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The Supremes "Baby Love" Diabetes & pregnancy 2015:

clairvoyance, clarity or controversy?

Dr Robbie Lindsay, Glasgow.

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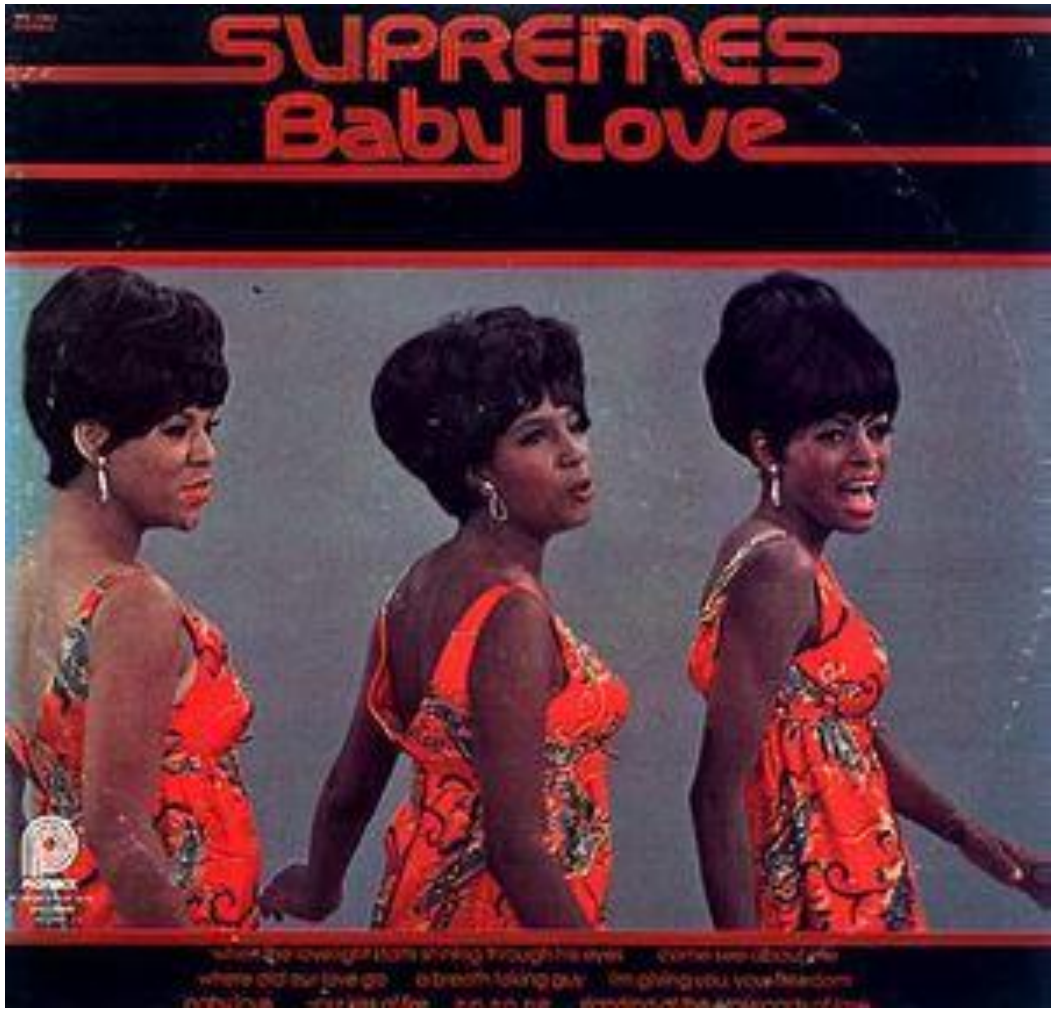

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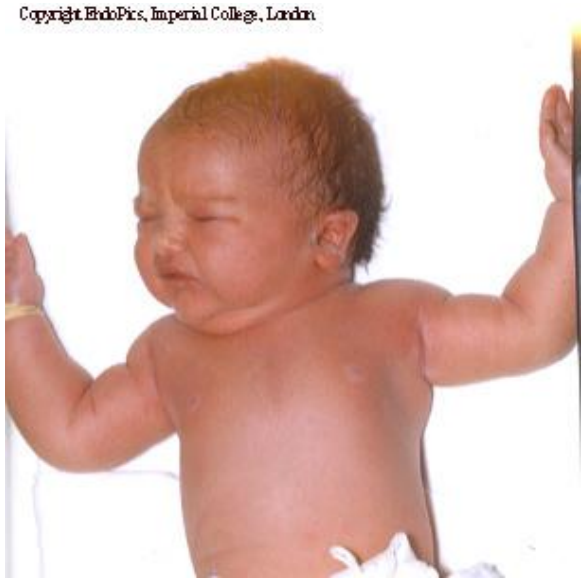
type 2 diabetes

type 1 diabetes

Gestational diabetes

MODY

secondary forms of diabetes



Congenital Malformations

Perinatal Mortality

Hypoglycaemia

Macrosomia

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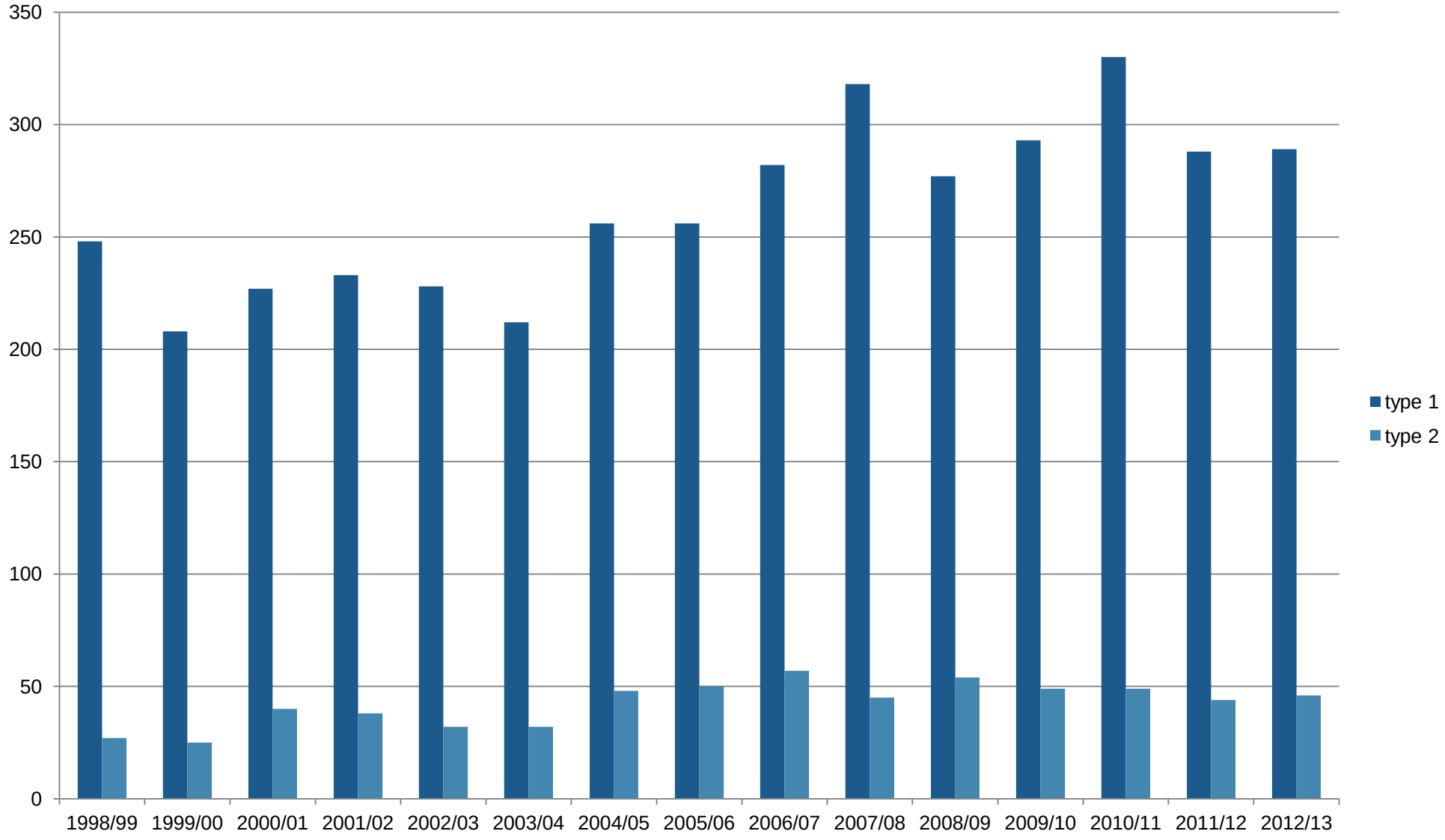
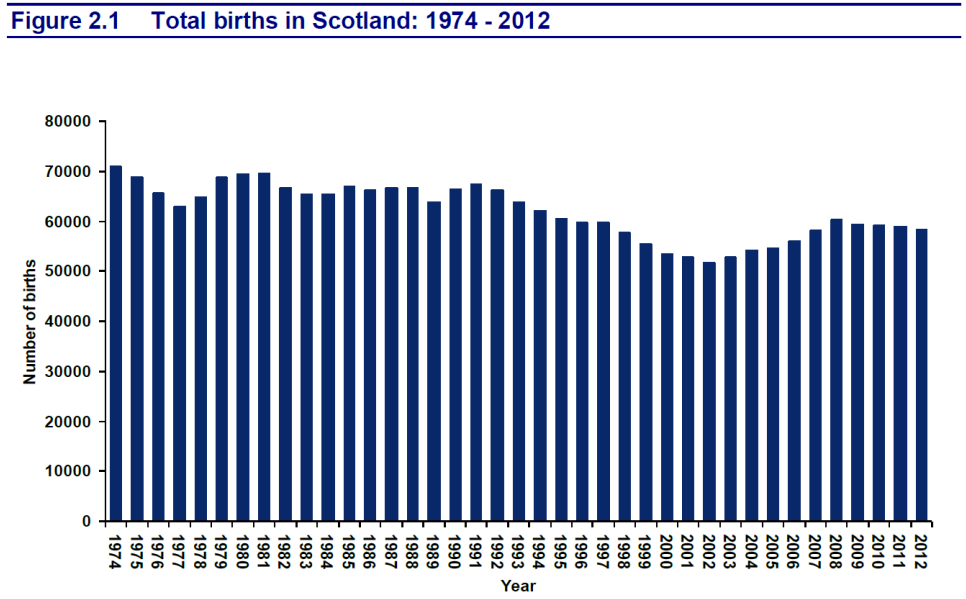
Number of deliveries in Scottish hospitals 1998-2013



Courtesy Jan Kerssens ISD

Number of deliveries in Scottish hospitals 1998-2013



Courtesy Jan Kerssens ISD

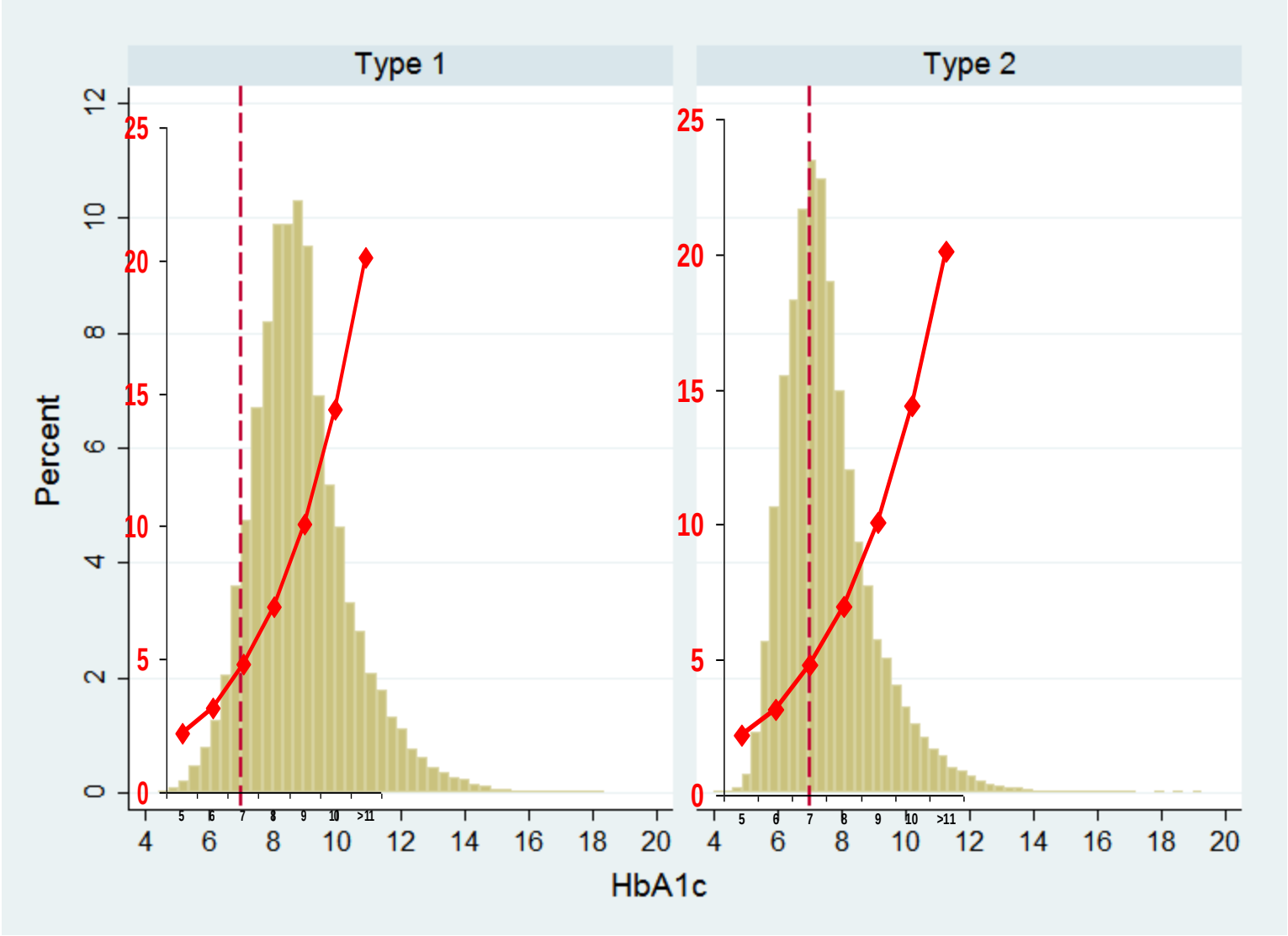
HbA1c and congenital anomaly – SIGN 116

Table 3: Derived absolute risk of a major or minor congenital anomaly in association with the number of standard deviations (SD) of glycosylated haemoglobin above normal, and the approximate corresponding HbA1c concentration, measured periconceptionally.[318]

