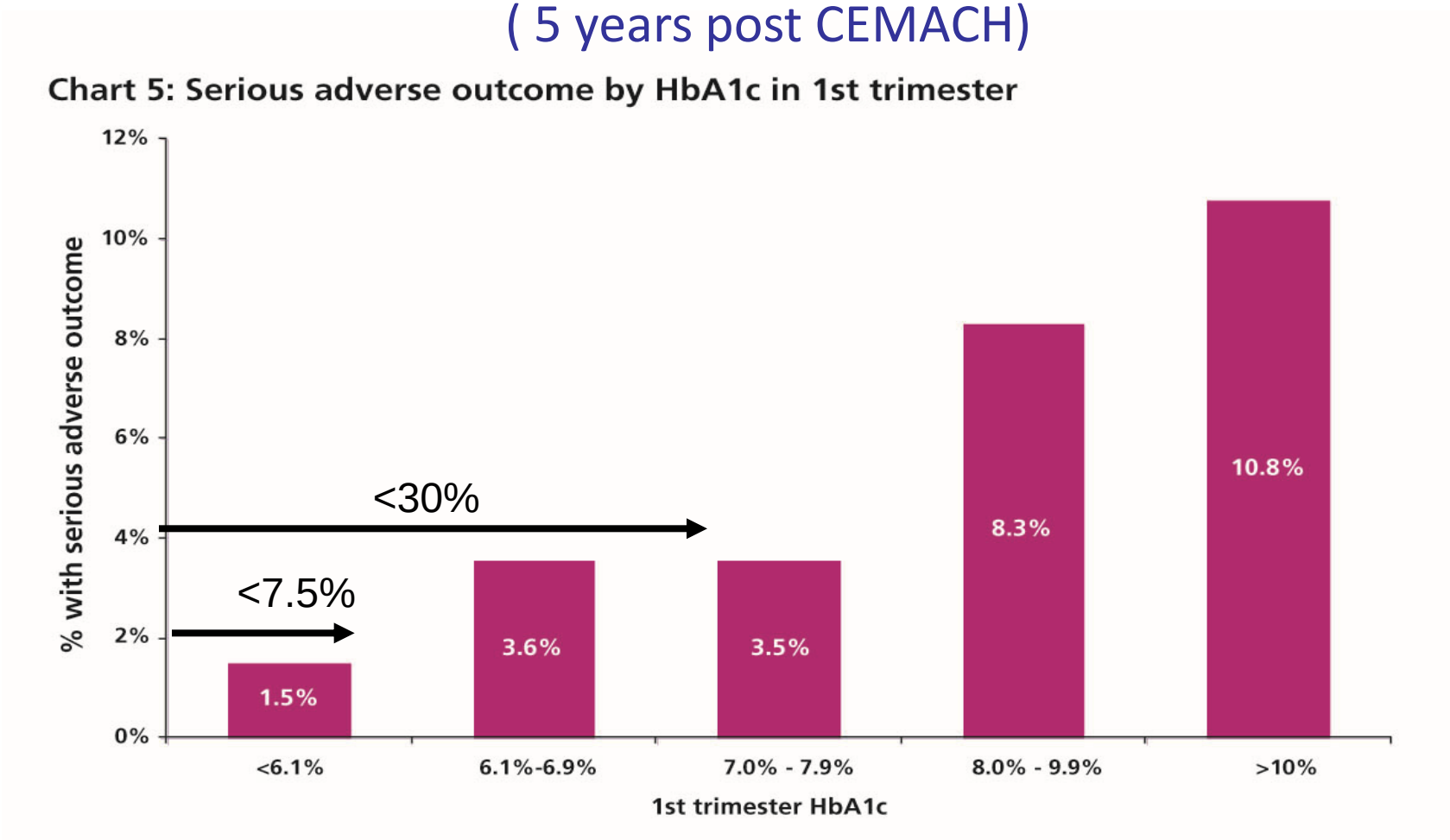


Similar outcomes Netherlands, Denmark, Sweden, Norway

Macintosh M 2006, Evers IM 2004, Persson M 2009

Serious adverse pregnancy outcomes

N= 1,381 UK pregnancies NE, NW & EA during 2007-2008
(5 years post CEMACH)



OR 1.38, 95% CI 1.21-1.57; p<0.0005

Holman et al Diab Med 2011

EASIPOD Patient Information Leaflet

Why have we sent you this?

Most women with diabetes have normal pregnancies resulting in healthy babies but having diabetes does increase the chances of serious complications both for the mother and baby. For women with diabetes, who do not plan their pregnancy, the risk of a serious complication is about 1 in 10. That is they have a stillbirth or an infant with a malformation.

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For women without diabetes about 1 in 50 have a serious complication when they get pregnant.

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If you plan your pregnancy with your diabetes team, your risk of serious complications returns to much nearer that of women without diabetes.

Most of the damage is done very early (first six to seven weeks) in pregnancy, so it is important to get advice about preventing these complications if you are thinking about having a baby i.e. before you stop your contraception to become pregnant

What are the risk factors for serious complications during pregnancy in women with diabetes?

1. Your pregnancy was not planned with your diabetes team
2. Blood glucose levels higher than is healthy for your baby in the first six to seven weeks of pregnancy
3. Not starting 5mgs of folic acid daily when you stop your contraception (this is higher than the usual 400µg dose recommended for women without diabetes)
4. Taking medication, other than insulin, for your diabetes. This includes some tablets taken for blood sugar control, blood pressure (ACE inhibitors) and cholesterol (statins)
5. Smoking yourself, or passively from other people you live with
6. Being overweight before pregnancy
7. If you are not immune to Rubella

If any of these risk factors are true for you, then if you even start thinking about having a baby, please contact your GP or diabetes care team. They can help you reduce your risks of serious pregnancy complications

How You Can Plan Your Pregnancy?

1. See your GP as soon as you even start thinking about having a baby
2. Make an appointment with your diabetes team, if you are thinking about having a baby within the next 12 months. They will review your diabetes treatment, as you may want to change it to get the best possible control you can manage, before stopping contraception
3. Ask your GP to review all your medications especially tablets for blood sugar control, blood pressure and cholesterol
4. Ask your GP for folic acid 5mgs daily
5. Start monitoring your blood glucose levels at least 4 times daily
6. Stop smoking or discuss this with the people you live with
7. Ask for support on food choices to provide you and your baby with the best start
8. Ask if you have been vaccinated against Rubella

Effects of PPC on pregnancy preparation

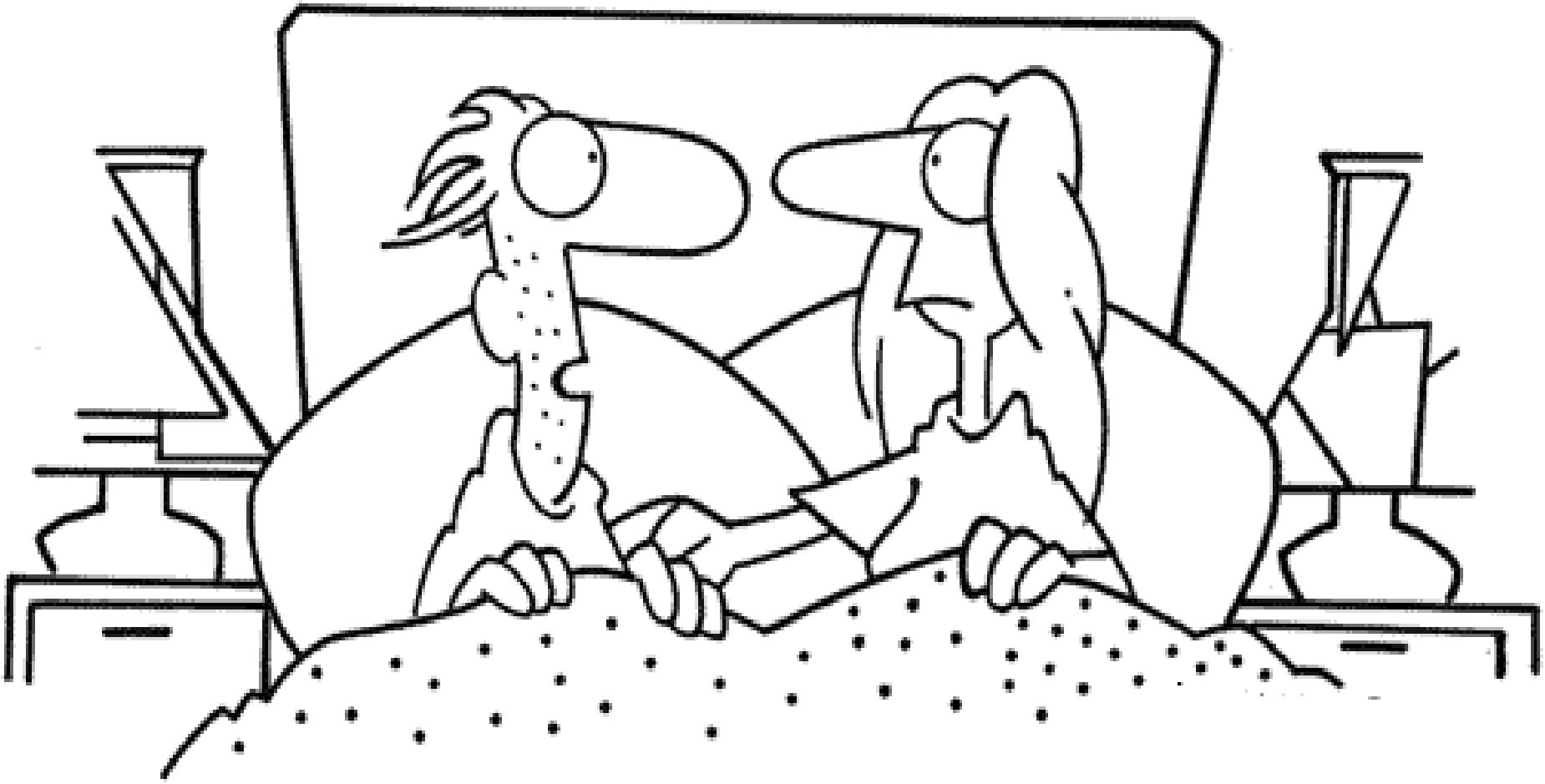
	PPC (n=181)	No PPC (n=499)	P
Planned	91%	37.5%	<0.0001
Precon counselling	83%	32%	<0.0001
EASIPOD leaflet	43%	15%	<0.0001
Folic acid	88%	27%	<0.0001
ACE	2 (1%)	23 (5%)	0.05
Statin	0	38 (7.6%)	0.0003
Booking gestation	6.7 (4.4 -10)	7.7 (5.1-15)	<0.0001