SD of GHb	Corresponding HbA1c (%)	Corresponding HbA1c (mmol/mol)	Absolute risk of a congenital anomaly (%, 95% CI)
0	5.0	31	2.2 (0.0 to 4.4)
2	6.0	42	3.2 (0.4 to 6.1)
4	7.0	53	4.8 (1.0 to 8.6)
6	8.0	64	7.0 (1.7 to 12.3)
8	9.0	75	10.1 (2.3 to 17.8)
10	10.0	86	14.4 (2.8 to 25.9)
≥12	≥11	≥97	20.1 (3.0 to 37.1)

Assumes a DCCT-aligned HbA1c assay with mean (SD) of 5.0% (0.5%) among non-diabetic, non-pregnant controls. Copyright 2007 American Diabetes Association. From Diabetes Care, Vol. 30, 2007; 1920-1925. Reprinted with permission from The American Diabetes Association. [318]

HbA1c of all Scottish patients and risk of congenital anomaly



…type 1 **8%< 7%,** **16%< 7.5%**

1700 pregnancies

45% type 2 diabetes

33% 5mg folic acid (7.1% 400mcg)

type 1 47.2%

type 2 34.4%

A1c <43 mmol/mol

5.1% type 1

18.5% type 2

9.4% taking inappropriate blood glucose lowering meds for pregnancy

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Pearson Penney 1998/ 2003 surveys of Diabetes Care

established multidisciplinary teams in all Scottish hospitals

Unplanned pregnancies 50%

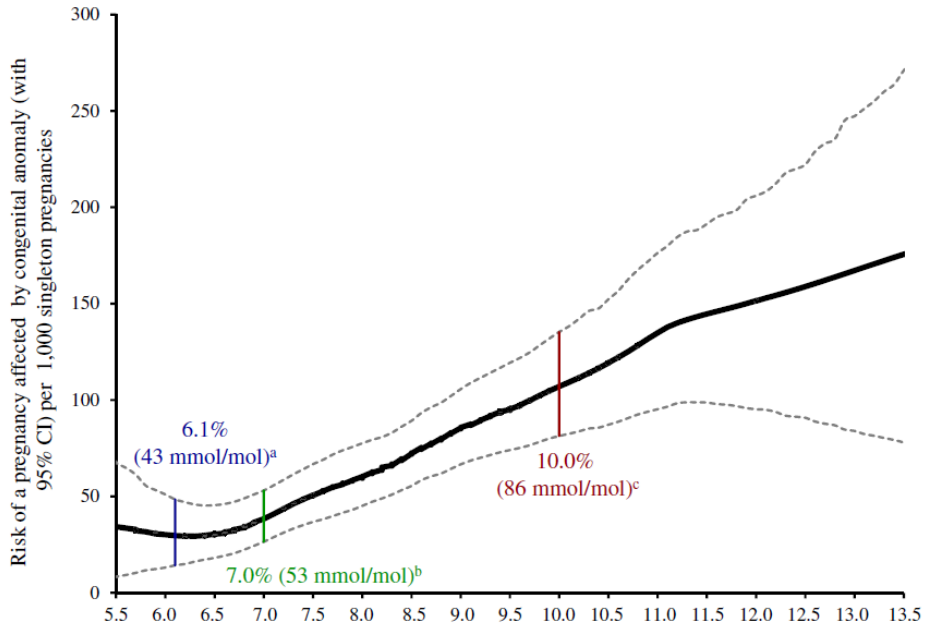
Formal pre-pregnancy counselling- 29%

Folate taken (any dose)- 54%

Discontinued contraception after optimal A1c 16%

Diabetologia (2012) 55:936–947

Fig. 1 Association between peri-conception HbA_{1c} in women with pre-existing diabetes and the risk (with 95% CIs) of a pregnancy affected by major congenital anomaly. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929



HbA_{1c}	5.5–6.4	6.5–7.4	7.5–8.4	8.5–9.4	9.5–10.4	10.5–11.4	11.5–12.4	12.5–13.5
Singleton pregnancies	195	322	346	220	158	70	32	24
Cases	6	10	21	19	17	10	4	5

[a]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.2) 'If it is safely achievable, women with diabetes who are planning to become pregnant should aim to maintain their HbA_{1c} below 6.1%. Women should be reassured that any reduction in HbA_{1c} towards the target of 6.1% is likely to reduce the risk of congenital malformations.' [27]

[b]American Diabetes Association (USA), 2011: (VII.B) 'A_{1c} levels should be as close to normal as possible (<7%) in an individual patient before conception is attempted.' [26]

[c]National Institute for Health and Clinical Excellence (UK), 2008: (1.1.4.3) 'Women with diabetes whose HbA_{1c} is above 10% should be strongly advised to avoid pregnancy.' [27]

Bell et al Diabetologia


Tamla Motown
NOTHING BUT HEARTACHES
THE SUPREMES
Florence
Diana
Mary

Pre pregnancy counselling

Age 24

Type 1 diabetes 10 years

Treated

- **thyroxine 200 mcg**
- **novorapid tid**
- **levemir 6, 20**

Para 1+2

Age 24

Type 1 diabetes 10 years

Treated

- **thyroxine 200 mcg**
- **novorapid tid**
- **levemir 6, 20**

TSH 72 free T4 9

HBA1c 102

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MB age 30

2004 pregnancy, gestational diabetes treated insulin,
abnormal postpartum OGTT
treated insulin then metformin

2006 miscarriage

2011 pregnancy

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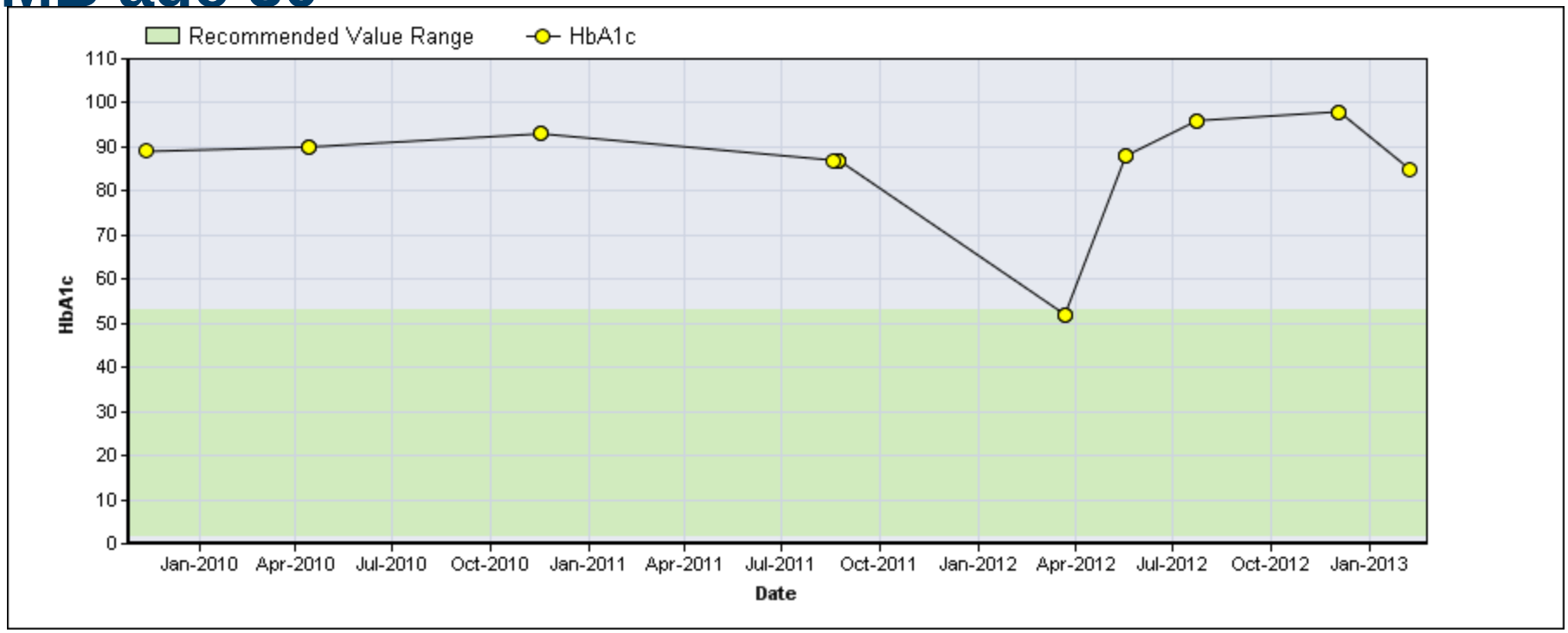
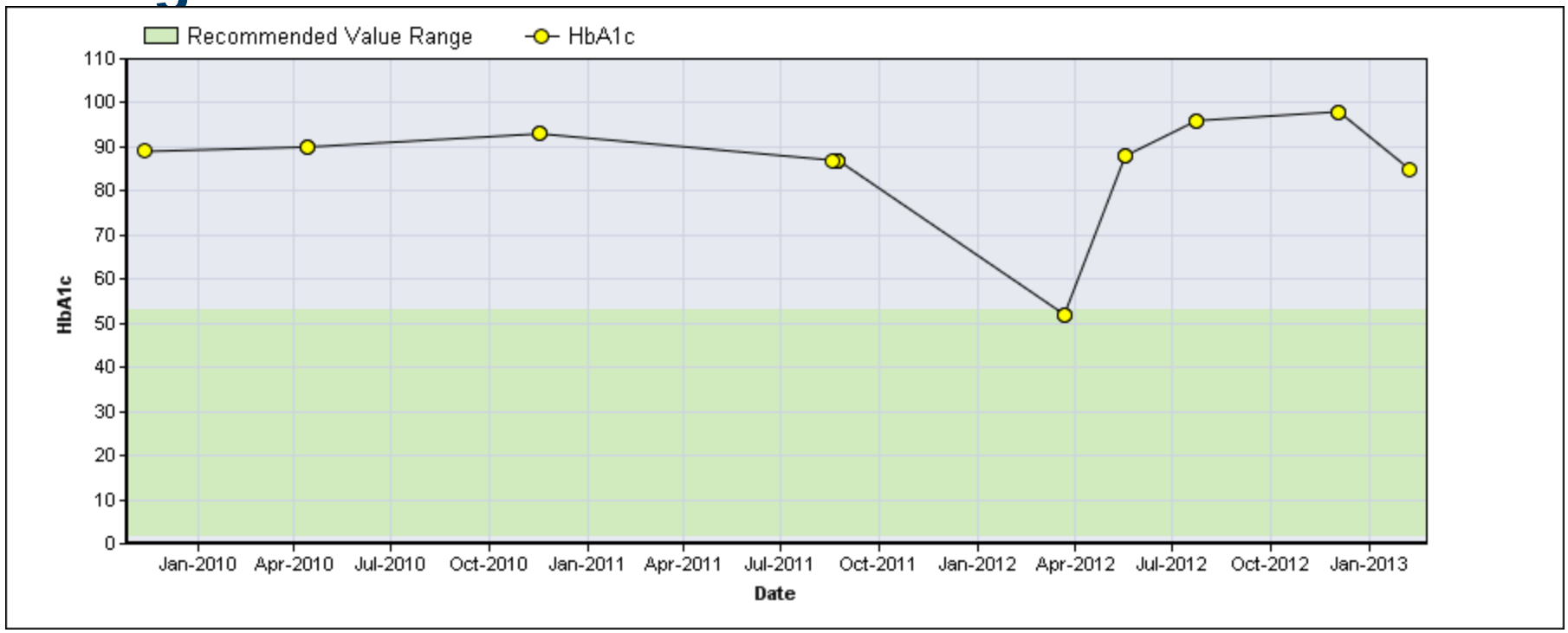
MB age 30