Murphy HR et al, 2010

Effects of PPC on glycaemic control

	PPC (n=181)	No PPC (n=499)	P
Pre-pregnancy	7.2 (6.0-8.8)	8.1 (6.1-11.7)	<0.0001
HbA1c (1st trimester)	6.9 (5.8-8.4)	7.4 (6.0-9.7)	<0.0001
HbA1c (2nd trimester)	6.4 (5.4-7.4)	6.5 (5.5-8.2)	0.001
HbA1c (3rd trimester)	6.4 (5.5-7.5)	6.5 (5.3-7.9)	0.05
Booking HbA1c ≤ 7%	53%	38%	<0.0001
HbA1c <6.1%*	17.8%	10.4%	<0.0001

* **17.8% PPC (10.9%T1D, 32% T2D) vs. 10.4% (5.1% T1D, 16.5% T2D) (p=0.05)**



"Let's try getting up every night at 2:00 AM to feed the cat. If we enjoy doing that, then we can talk about having a baby."

Comparisons with 1999-2004 audit

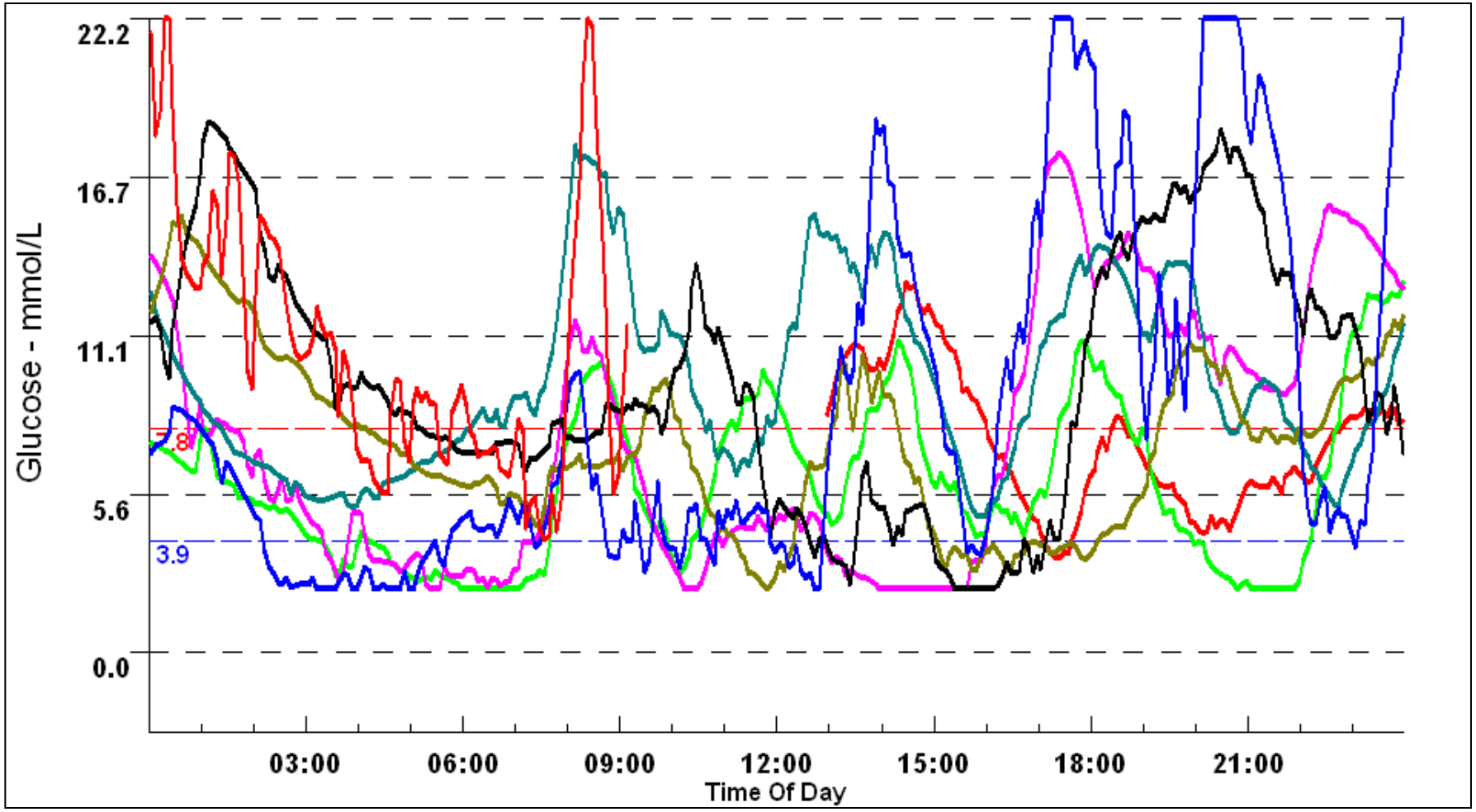
Outcome	1999-2004	2006-2009	P value
Malformation (CM)	7.3%	4.3%	0.04
CM T1D	4.4%	4.2%	0.1
CM T2D	12.3%	4.4%	0.0009
PN Mortality	3.7%	1.8%	0.07
PNM T1D	2.8%	2.4%	0.9
PNM T2D	6.2%	0.9%	0.009
Serious adverse Outcome (CM, PNM)	9.2%	6.0%	0.07
T1D	6.4%	6.5%	0.9
T2D	16.4%	5.3%	0.0008

Perinatal Consequences T1D vs T2D

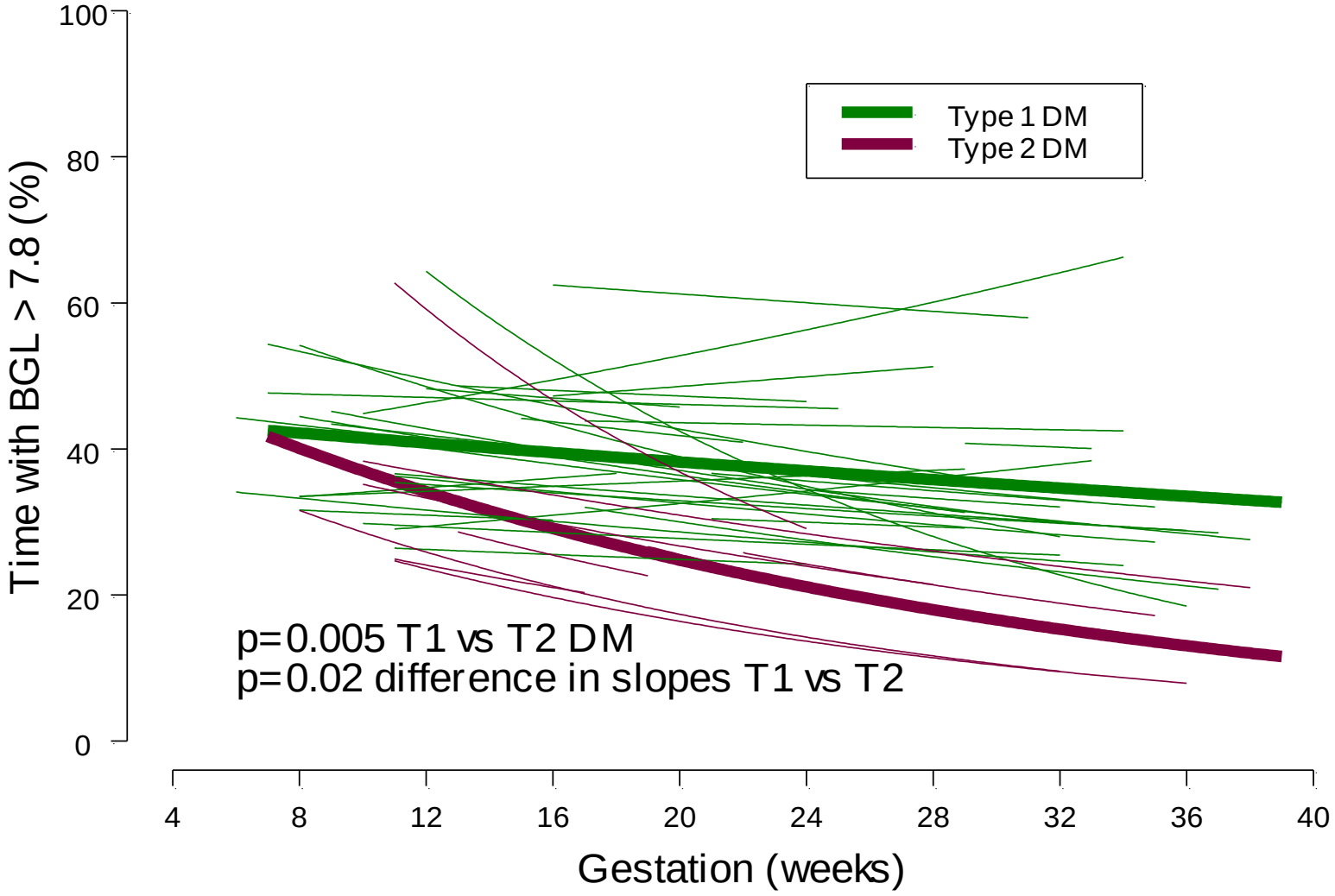
- Vaginal delivery 33%T1D vs. 49%T2D; p=0.006
- Preterm delivery 37%T1D vs. 17% T2D; p<0.0001
- LGA/macrosomia 53%T1D vs. 37%T2D; p=0.0008
- Neonatal care admission 44%T1D vs. 30% T2D; p=0.001