MB age 30



2012 baby hypoplastic left heart 2 surgeries

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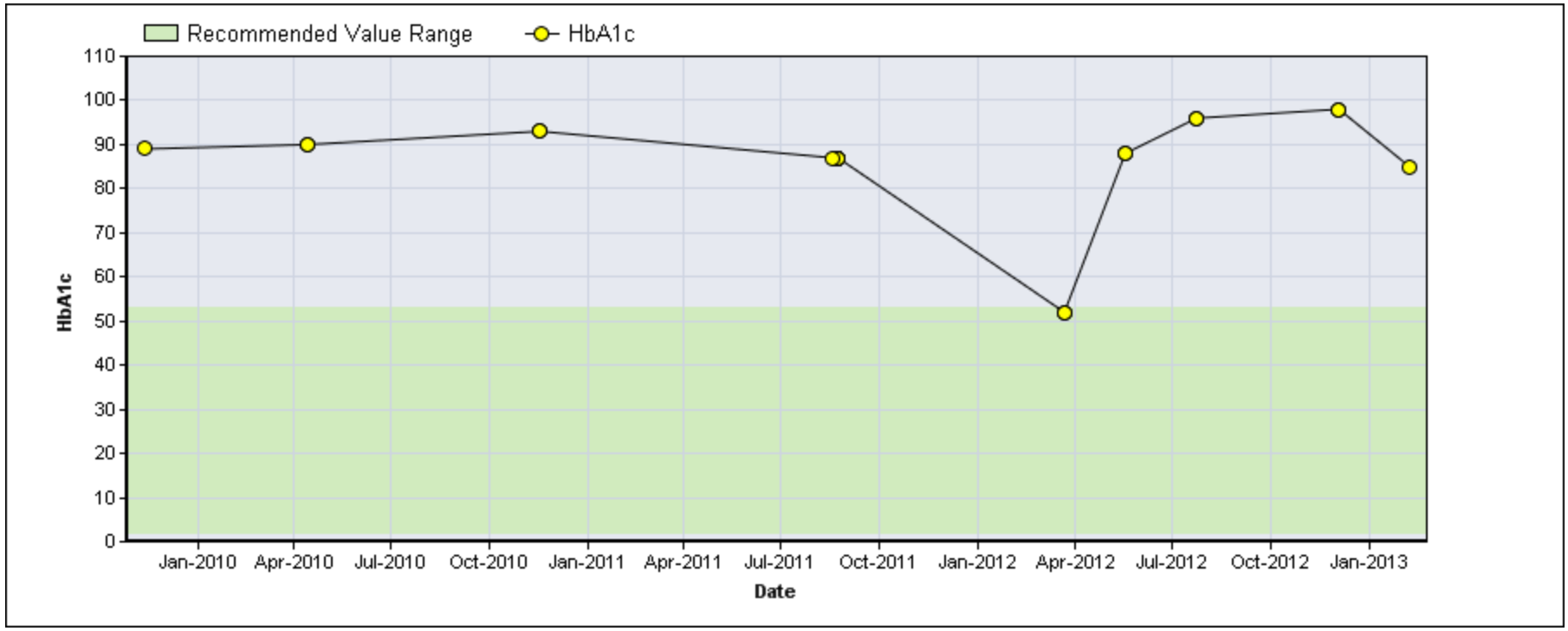
MB age 30



2012 **baby hypoplastic left heart 2 surgeries**

2012 **pregnancy**

metformin, sitagliptin HbA1c 85, exencephaly

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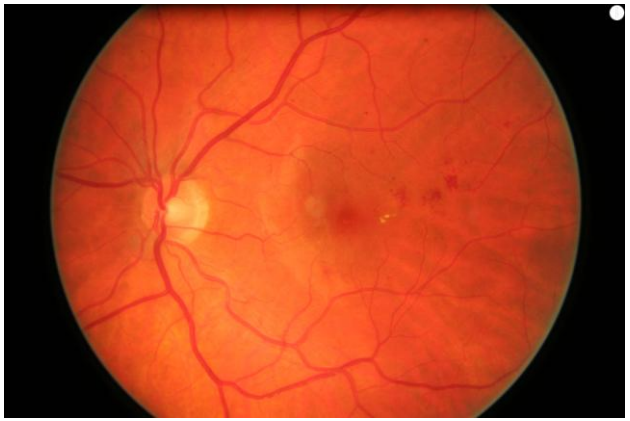
prepregnancy

- counselling
- target A1c’s
- medication (type 2)

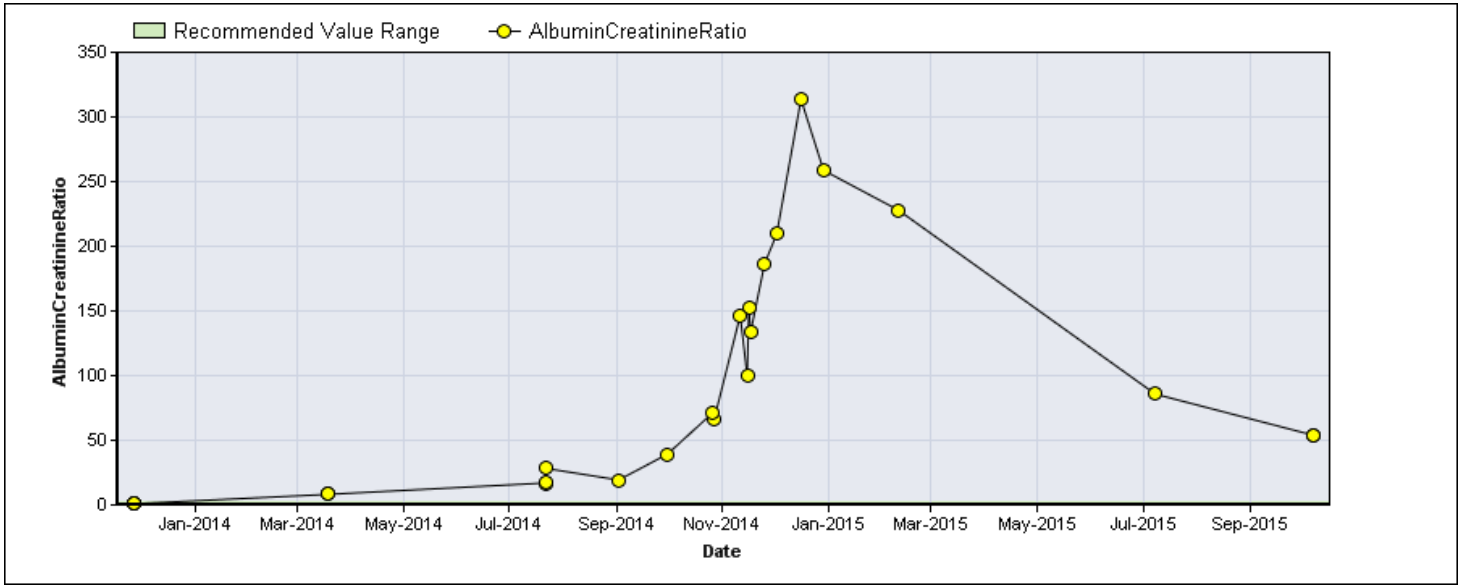
36 year old woman with type 1 diabetes for 18 years

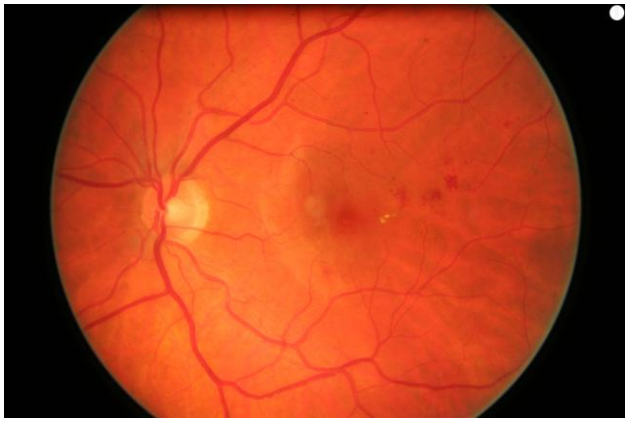
established microalbuminuria

previous treated maculopathy



BP 124/76 on ACEI prior to pregnancy

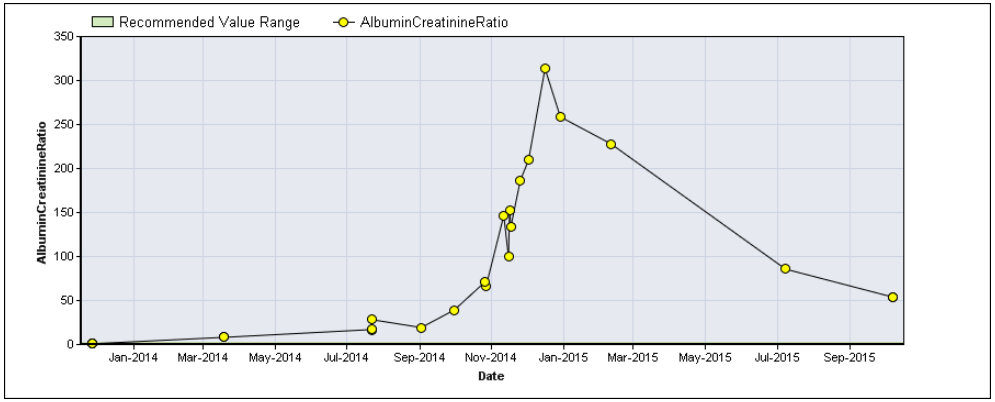




Treated labetalol nifedipine

Clexane

Proliferative retinopathy treated with laser 32 weeks (small haemmorhage)



Delivered at 36 weeks

(protein 5.7g l)

Table 2—*Comparison of pregnancy outcomes in studies of pregnant type 1 diabetic women with microalbuminuria covering the same geographical area in Eastern Denmark*

	Ekbom et al., 2001 (3)	Nielsen et al., 2006 (5)	Current study
Antihypertensive therapy strategy	Preeclampsia Diastolic BP >95 mmHg	BP >140/90 mmHg UAE >2 g/24 h ACE inhibitor before pregnancy	BP >135/85 mmHg UAE ≥300 mg/24 h ACE inhibitor before pregnancy
n	26	20	10
Duration of diabetes (years)	19 ± 5	18 ± 8	15 ± 10
A1C at inclusion (%)	8.1 ± 0.9	6.8 ± 0.5	7.3 ± 1.5
Antihypertensive therapy (week of onset)	29 (20–34)	13 (before to 34)	Before (before to 14)
Patients on antihypertensive therapy during pregnancy (*n*)	9 (35)	10 (50)	5 (50)
ACE inhibitor before pregnancy (*n*)	5 (19)	9 (45)	4 (40)
Systolic BP at inclusion (mmHg)	121 ± 13	121 ± 14	117 ± 14
Diastolic BP at inclusion (mmHg)	71 ± 8	73 ± 8	74 ± 8
UAE (mg/24 h)	69 (16–278)	74 (30–287)	91 (30–198)
Preeclampsia (*n*)	11 (42)	4 (20)	0
Gestational age at delivery (days)	250 (182–270)	259 (244–271)	264 (252–272)
Preterm delivery before 34 weeks (*n*)	6 (23)	0	0
Preterm delivery before 37 weeks (*n*)	16 (62)	8 (40)	2 (20)
Birth weight (g)	3,124 ± 767	3,279 ± 663	3,471 ± 670
Perinatal mortality (*n*)	1 (4)	0	0
Major congenital malformations (*n*)	1 (4)	0	0

Data are means ± SD, medians (range), or *n* (%). BP, blood pressure. Duration of diabetes, A1C, BP, and birth weight in the current study are given as means ± SD to compare results with previous studies from our center (3,5).

Improved Pregnancy Outcome in Type 1 Diabetic Women With Microalbuminuria or Diabetic Nephropathy

Effect of intensified antihypertensive therapy?