Murphy HR et al, Diab Med 2011

7-day CGM profile in T1D pregnancy



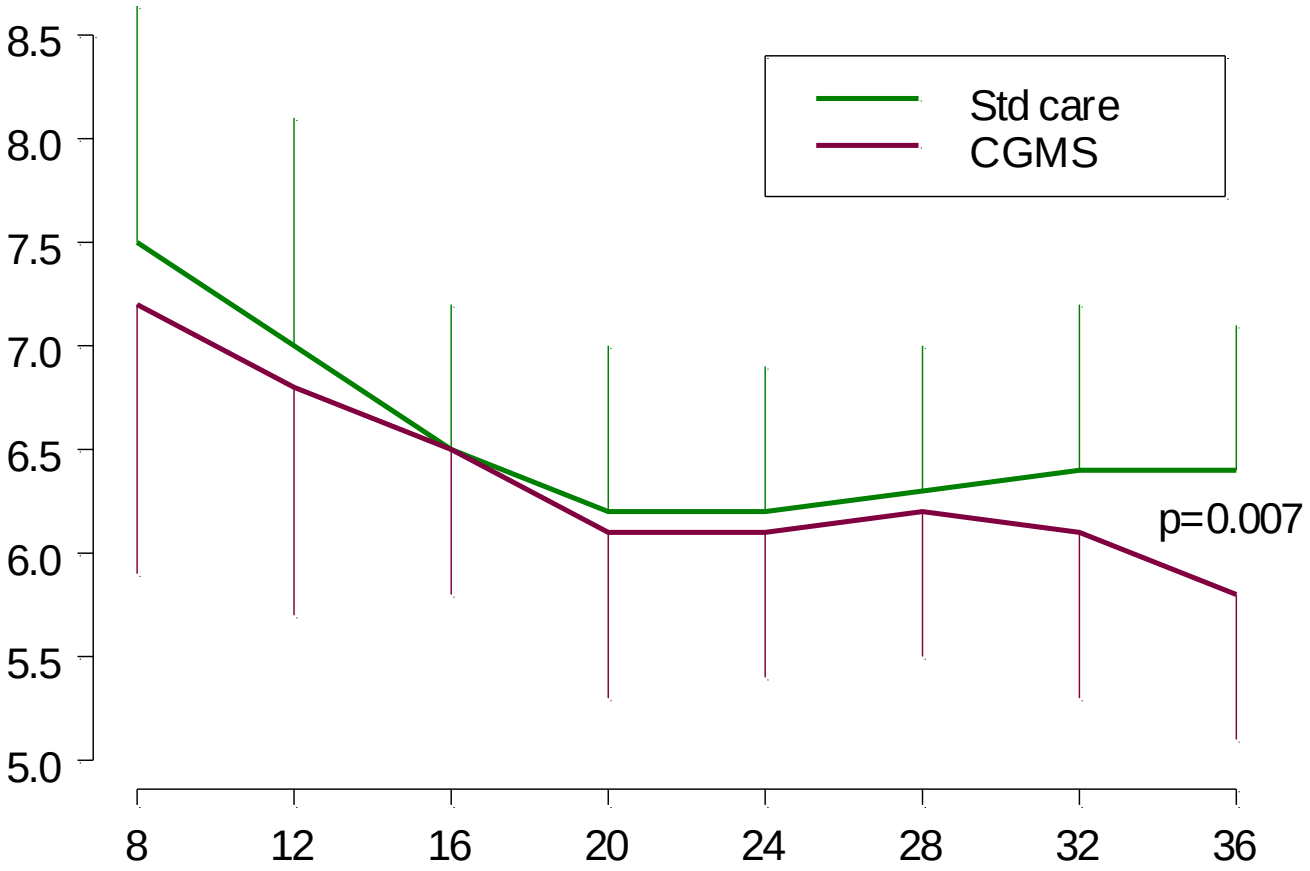
Time spent hyperglycaemic > 7.8 mmol/L



Murphy HR et al, 2007

Influence on maternal HbA1c

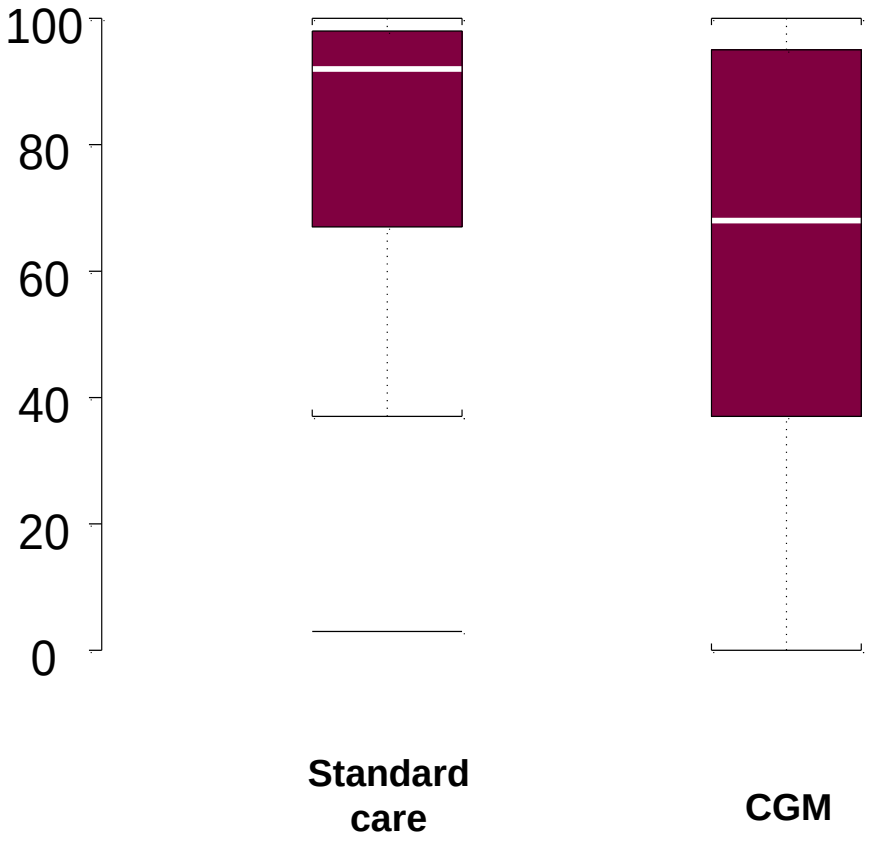
Mean HbA1c 6.4+/-0.7% Standard Care vs. 5.8%+/-0.6 CGMS (p=0.007)



Murphy HR et al, 2008

Infant birth weight centile

Median birth weight percentile 93 Standard Care vs. 69 CGMS, p=0.02



Reduced risk of LGA: Odds ratio 0.36 (95% CI 0.13 – 0.98; p = 0.05)

Insulin Pump Therapy

REVIEWS www.AJOG.org

OBSTETRICS

Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials

Asima Mukhopadhyay, MD; Tom Farrell, MD, MRCOG; Robert B. Fraser, MD, FRCOG; Bolarinde Ola, MRCOG, MD

"CSII seems to be a more physiological mode of insulin supply because it more or less mimics the pattern of insulin release of the pancreas, and the bolus from the pumps can be modified to fit with the slower absorption of nutrients associated with delayed gastric emptying seen in pregnancy".

"This systematic review does not show any advantage or disadvantage of using CSII over MDI in pregnant diabetic women".

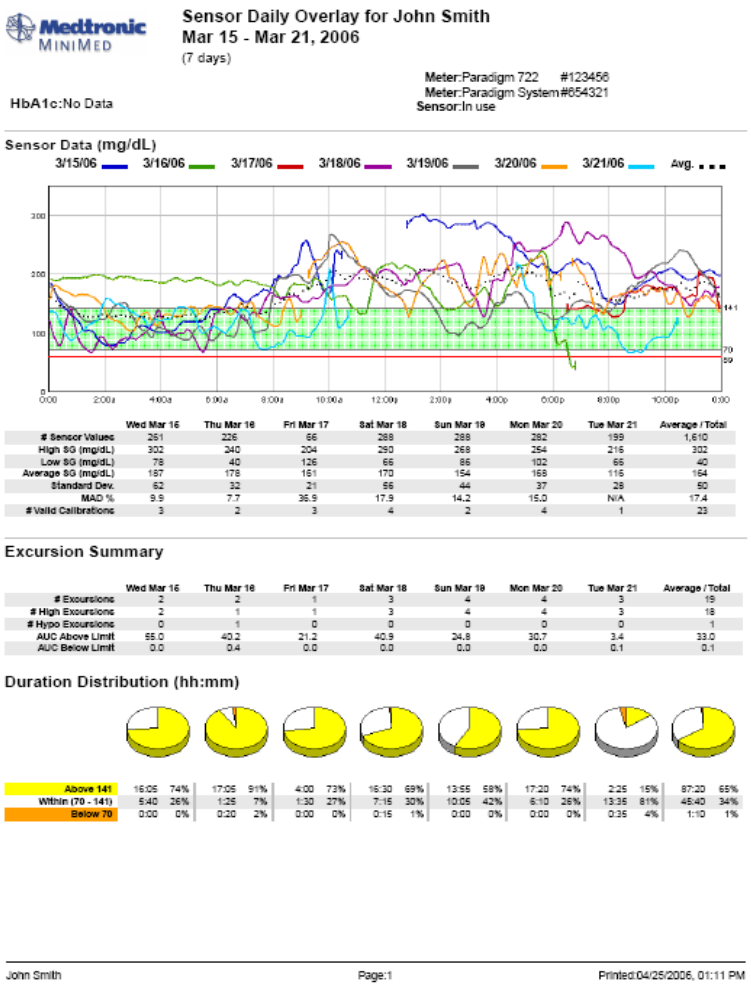
CSII literature review

Coustan D, 1986	RCT	11/11	No difference	No difference
Botta R, 1986	RCT	5/5	No difference	No difference
*Carta Q, 1986	RCT	14/15	No difference	↓ LGA on MDI
Laatikainen L, 1987	RCT	13/18	2 women with rapid ↓ HbA1c on CSII had progression of retinopathy	
Burkart W, 1988	RCT	48/41	No difference	No difference
Leveno K, 1988	Observational	10/11	No difference	No difference
Gabbe S, 2000	Observational	36/24	2 DKA CSII	No difference
Lapolla A, 2003	Observational	25/68	No difference	No difference
Hieronimus S, 2005	Observational	33/23	No difference	No difference
Chen et al, 2007	Observational	30/60	↑ DKA and neonatal hypoglycaemia on CSII	
Gimenez M, 2007	Observational	29/29	No difference	No difference
Kernaghan D, 2008	Observational	18/24	No difference	No difference
Cyganek K, 2010	Observational	112/157	CSII used to best effect before pregnancy	
González-Romero S, 2010	Observational	35/64	CSII associated with ↓ preconception HbA1c	
Neff, K 2010†	Observational	46/461	CSII associated with ↓ HbA1c at delivery	
Shanmugasundaram M, 2010†	Observational	38/52	CSII conversion safe during pregnancy	
Banerjee A, 2011†	Observational	38/370	CSII use more prevalent in high risk women. Prospective RCT needed.	

*Excluded from systematic reviews as included women with T1 and T2D

† Published only in abstract format

Sensor augmented CSII



Medtronic MiniMed

Sensor Daily Overlay for John Smith
Mar 15 - Mar 21, 2006
(7 days)

Meter:Paradigm 722 #123456
Meter:Paradigm System#654321
Sensor:In use

HbA1c:No Data

Sensor Data (mg/dL)

3/15/06 3/16/06 3/17/06 3/18/06 3/19/06 3/20/06 3/21/06 Avg.

	Wed Mar 16	Thu Mar 16	Fri Mar 17	Sat Mar 18	Sun Mar 19	Mon Mar 20	Tue Mar 21	Average / Total
# Sensor Values	261	226	66	288	288	282	199	1,610
High SG (mg/dL)	302	240	204	290	268	254	216	302
Low SG (mg/dL)	78	40	126	66	86	102	66	40
Average SG (mg/dL)	187	178	161	170	154	168	116	164
Standard Dev.	62	32	21	66	44	37	28	60
MAD %	9.9	7.7	36.9	17.9	14.2	15.0	N/A	17.4
# Valid Calibrations	3	2	3	4	2	4	1	23

Excursion Summary

	Wed Mar 16	Thu Mar 16	Fri Mar 17	Sat Mar 18	Sun Mar 19	Mon Mar 20	Tue Mar 21	Average / Total
# Excursions	2	2	1	3	4	4	3	19
# High Excursions	2	1	1	3	4	4	3	18
# Hypo Excursions	0	1	0	0	0	0	0	1
AUC Above Limit	65.0	40.2	21.2	40.9	24.8	30.7	3.4	33.0
AUC Below Limit	0.0	0.4	0.0	0.0	0.0	0.0	0.1	0.1

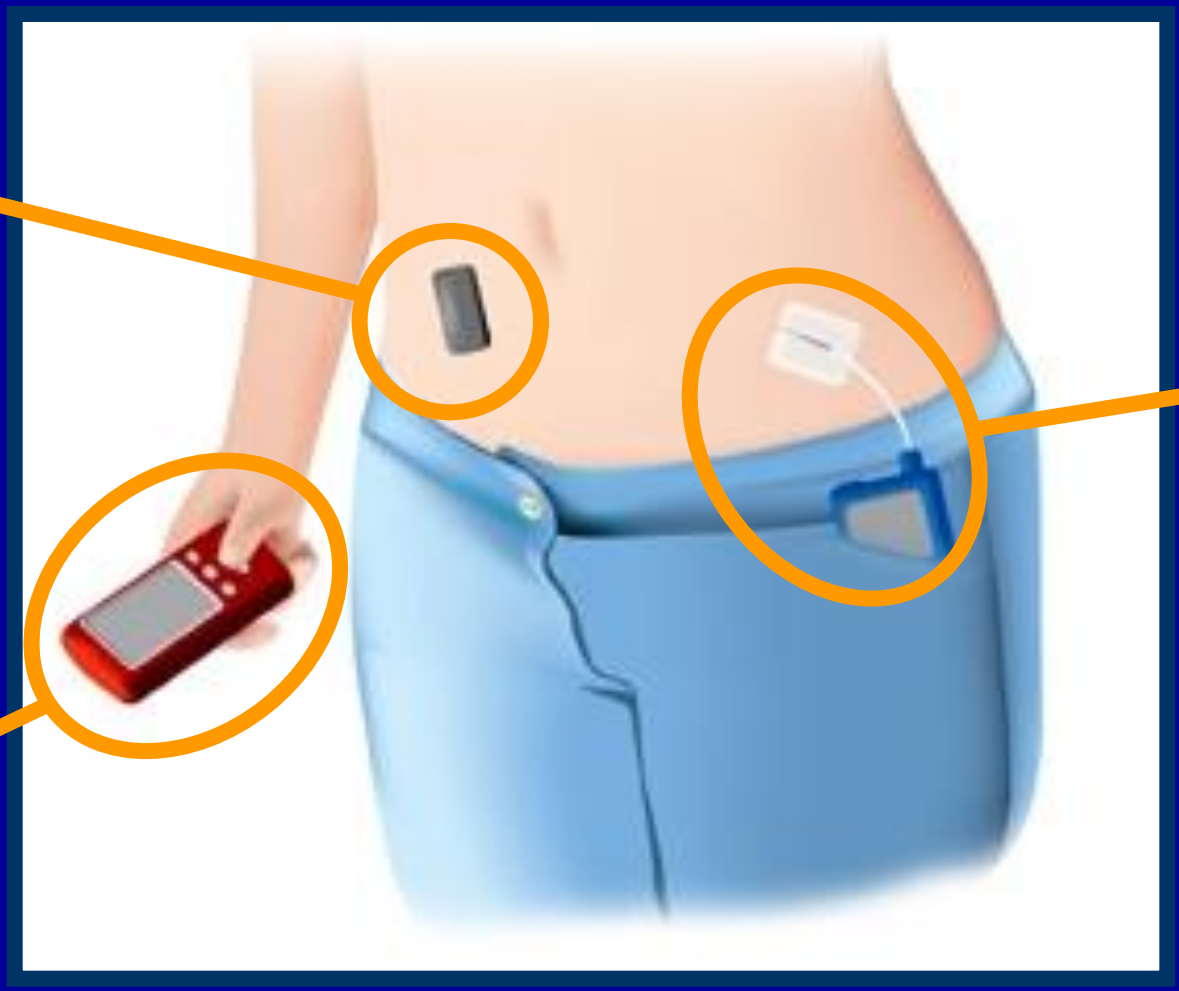
Duration Distribution (hh:mm)

Above 141	16:05	74%	17:05	91%	4:00	73%	16:30	69%	13:55	58%	17:20	74%	2:25	15%	87:20	65%
Within (70 - 141)	5:40	26%	1:25	7%	1:30	27%	7:15	30%	10:05	42%	6:10	26%	13:35	81%	45:40	34%
Below 70	0:00	0%	0:20	2%	0:00	0%	0:15	1%	0:00	0%	0:00	0%	0:35	4%	1:10	1%