Lene Ringholm Nielsen, MD, PHD[1,2]
Peter Damm, MD, DMSC[1,3]
Elisabeth R. Mathiesen, MD, DMSC[1,2]

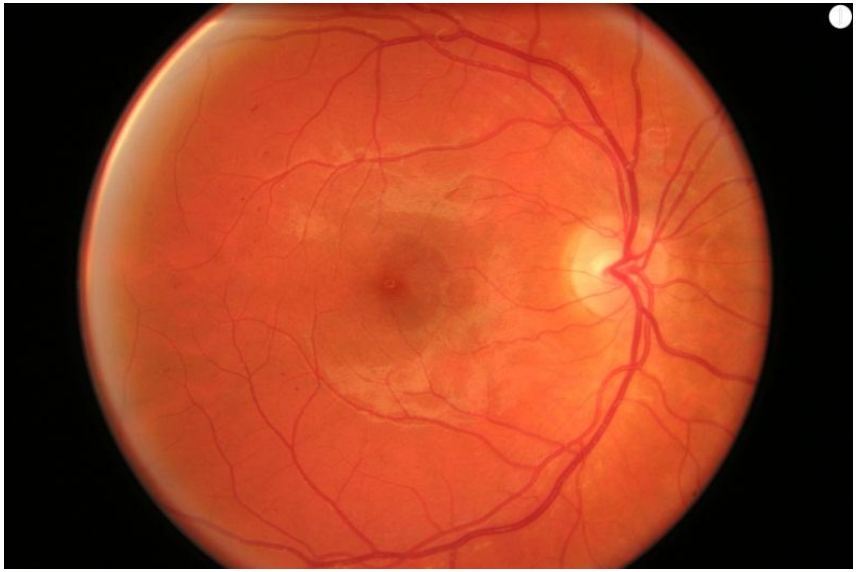
OBJECTIVE — To describe pregnancy outcome in type 1 diabetic women with normoalbu-

(8). To prevent development of hypertension and proteinuria, ACE inhibition has been documented to be effective even in normotensive diabetic women with microalbuminuria (7). However, ACE inhibition in early pregnancy has been

SIGN

monitoring eyes, albuminuria early pregnancy, 20, 28, 36 weeks

NICE uncomplicated women basal and 28 weeks



Ms M

29 years old

para 1+1, type 1 diabetes presented with a feeling of being pregnant and distended abdomen

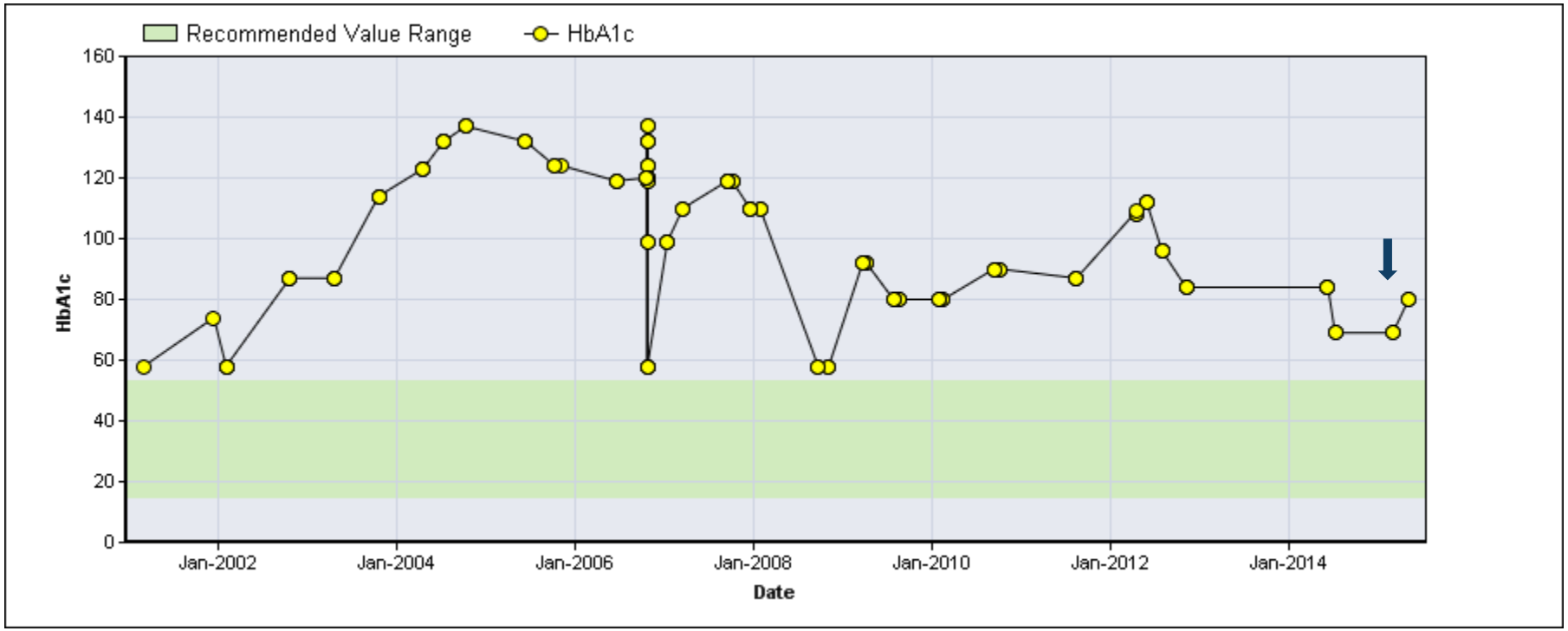
fundus at 28 weeks

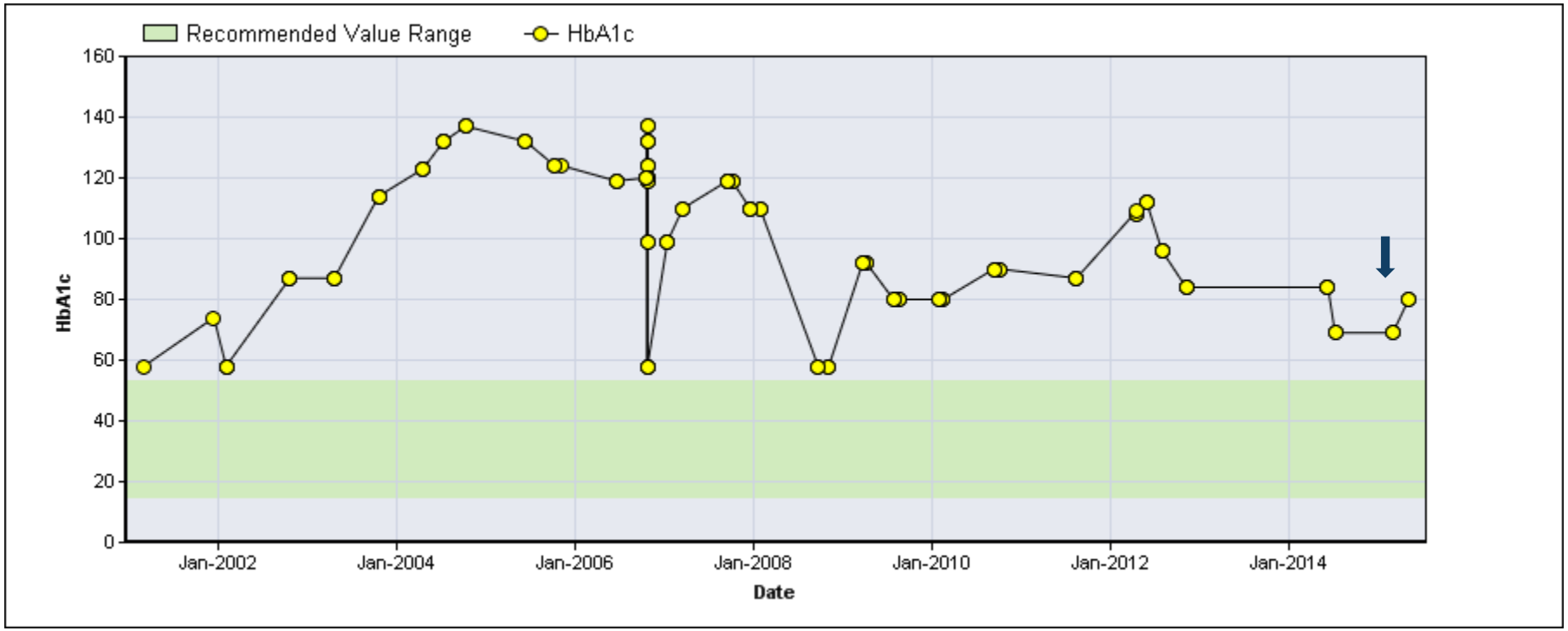
last pregnancy caesarean section at 28 weeks after antepartum haemmorhage

(known background retinopathy, no nephropathy, last HbA1c 69mmol/mol)

2 days later- emergency forceps for fetal bradycardia

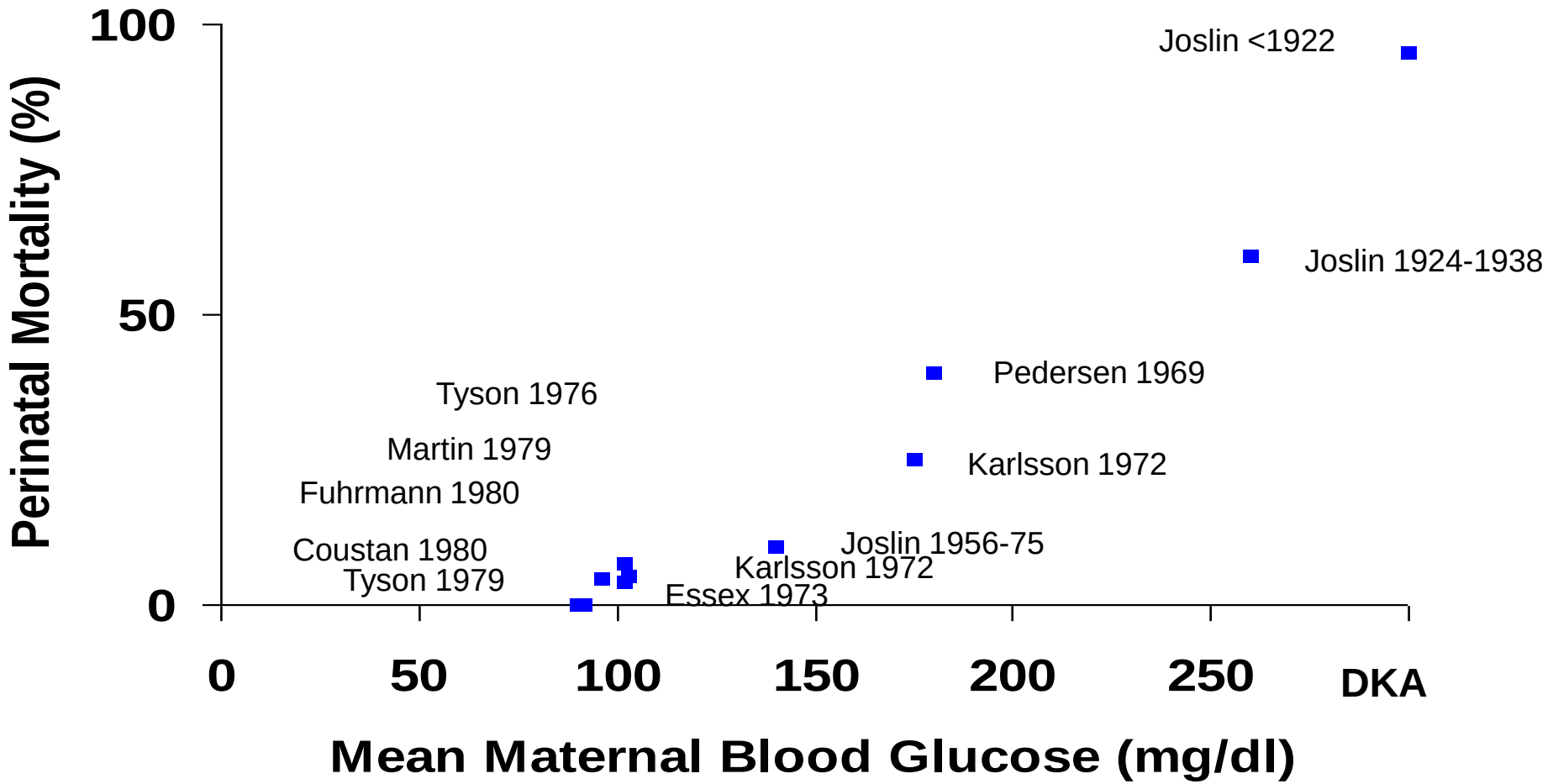
small placenta , evidence previous haemmorhage


Recommended Value Range
HbA1c
160
140
120
100
80
60
40
20
0
HbA1c
Jan-2002
Jan-2004
Jan-2006
Jan-2008
Jan-2010
Jan-2012
Jan-2014
Date