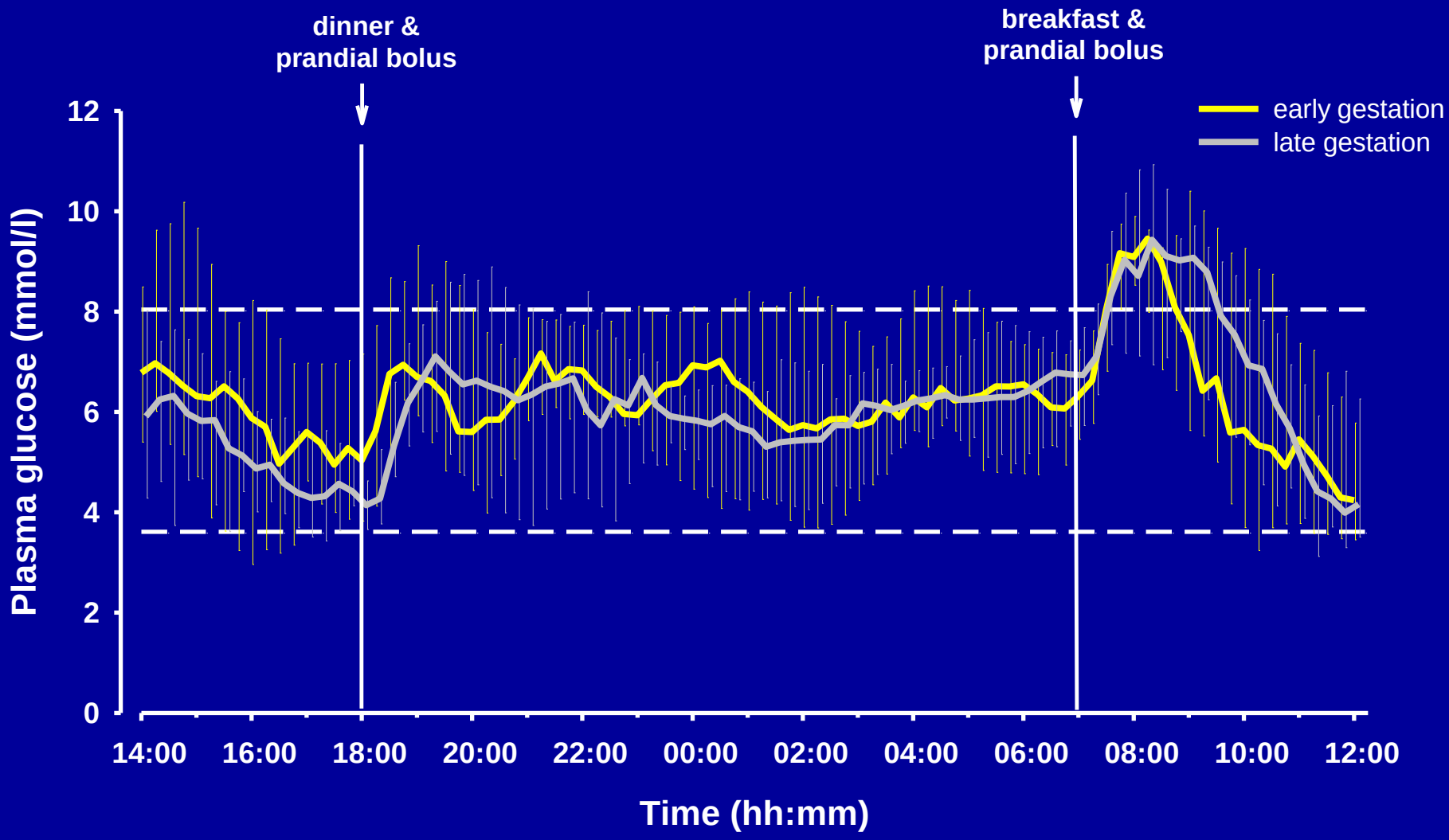
John Smith Page:1 Printed:04/25/2006, 01:11 PM

- Takes time, effort, commitment
- Only 34% adults HbA1c <7% (STAR3 2010 & Eurythmics 2011)
- Optimal prandial and basal dosing???
  - high levels literacy & numeracy
  - 75% UK population <level 2 GCSE
- Effects on maternal & perinatal outcomes ??

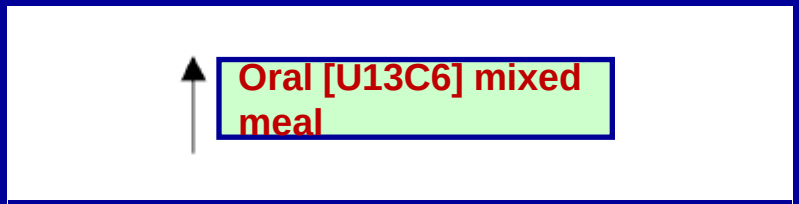
Closed-loop insulin delivery



Closed-loop in pregnancy

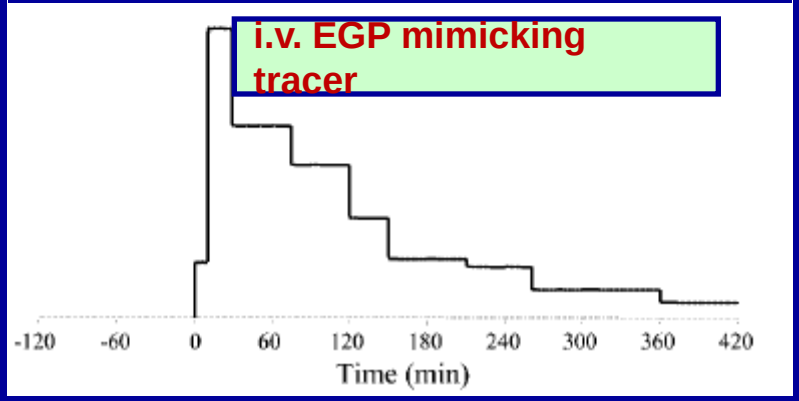


Physiological insights into gut absorption of glucose



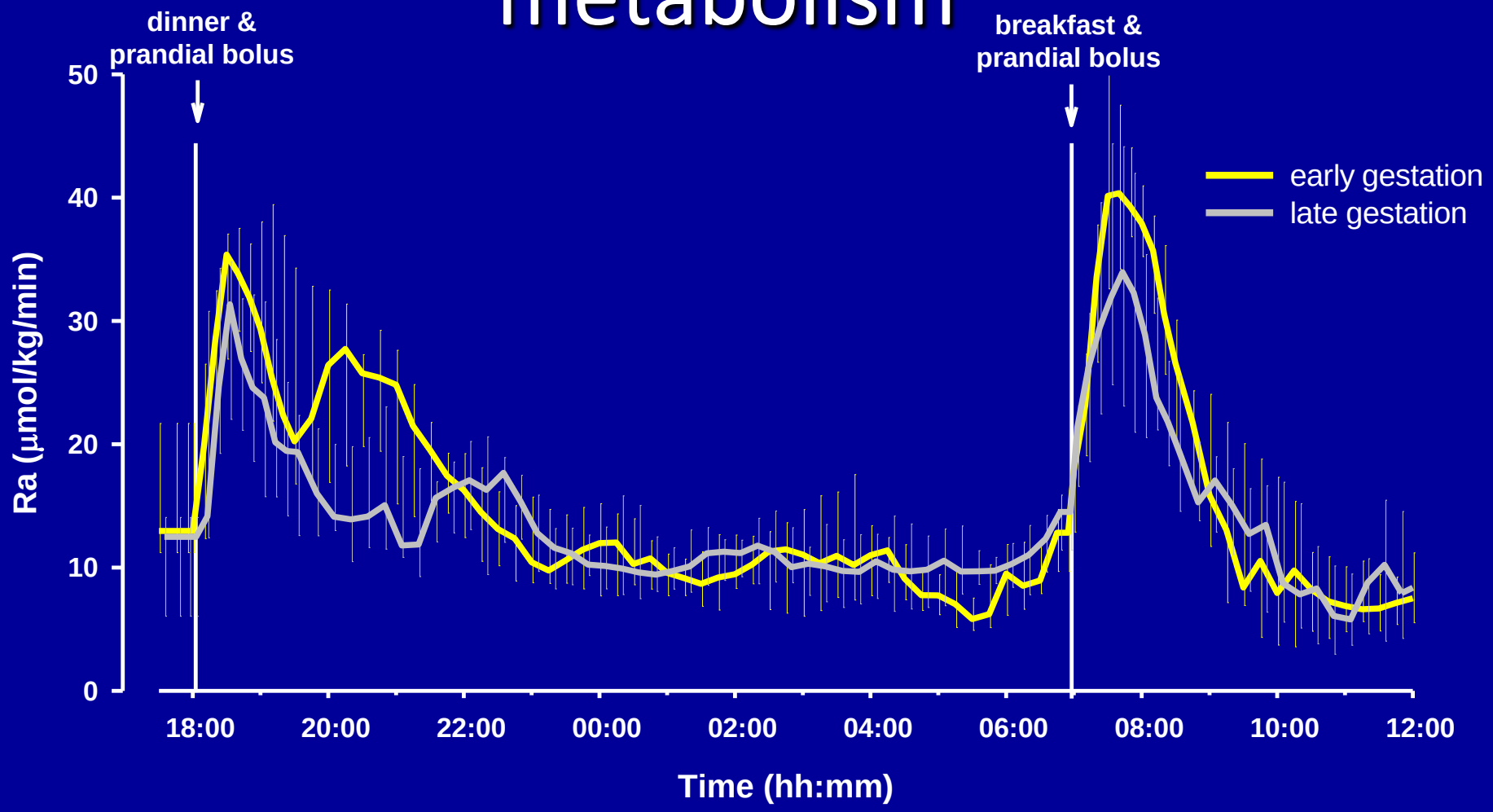
Evening meal and Breakfast

Dinner: 80g CHO (50%), 9g protein (31%), 4g fat (15%)
Breakfast: 57g CHO (60%), 7.6g protein (8%), 11g fat (28%)



5 hours post-meal
(Evening meal and Breakfast)

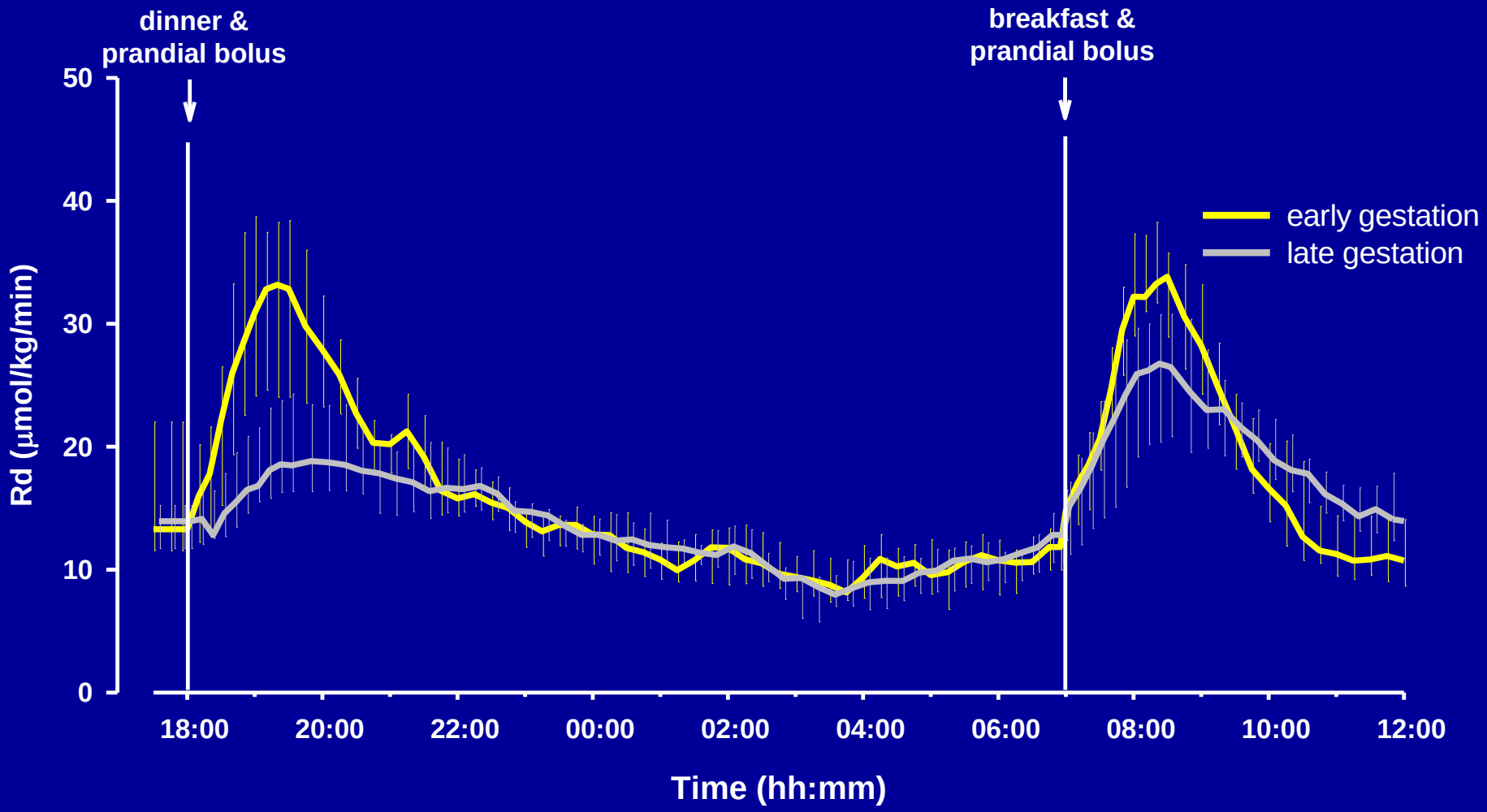
Complexity of carbohydrate metabolism



No changes in postprandial Ra in early vs. late pregnancy; p=0.61

Ra t50% 109±24 vs. 97±39min dinner and 58±18 vs. 52±33min breakfast

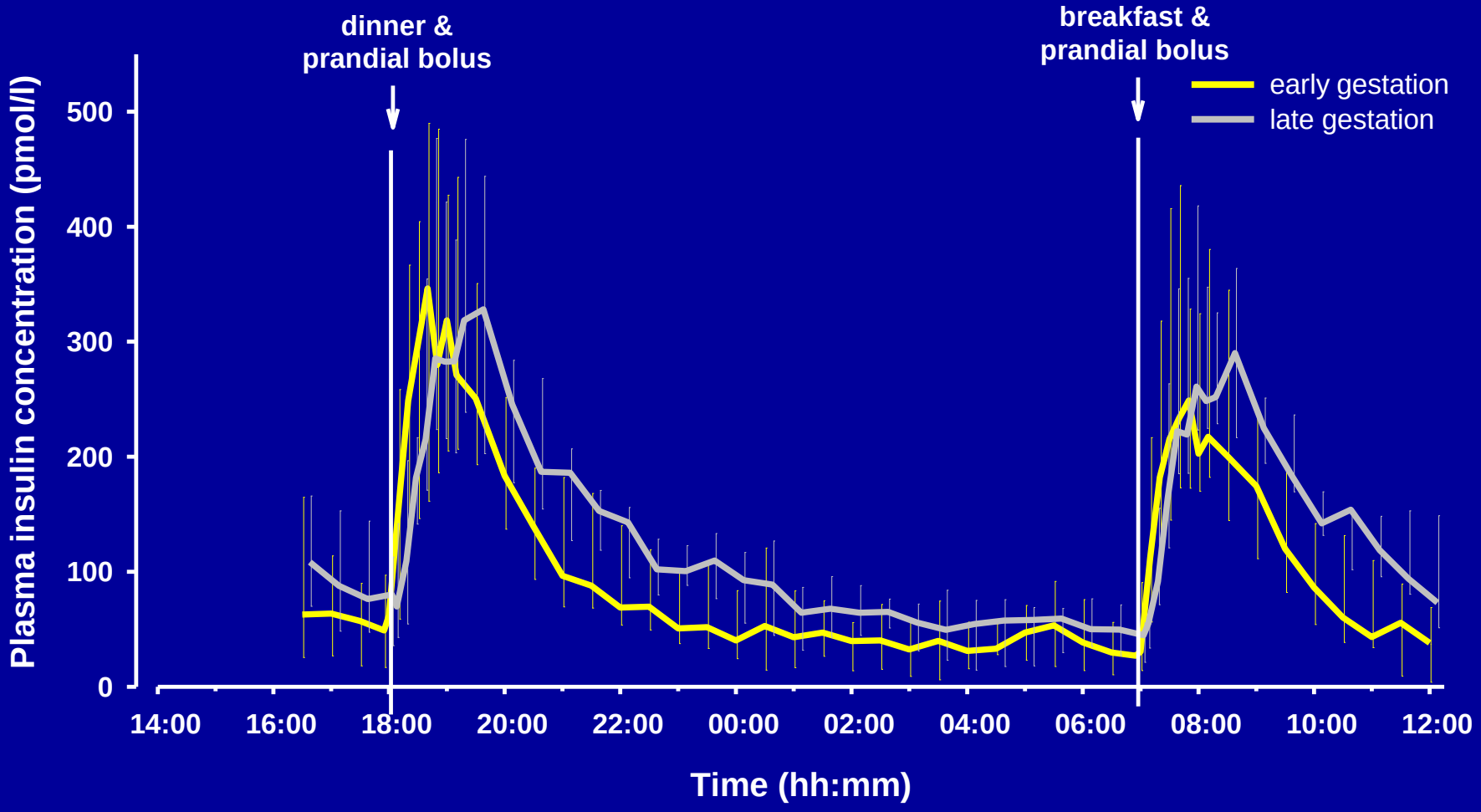
Postprandial glucose disposal



Postprandial Rd significantly reduced late pregnancy; P=0.003

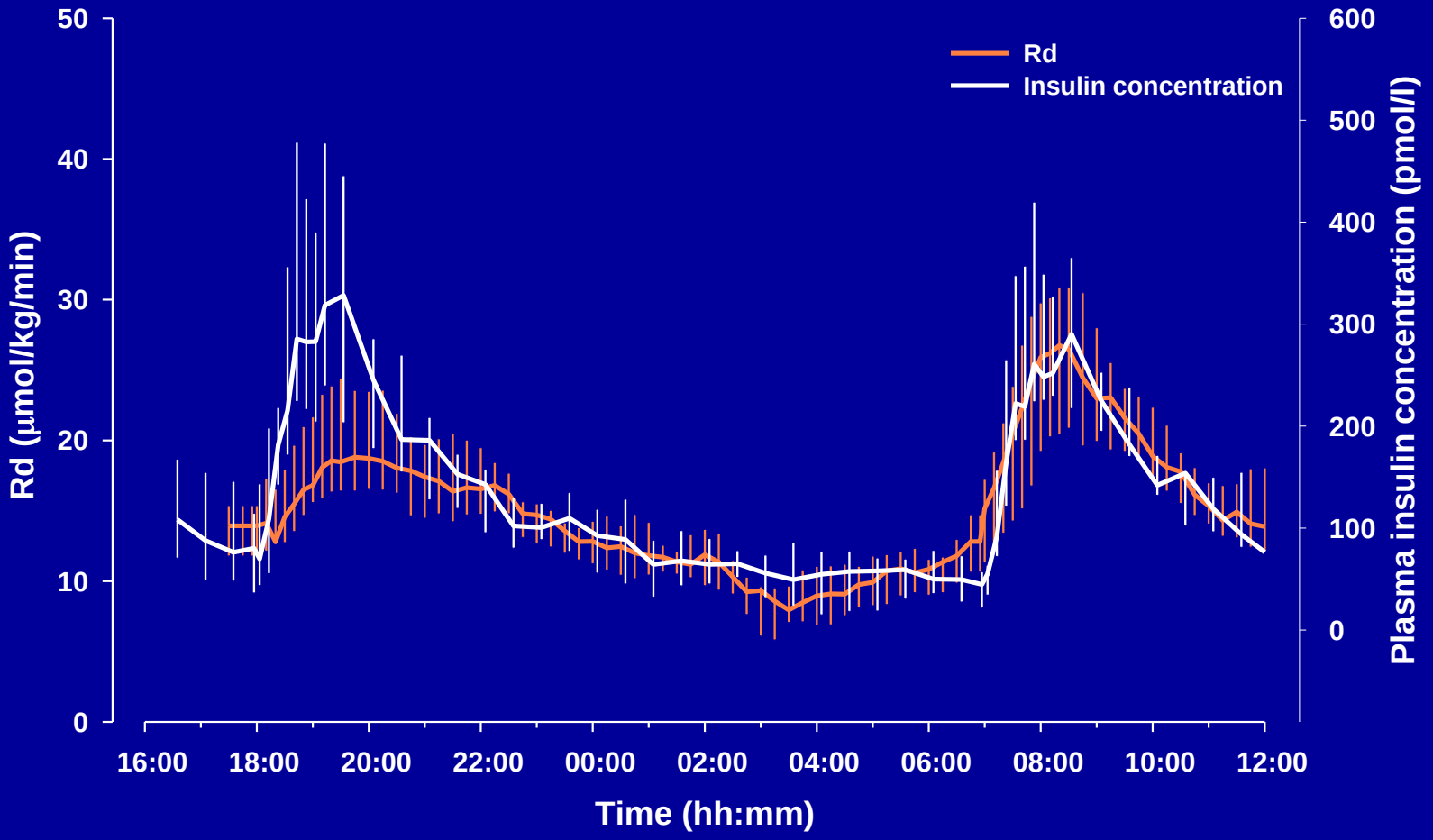
Rd t50% 103 ± 17 vs. 125 ± 21 dinner and 103 ± 17 vs. 125 ± 21 breakfast