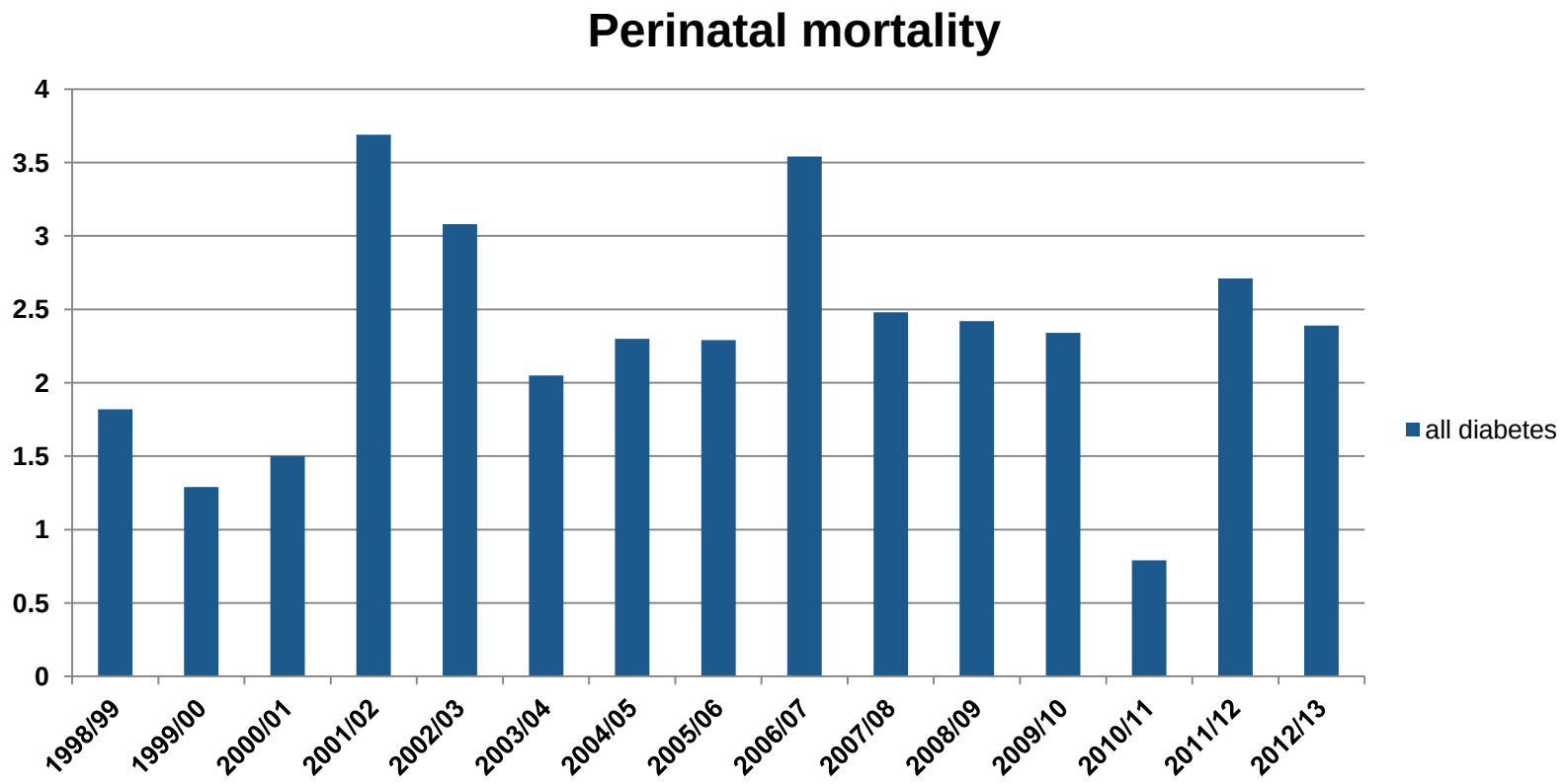
Loss of fetal movements, delivery stillborn baby

Perinatal Mortality in women with diabetes



Redrawn after Jovanovic, Diabetes Care 3: 63 1980

Perinatal mortality in mothers with diabetes: Scotland



	Diabetes	All births in Scotland
Perinatal mortality rate	2.33%	0.65%
Stillbirth	2.01%	0.49%
early neonatal	0.32%	0.16%

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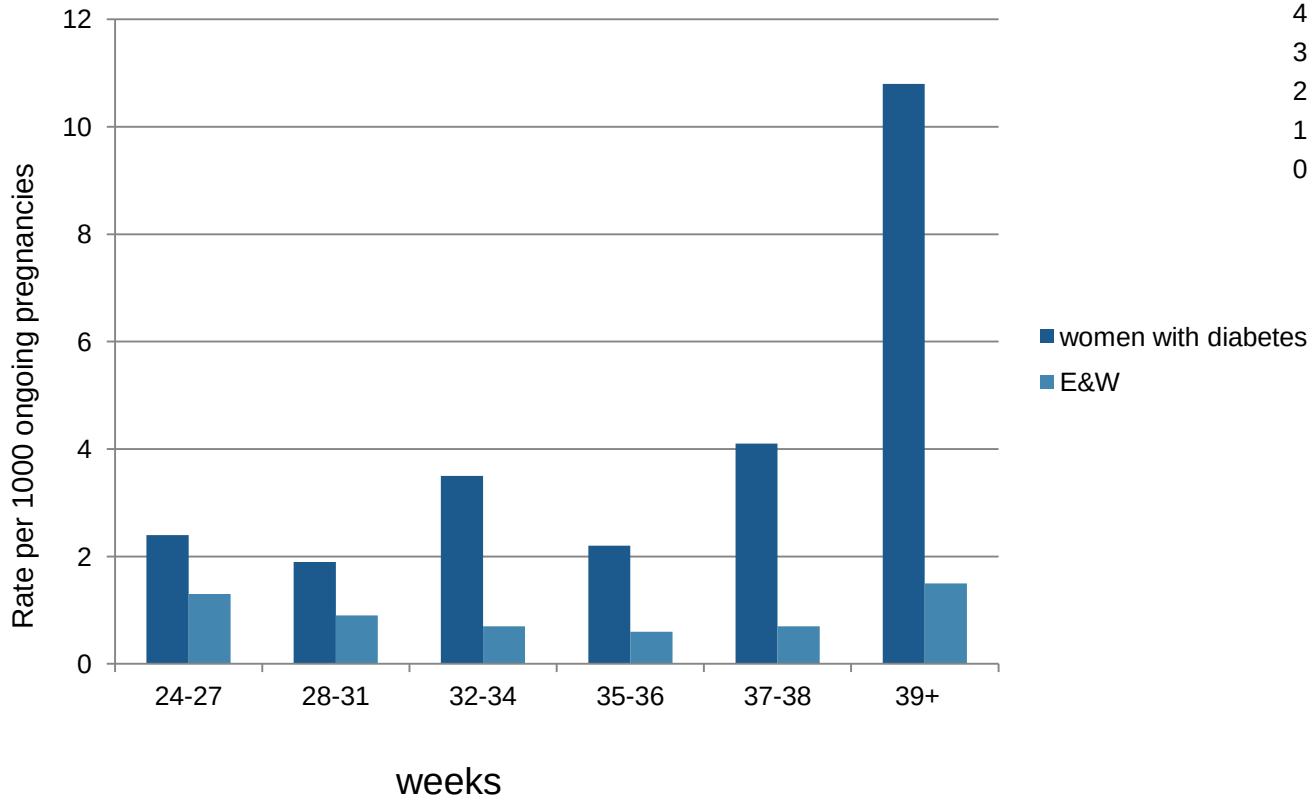
Short Report: Complications

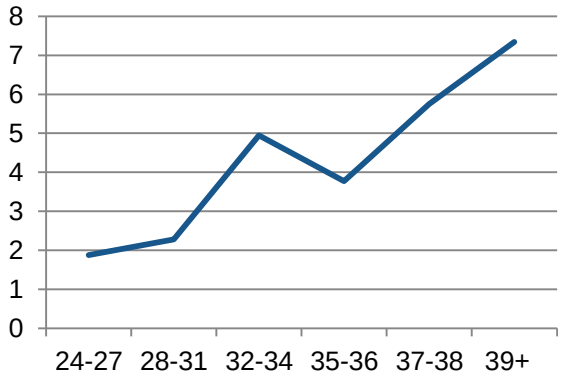
Women with pre-gestational diabetes have a higher risk of stillbirth at all gestations after 32 weeks

N. Holman[1,2], R. Bell[3], H. Murphy[4] and M. Maresh[5]

[1]National Cardiovascular Intelligence Network, Public Health England, York, [2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, [3]Institute of Health and Society, Newcastle University, Newcastle, [4]Institute of Metabolic Science, University of Cambridge, Cambridge and [5]St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

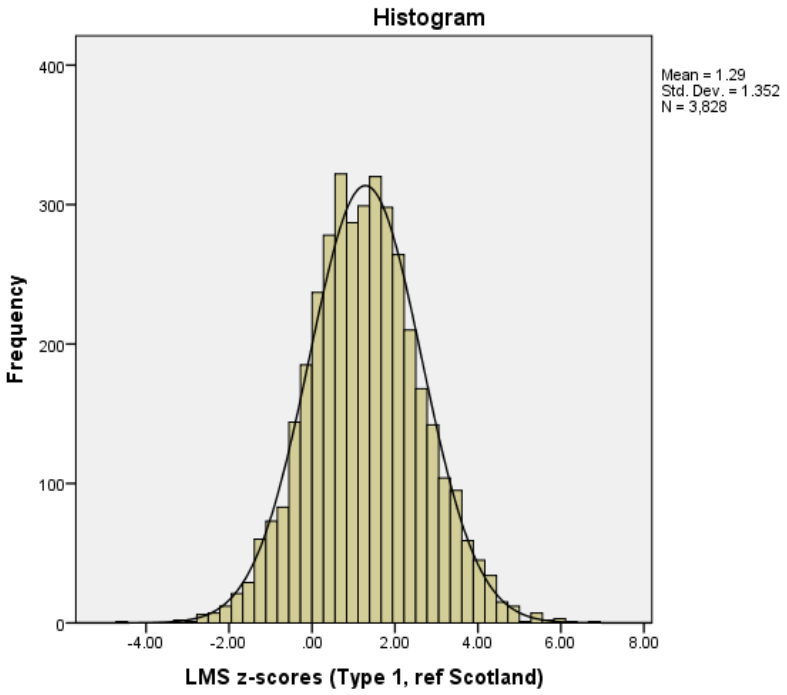
Accepted 13 May 2014

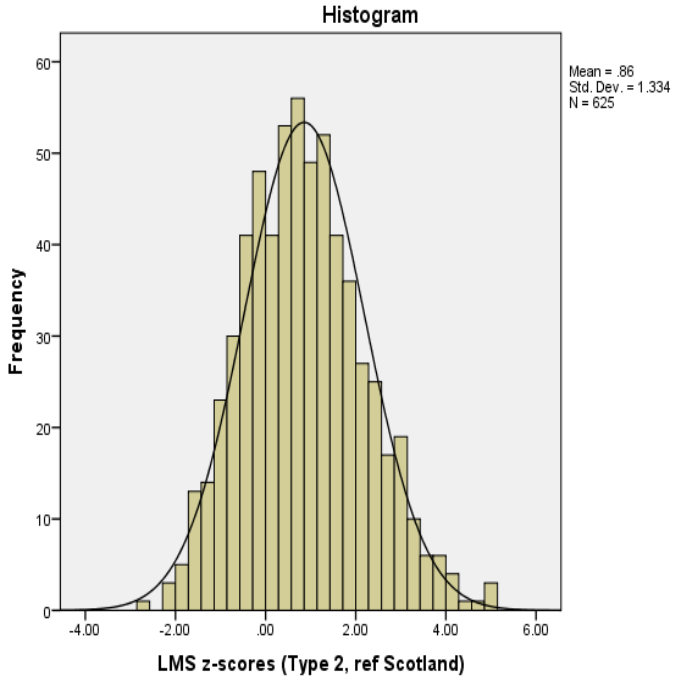




	SB	total
24-27	5	20
28-31	4	49
32-34	7	161
35-36	4	392
37-38	6	1185
39+	3	278

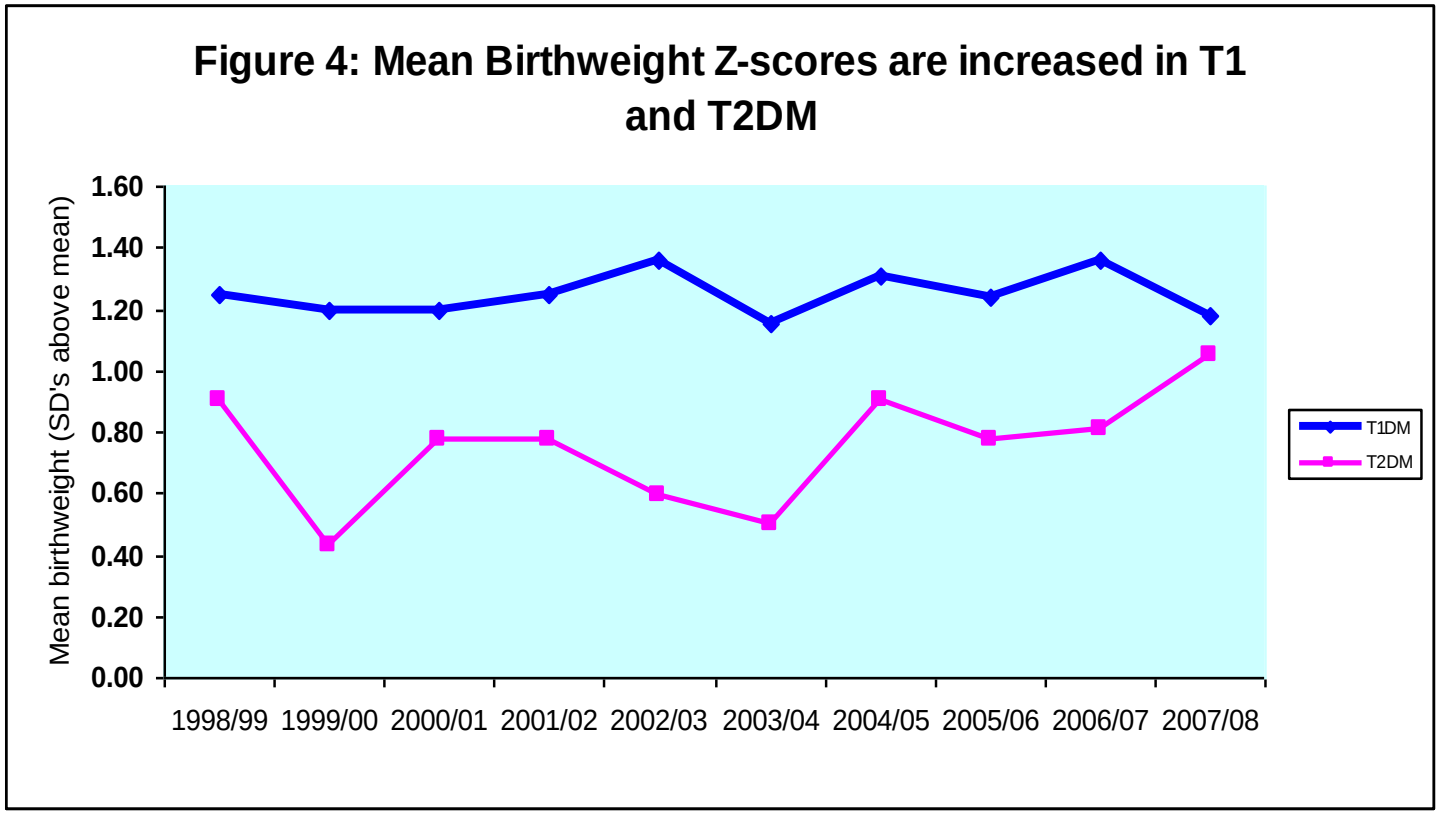
Increased birth weight in women with diabetes