Gestational changes in Insulin kinetics



No change in Insulin MCR

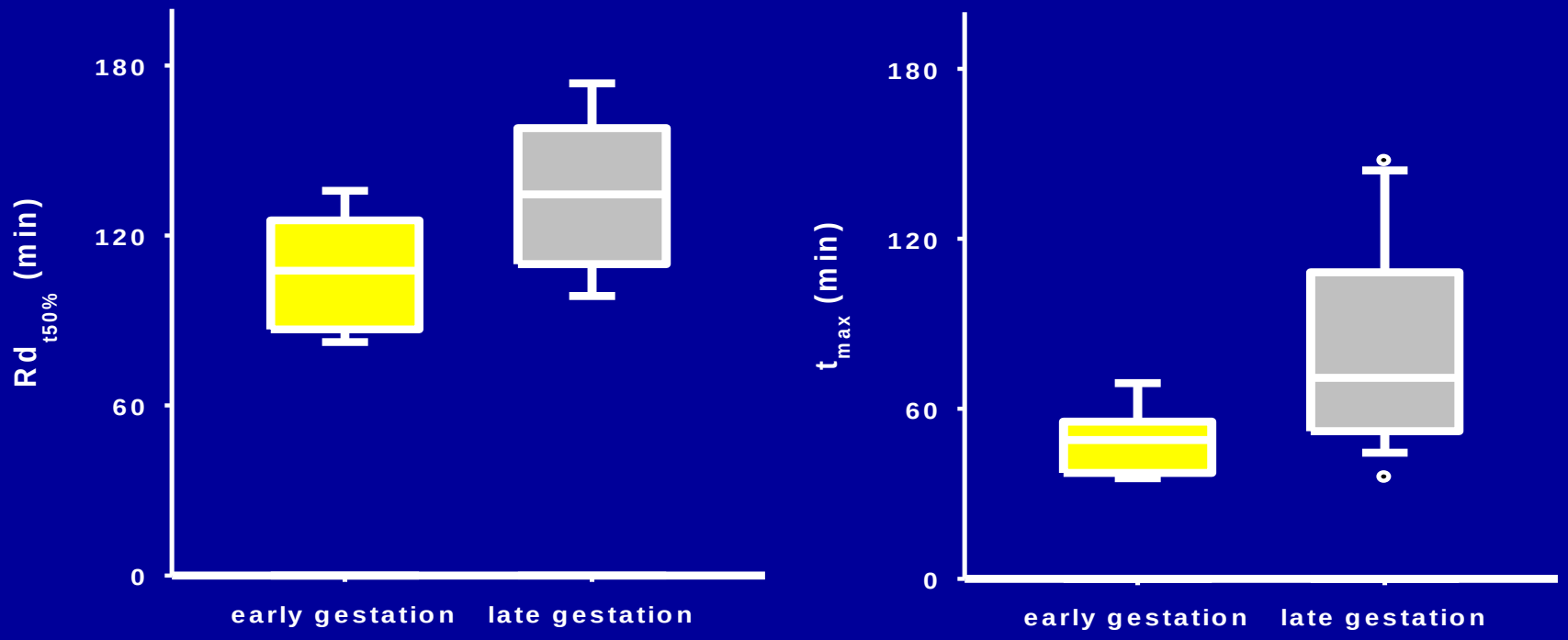
Postprandial insulin resistance in late gestation



Increased hepatic insulin resistance and reduced peripheral insulin sensitivity: $p<0.004$

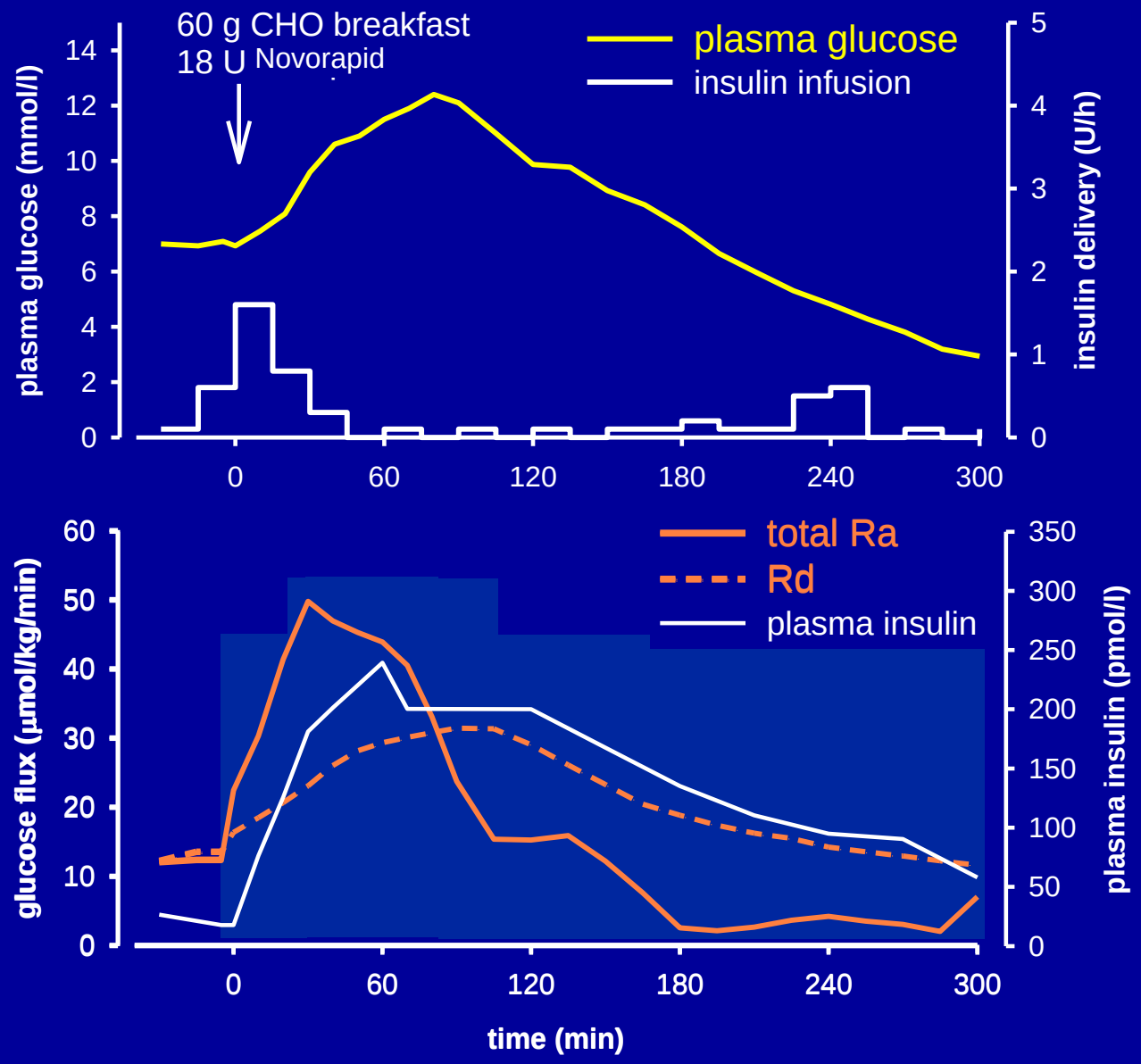
Mechanisms ??