	Type 1	Type 2	Scotland
Birth weight Z score	1.29 (SD 1.34)	0.85 (SD 1.32)	0.05 (1)
Gestation at delivery	36.8 (SD 2.2)	37.4 (SD 2.2)	39.3 (SD 1.9)
Preterm (<37 wks)	32.8%	21.3 %	5.9%

Scottish Pregnancy Outcomes for type 1 and type 2 diabetes



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Maternal, Newborn and Infant Clinical Outcome Review Programme

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

Saving Lives, Improving Mothers' Care

Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-2012

December 2014

321 deaths

87 women with BMI 30kg/m2

11 women with diabetes (3.4%)

12 women with endocrine disease (3.7%)

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Figure 2.3: *Direct* maternal mortality rate per 100,000 maternities; UK: 1985–2011

Figure 2.4: *Indirect* maternal mortality rates per 100,000 maternities; UK: 1985–2011

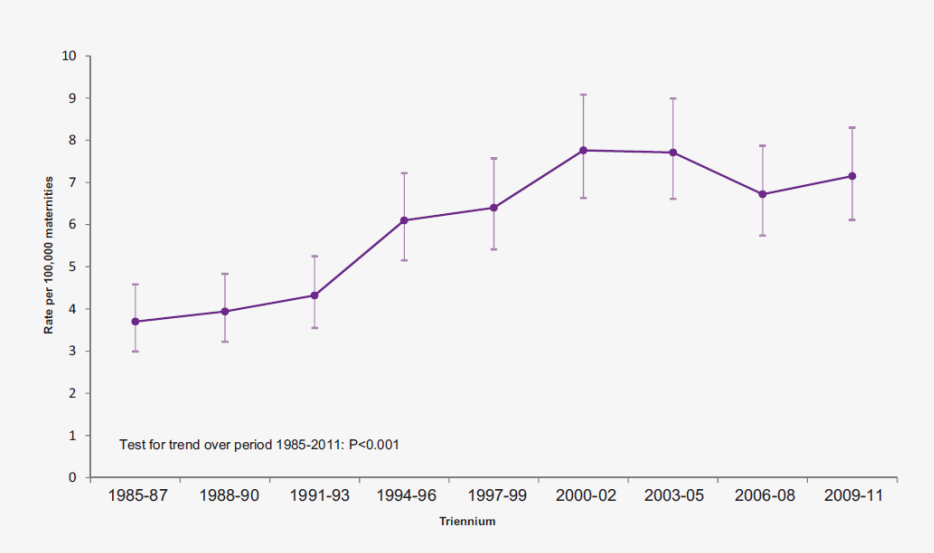

Table 2.4: Maternal mortality rates by cause, per 100,000 maternities, 2006 to 2012

Cause of death	2006–08			2009–11			2010–12		
	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
All Direct and Indirect deaths†	261	11.39	10.09–12.86	253	10.63	9.36–12.03	243	10.12	8.89–11.47
Direct deaths									
*Genital tract sepsis**	26	1.13	0.77–1.67	15	0.63	0.35–1.04	12	0.50	0.26–0.87
Pre–eclampsia and eclampsia	19	0.83	0.53–1.30	10	0.42	0.20–0.77	9	0.38	0.18–0.71
Thrombosis and thromboembolism	18	0.79	0.49–1.25	30	1.26	0.85–1.80	26	1.08	0.71–1.59
Amniotic fluid embolism	13	0.57	0.33–0.98	7	0.29	0.12–0.61	8	0.33	0.14–0.66
Early pregnancy deaths	11	0.48	0.27–0.87	4	0.17	0.05–0.43	8	0.33	0.14–0.66
Haemorrhage	9	0.39	0.20–0.75	14	0.59	0.32–0.99	11	0.46	0.23–0.82
Anaesthesia	7	0.31	0.15–0.64	3	0.12	0.03–0.37	4	0.17	0.05–0.43
Other Direct‡	4	0.17	0.07–0.47	‡	‡	‡	‡	‡	‡
All Direct	107	4.67	3.86–5.64	83	3.49	2.78–4.32	78	3.25	2.57–4.05
Indirect									
Cardiac disease	53	2.31	1.77–3.03	51	2.14	1.60–2.82	54	2.25	1.69–2.93
Other Indirect causes	49	2.14	1.62–2.83	72	3.03	2.37–3.81	61	2.54	1.94–3.26
Indirect neurological conditions	36	1.57	1.13–2.18	30	1.26	0.85–1.80	31	1.29	0.88–1.83
Psychiatric causes	13	0.57	0.33–0.98	13	0.55	0.29–0.93	16	0.67	0.38–1.08
Indirect malignancies	3	0.13	0.04–0.41	4	0.17	0.05–0.45	3	0.13	0.03–0.37
All Indirect	154	6.72	5.74–7.87	170	7.15	6.11 –8.30	165	6.87	5.86–8.00
Coincidental	50	2.18	1.65–2.88	23	0.98	0.61–1.45	26	1.08	0.71–1.59
Late deaths	33†	†	†	325	13.66	12.22–15.33	313	13.03	11.63–14.56

Diabetes

6 women T1DM

- 5 established
  - Alcohol problems and chronic pancreatitis
  - 2 died DKA
    - Addison's post partum with DKA after delivery
  - Drowning (likely hypoglycaemia)
  - Diabetic "dead in bed"
    - All had poor control prior to conception and during pregnancy

- 1 new T1DM with DKA post partum

3 women with diabetes and "direct" cause

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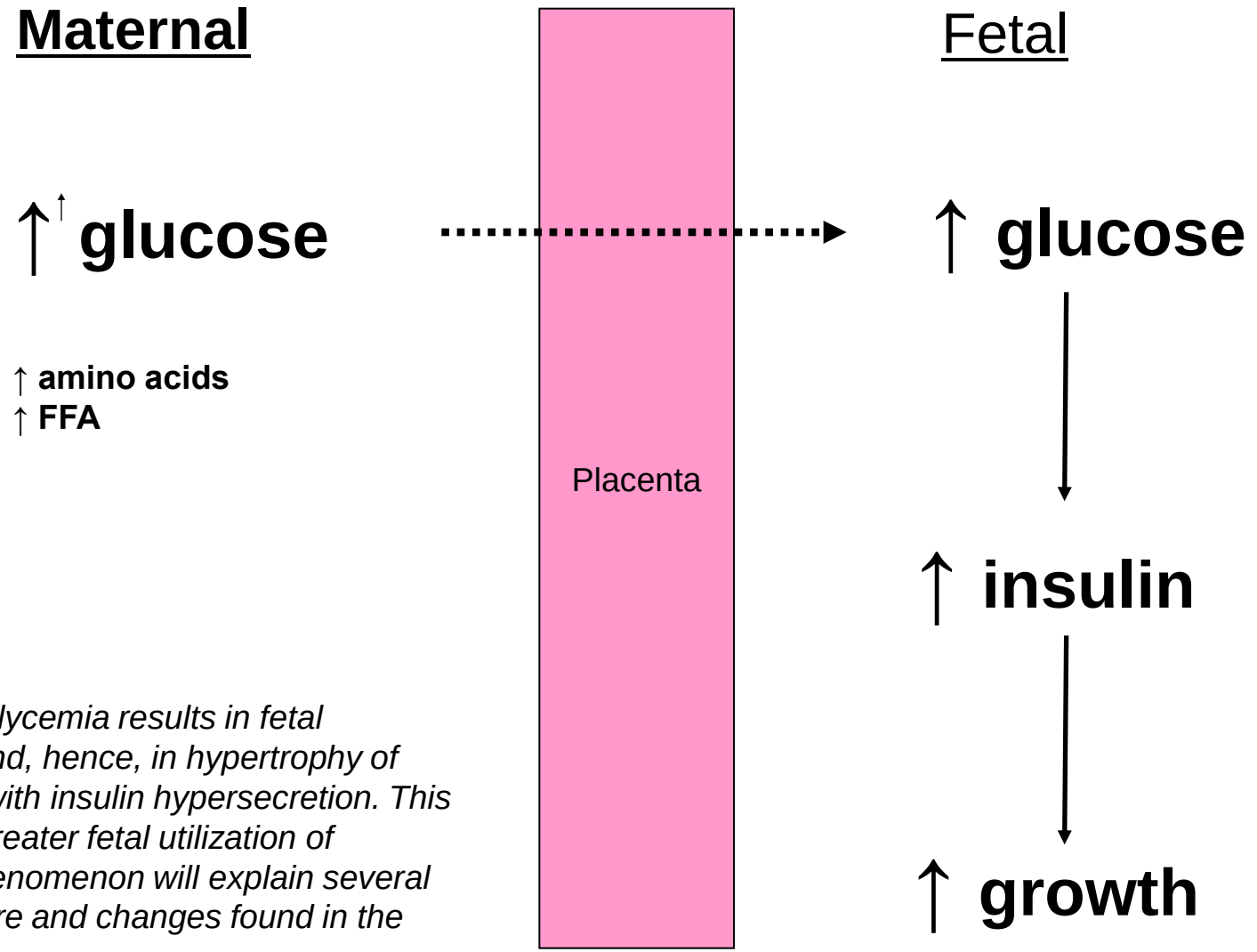
Gestational diabetes