1. Delayed Rd
2. Peripheral insulin resistance
3. Delayed insulin absorption



Insulin tmax 53±13 vs. 79±33min dinner; 46±10 vs. 78±34min breakfast; p=0.0002

28 wks, 5.4% HbA1c, 54U TDD, 72 kg



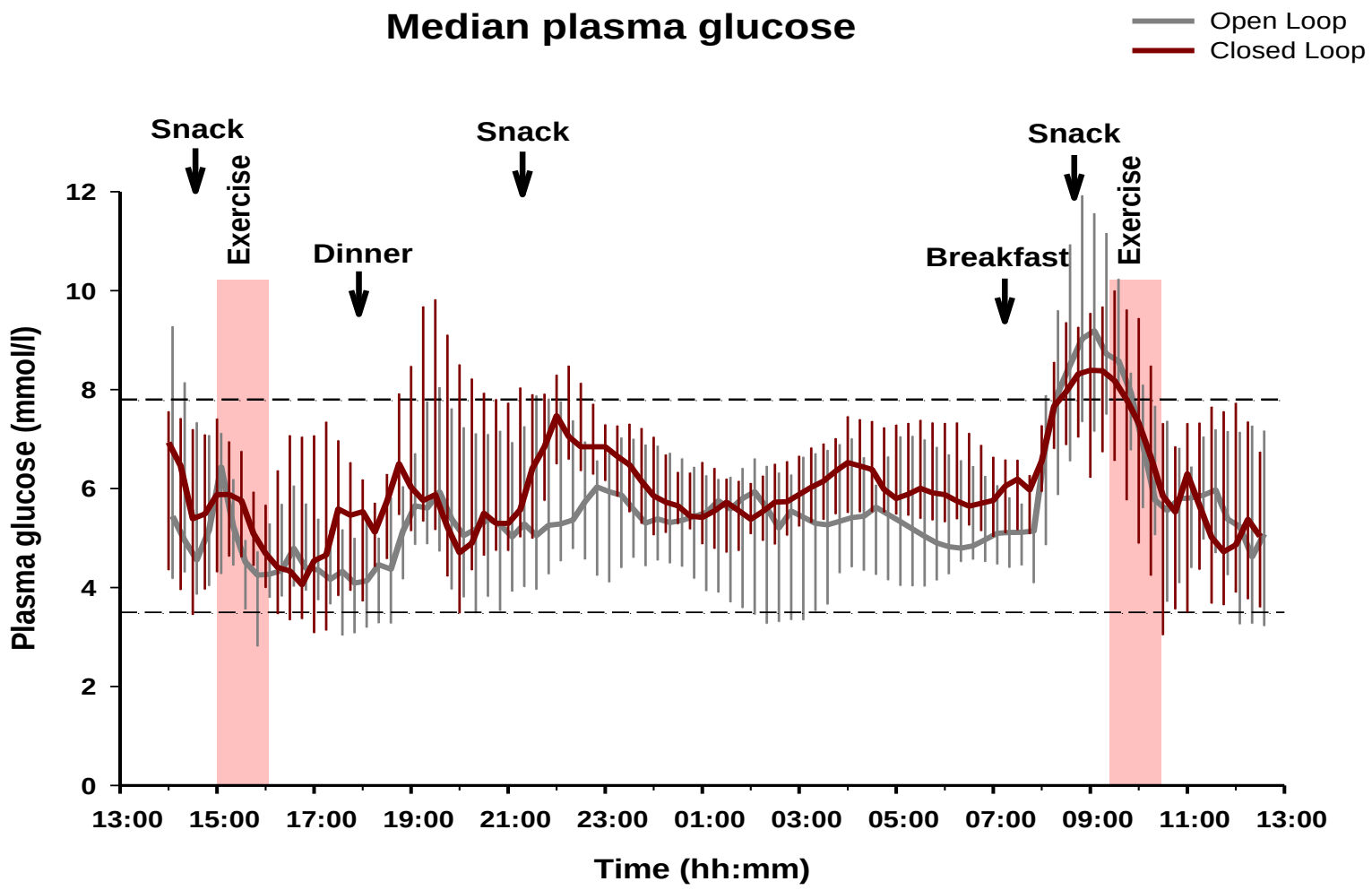
Therapeutic Implications

Can we achieve postprandial near-normoglycaemia ???

1. Slow down Ra: lower CHO and/or low GI meals, acarbose or amylin analogues
2. Speed up Rd: Physical activity (PA)
3. Stimulate peripheral insulin sensitivity ??

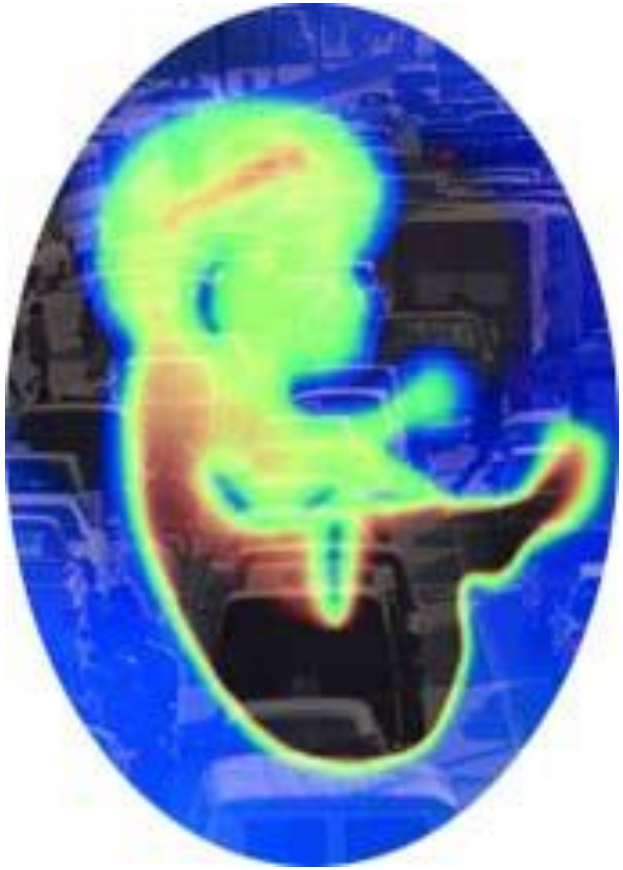
Realistic expectations: Insulin does not effect glucose Ra
More research: dietary aspects and risks benefits of PA in T1D pregnancy

CLIP_02 Physical Activity Study



Diab Care Online Oct 2011

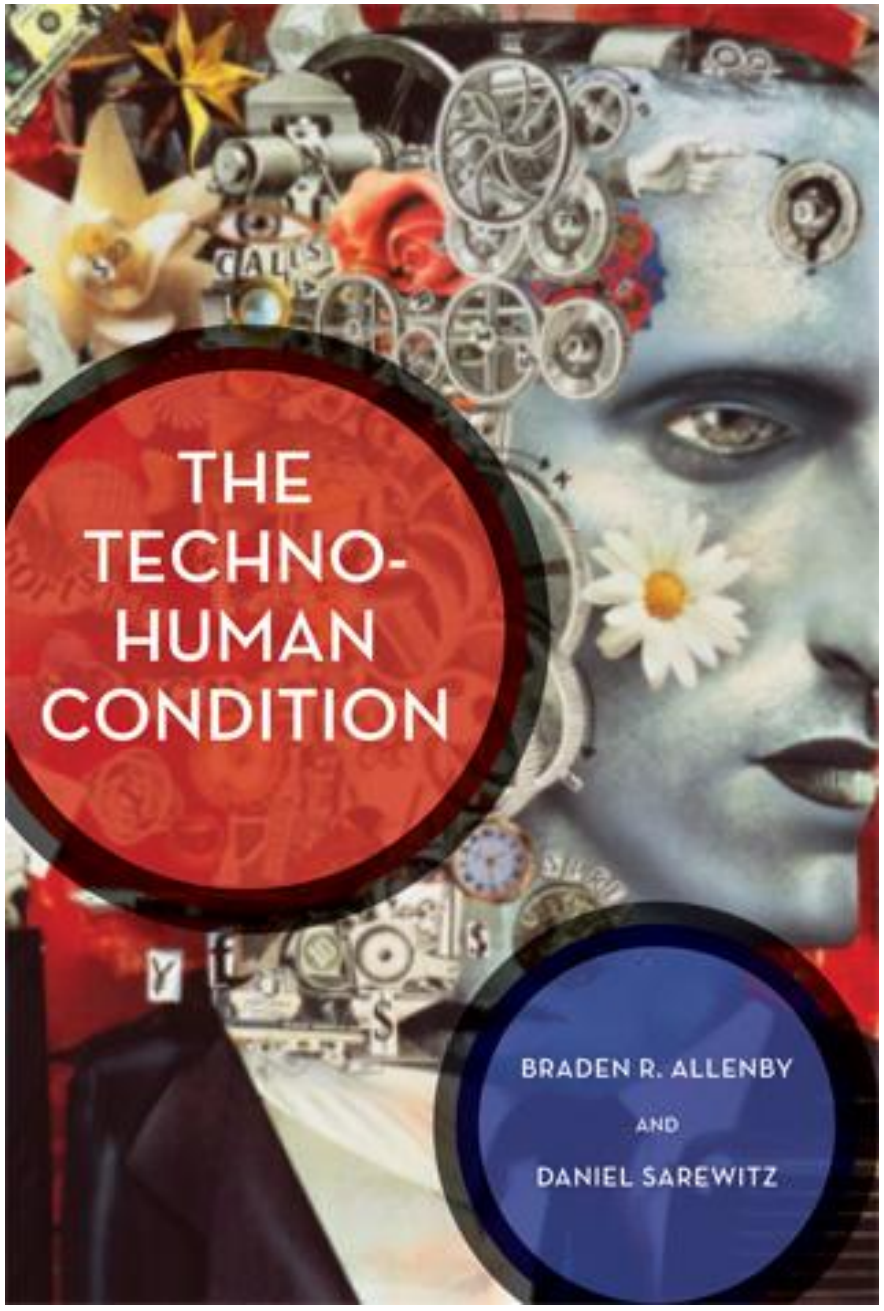
What's new in Pregnancy ??



Better organisation of care T2D

Technological progress towards near-normoglycaemia T1D

- CGMS 50% time in target
- RT-CGM + CSII: 60% (40-80%)
- CL: 65-75% day 85-100% night
- CL + PA: 80% (55-90%), 100% night


THE
TECHNO-
HUMAN
CONDITION
BRADEN R. ALLENBY
AND
DANIEL SAREWITZ

Cambridge Artificial Pancreas Team

Acknowledgments

AP Team at Cambridge

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Kings' College

- Stephanie Amiel

Funders

- JDRF AP Consortium (Aaron Kowalski)
- Diabetes UK/NIHR
- Abbott Diabetes Care/Animas (Johnsons & Johnsons)/Medtronic

Key collaborators

- Health Psychology Prof TC Skinner
- Gerry Rayman/Jonathan Roland/Rosemary Temple