Clairvoyance

Clarity

Controversy

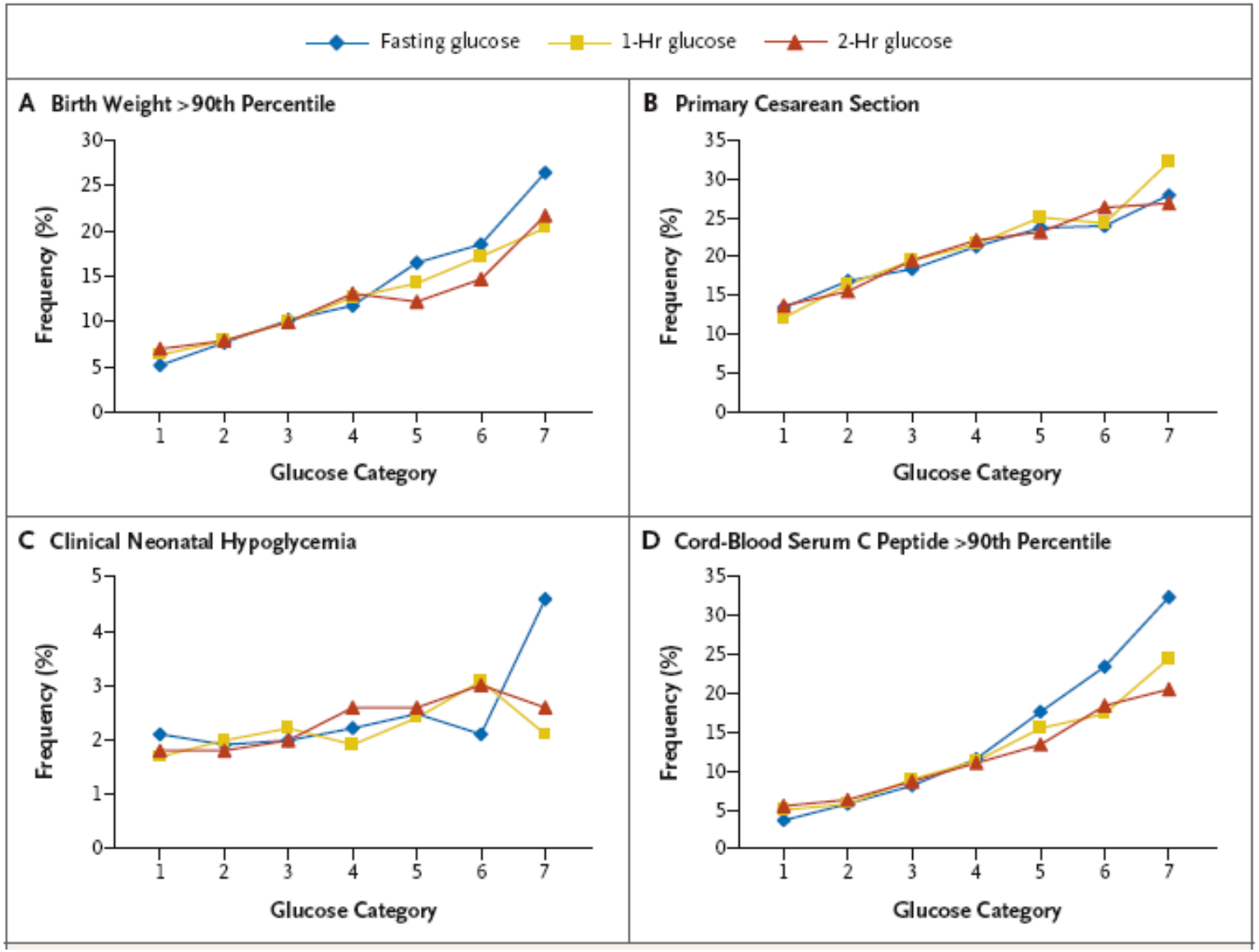
GDM Clarity: Pedersen Hypothesis



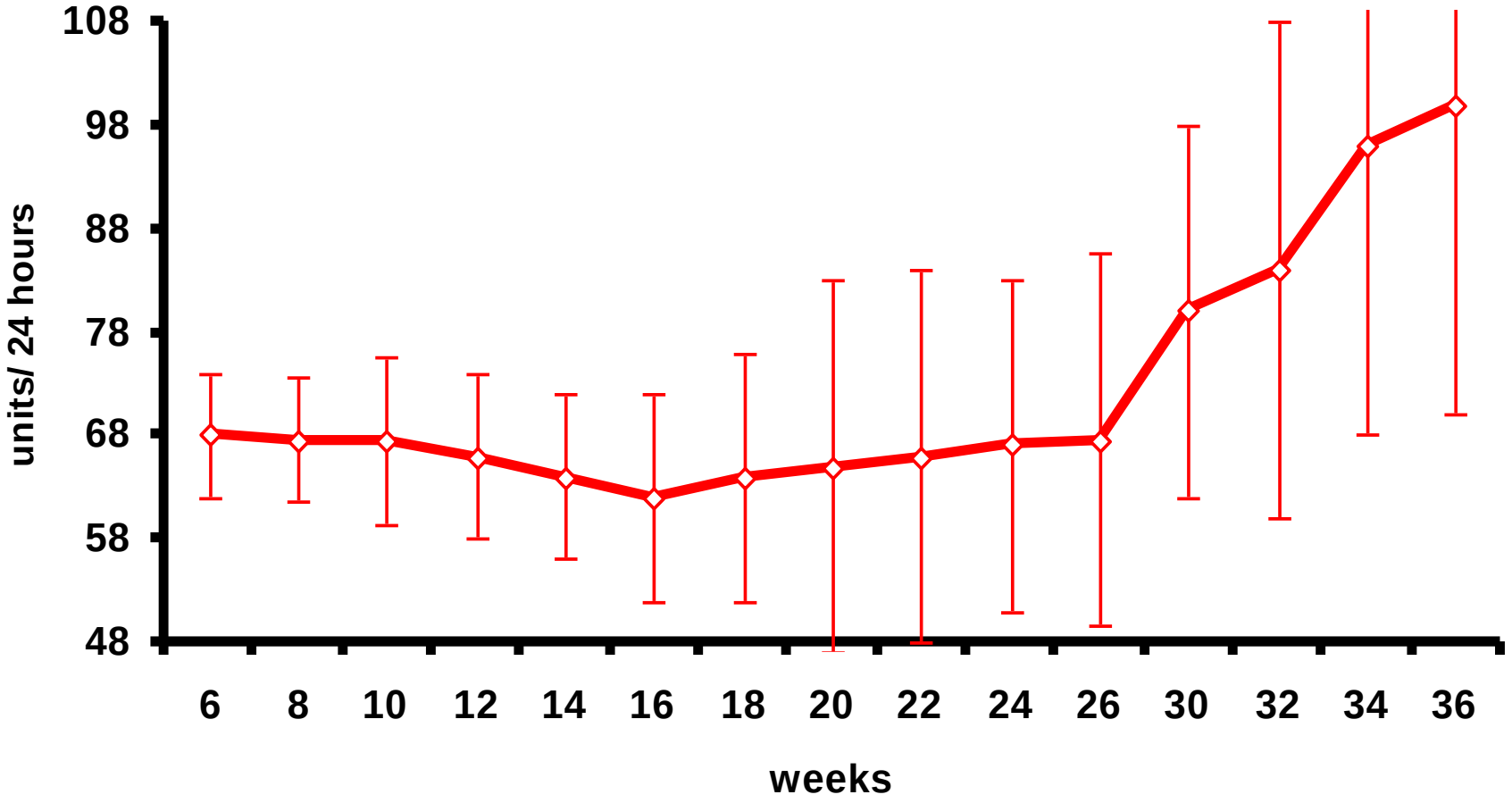
"Maternal hyperglycemia results in fetal hyperglycemia and, hence, in hypertrophy of fetal islet tissue with insulin hypersecretion. This again means a greater fetal utilization of glucose. This phenomenon will explain several abnormal structure and changes found in the newborn"

HAPO: Hyperglycaemia and Pregnancy Outcomes

NEJM 2008



Change in insulin dose through pregnancy



(redrawn from Weiss et al Obstet Gynecol 1984)

GDM Clarity: Treatment of GDM improves outcomes

Table I. Comparison of treatment effect in ACHOIS study and MFMU trial neonatal outcomes.

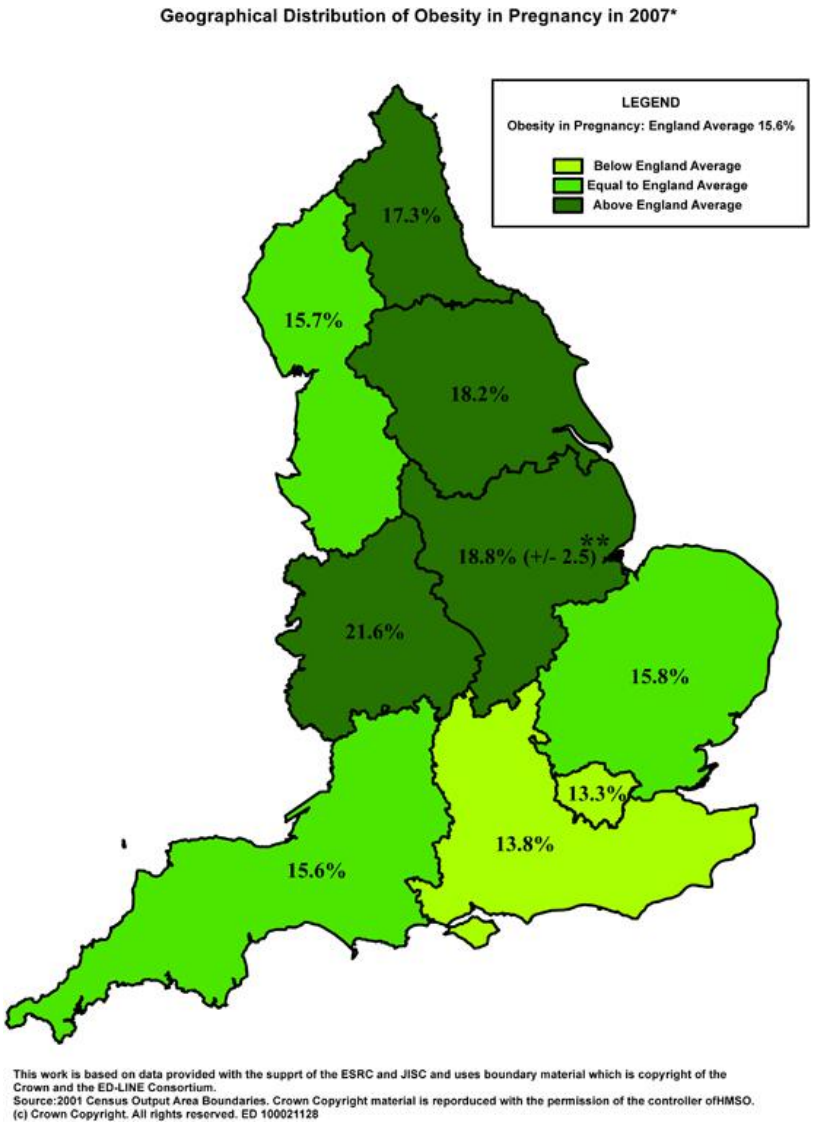
	ACHOIS study	MFMU trial
Primary outcome	Reduced	No difference
LGA infant	Reduced	Reduced
Birthweight ≥4000 g	Reduced	Reduced
Neonatal fat mass	–	Reduced
NICU admission	Increased	No difference

Table II. Comparison of treatment effect in ACHOIS study and MFMU trial maternal outcomes.

	ACHOIS study	MFMU trial
Shoulder dystocia	No difference	Reduced
Cesarean delivery	No difference	Reduced
Induction	Increased	No difference
Preeclampsia	Reduced	Reduced

GDM Clarity: declining metabolic health of the population

Heslehurst et al : International Journal of Obesity (2010) **34,** 420–428



Change in maternal first trimester BMI between 1989 and 2007 in a population of 619 323 deliveries.

GDM: controversy

Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus

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The Fifth International Workshop-Conference on Gestational Diabetes Mellitus (GDM) was held in Chicago, IL, 11–13 November 2005 under the sponsorship of the American Diabetes Association. The meeting provided a forum for review of new information

of GDM that are based on perinatal outcomes. Thus, for the interim, the participants of the Fifth International Workshop-Conference on GDM endorsed a motion to continue use of the definition, classification criteria, and strategies for detection and diagnosis of

PANEL I: PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Pathophysiology

General considerations. Current diagnostic criteria assign the diagnosis of GDM to women with glucose levels in the upper ~5–10% of the population distribution. The hyperglycemia varies in severity from glucose concentrations that would be diagnostic of diabetes outside of pregnancy to concentrations that are asymptomatic and only slightly above normal, but associated with some increased risk of fetal morbidity.

International Consensus on Gestational Diabetes:

January 2010 Diabetes Care

GDM controversy: competing guidelines

Reviews/Commentaries/ADA Statements

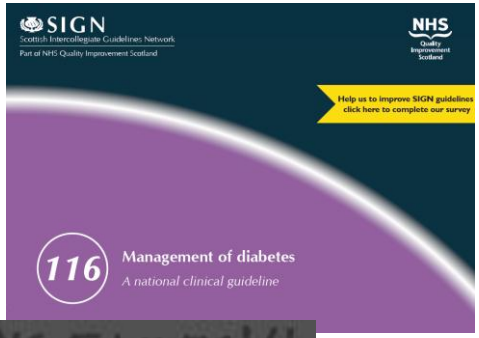
REVIEW ARTICLE

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*

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

Some have attributed risks of adverse

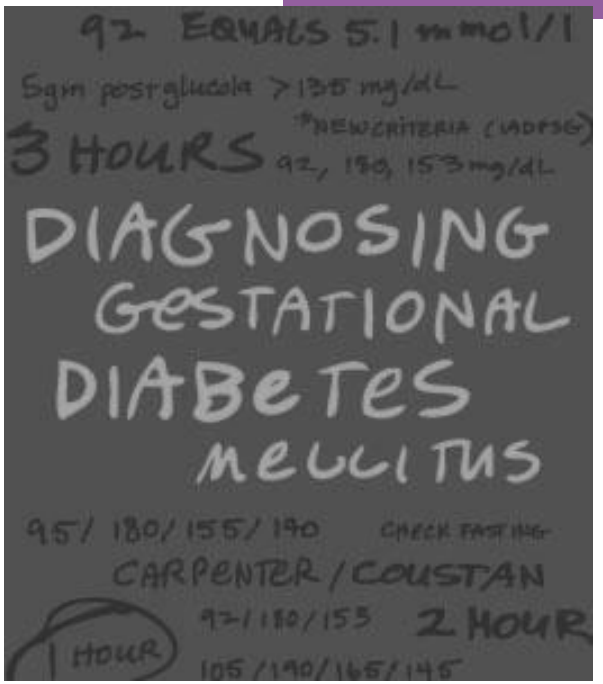


National Collaborating Centre for Women's and Children's Health

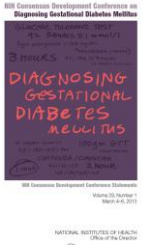
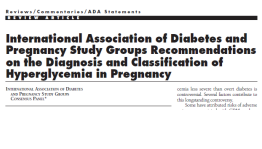
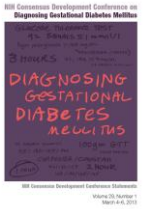
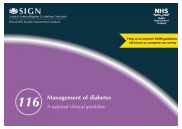
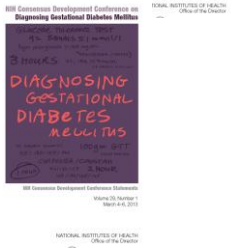
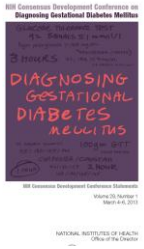
Diabetes in pregnancy

management of diabetes and its complications from preconception to the postnatal period

Clinical Guideline
March 2008 (revised reprint July 2008)
Funded to produce guidelines for the NHS by NICE



GDM controversy: competing guidelines

Screening	Universal	 	Risk factor	 
Glucose screening	One step		Two step	
OGTT	75g	  	100g	
Criteria (≥)	5.3, 10, 8.6		5.1/ 10/8.5	 
			5.6/ 7.8	

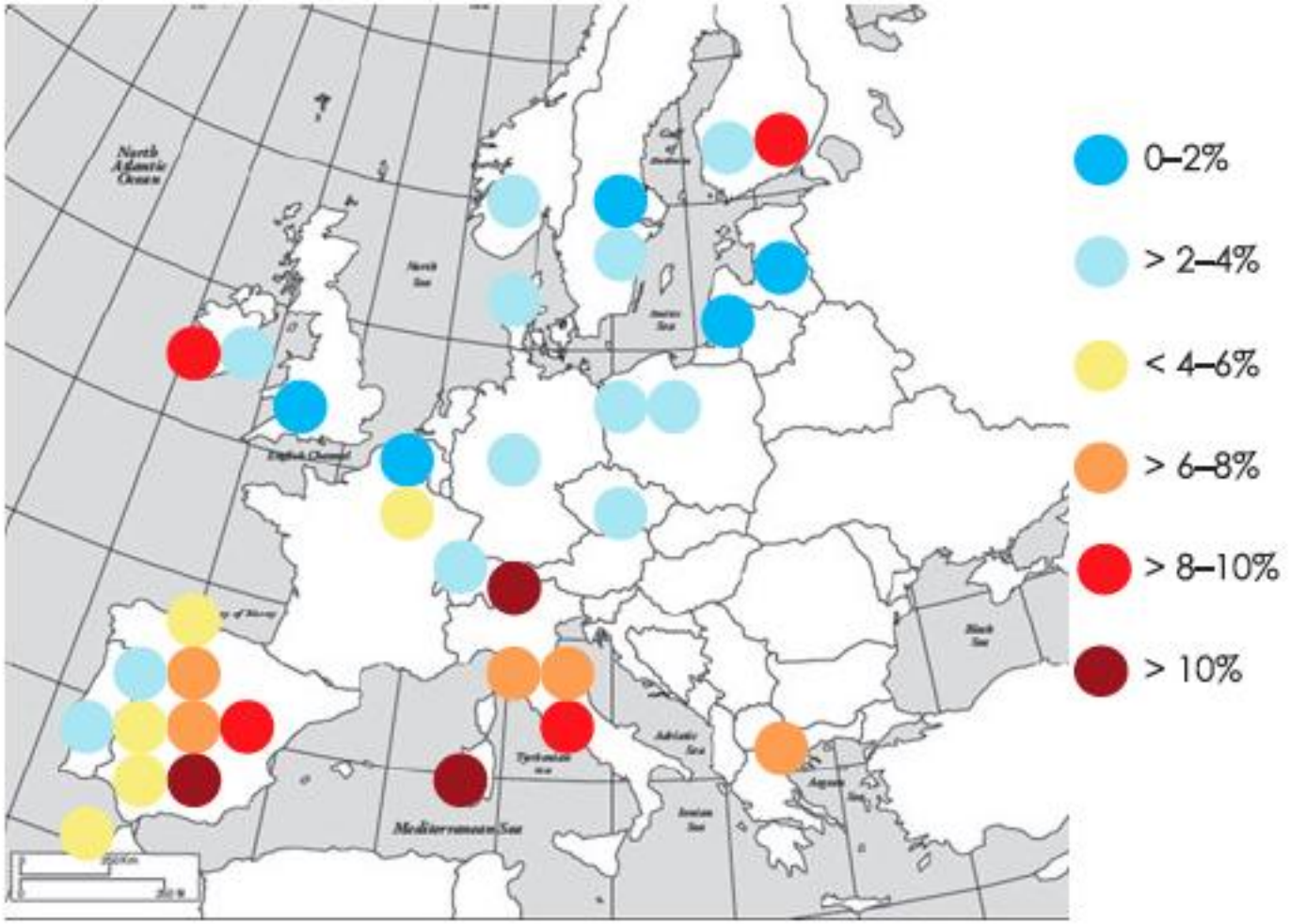


FIGURE 1 Reported prevalence of gestational diabetes in Europe.

Medicalisation : **A new deal on disease definition**

(on gestational diabetes)
"According to the critics, another case study of over-medicalisation is in the making, with the risk that millions of women will receive an unneeded label, and vast resources will be wasted"

BMJ May 14th 2011

GDM controversy

Glucose Tolerance

Normal

Gestational Diabetes

Type 1 and Type 2 Diabetes

Blood Sugar in Pregnancy

Congenital anomalies
(↑ Perinatal mortality)
Macrosomia
Shoulder dystocia
Neonatal hypoglyaemia

GDM Controversy: which outcomes are key?

Table I. Comparison of treatment effect in ACHOIS study and MFMU trial neonatal outcomes.

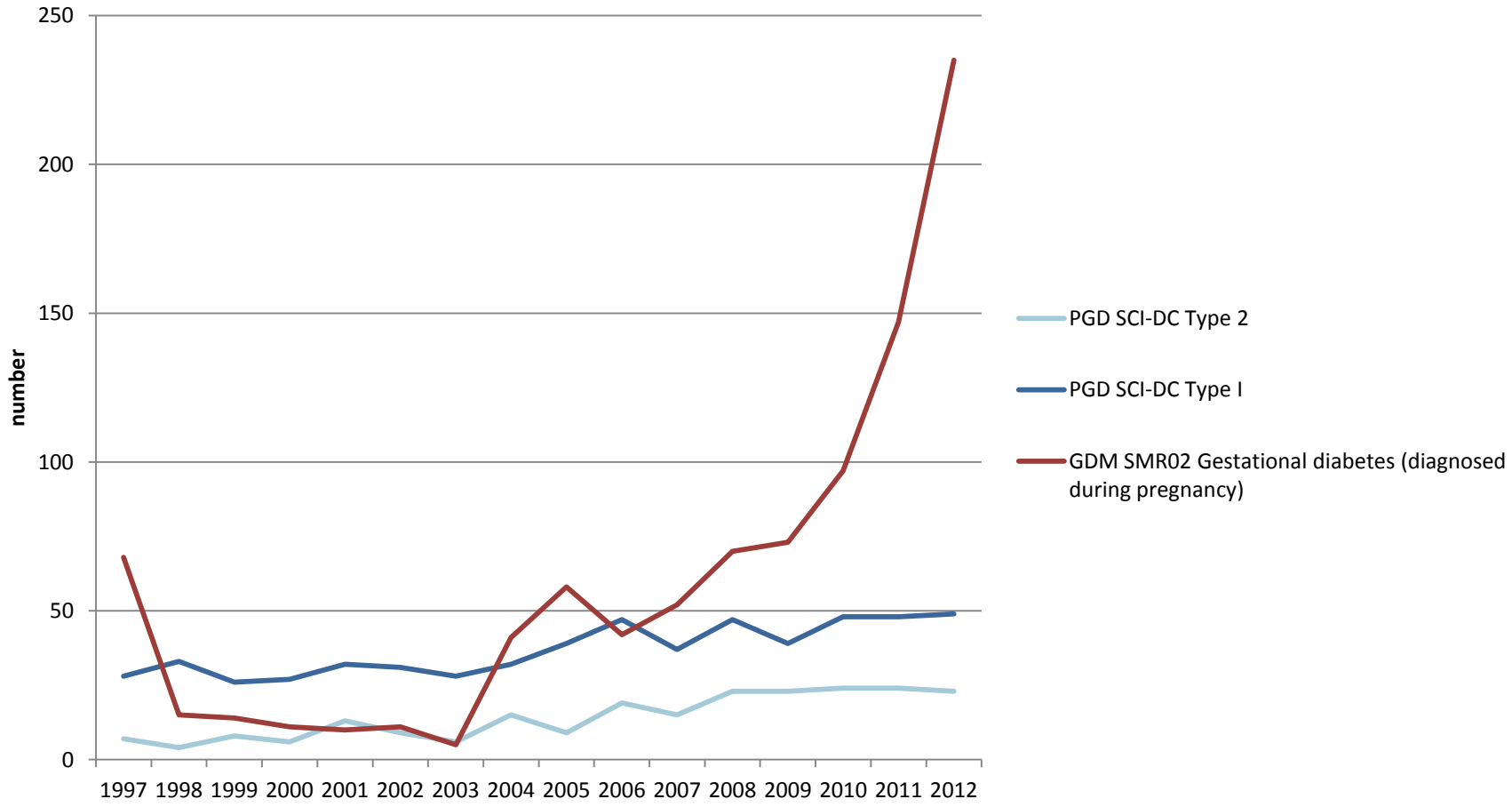
	ACHOIS study	MFMU trial
Primary outcome	Reduced	No difference
LGA infant	Reduced	Reduced
Birthweight ≥4000 g	Reduced	Reduced
Neonatal fat mass	–	Reduced
NICU admission	Increased	No difference

Table II. Comparison of treatment effect in ACHOIS study and MFMU trial maternal outcomes.

	ACHOIS study	MFMU trial
Shoulder dystocia	No difference	Reduced
Cesarean delivery	No difference	Reduced
Induction	Increased	No difference
Preeclampsia	Reduced	Reduced

University of Glasgow

GDM controversy



IADPSG guidelines

Table B. Frequency of outcomes when all glucose values are below threshold or any one or more is equal to or above threshold[+]

Outcome	FPG, 1-hr and 2-Hr OGTT values all < threshold	FPG and/or 1-hr and/or 2-hr OGTT values ≥ threshold
Birthweight > 90th percentile	8.3%	16.2%**
Cord C-peptide > 90th percentile	6.7%	17.5%**
Percent body fat > 90th percentile	8.5%	16.6%**
Preeclampsia	4.5%	9.1%**
Preterm delivery (< 37 weeks)	6.4%	9.4%**
Primary cesarean section	16.8%	24.4%**
Shoulder dystocia and/or birth injury	1.3%	1.8%*
Clinical neonatal hypoglycemia	1.9%	2.7%*
Hyperbilirubinemia	8.0%	10.0%**
Intensive neonatal care	7.8%	9.1%*

[+]Threshold values: FPG ≥ 5.1 mmol/l (92 mg/dl), 1-hr PG ≥ 10.0 mmol/l (180 mg/dl), 2-hr ≥ 8.5 mmol/l (153 mg/dl)

*Difference between groups significant at $p < 0.01$

**Difference between groups significant at $p < 0.001$

GDM clairvoyance

Glucose Tolerance

Normal

Gestational Diabetes

Type 1 and Type 2 Diabetes

Blood Sugar in Pregnancy

Congenital anomalies
(↑ Perinatal mortality)
Macrosomia
Shoulder dystocia
Neonatal hypoglyaemia

Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial

Lucilla Poston, Ruth Bell, Helen Croker, Angela C Flynn, Keith M Godfrey, Louise Goff, Louise Hayes, Nina Khazaezadeh, Scott M Nelson, Eugene Oteng-Ntim, Dharmintra Pasupathy, Nashita Patel, Stephen C Robson, Jane Sandall, Thomas A B Sanders, Naveed Sattar, Paul T Seed, Jane Wardle, Melissa K Whitworth, Annette L. Briley, on behalf of The UPBEAT Trial Consortium*

	Standard care	Intervention	Effect of intervention		p
			Risk ratio (95% CI)	Mean difference (95% CI)	
Gestational diabetes	172/651 (26%)	160/629 (25%)	0·96 (0·79–1·16)	−1·2% (−5·8 to 3·8)*	0·68
Fasting blood glucose (mmol/L)	4·71 (0·6), n=651	4·68 (0·6), n=629	..	−0·02 (−0·09 to 0·04)	0·49
1 h blood glucose (mmol/L)	8·02 (2·1), n=605	7·91 (2·1), n=584	..	−0·10 (−0·33 to 0·14)	0·43
2 h blood glucose (mmol/L)	5·94 (1·5), n=650	5·96 (1·5), n=628	..	0·02 (−0·15 to 0·19)	0·81
Treatment of gestational diabetes†	..	..	..	..	..
Dietary advice	69/146 (47%)	62/127 (49%)	1·03 (0·81–1·32)	..	0·80
Metformin	35/146 (24%)	34/127 (27%)	1·12 (0·74–1·68)	..	0·60
Metformin and insulin	16/146 (11%)	14/127 (11%)	1·01 (0·51–1·98)	..	0·99
Insulin	26/146 (18%)	17/127 (13%)	0·75 (0·43–1·32)	..	0·32
All pre-eclampsia	27/752 (4%)	27/753 (4%)	1·00 (0·59–1·69)	..	>0·99
Severe pre-eclampsia	10/752 (1%)	6/753 (1%)	1·64 (0·60–4·49)	..	0·33
Labour and delivery	..	..	..	..	..
Induction of labour	275/757 (36%)	251/765 (33%)	0·90 (0·79–1·04)	..	0·15
Unassisted vaginal delivery	399/757 (52%)	400/765 (52%)	0·99 (0·90–1·09)	..	0·87
Operative vaginal delivery	84/757 (11%)	94/765 (12%)	1·11 (0·84–1·46)	..	0·47
Caesarean section	274/757 (36%)	271/765 (35%)	0·98 (0·86–1·12)	..	0·75
Elective caesarean section	136/757 (18%)	160/765 (21%)	1·16 (0·95–1·43)	..	0·15
Emergency caesarean section	138/757 (18%)	111/765 (14%)	0·80 (0·63–1·00)	..	0·051
Post partum haemorrhage (mL)	..	..	..	..	..
≥1000	91/747 (12%)	109/755 (14%)	1·19 (0·91–1·54)	..	0·20
≥2000	10/747 (1%)	20/755 (3%)	1·98 (0·93–4·20)	..	0·075
Inpatient nights (n)	2·3 (1·8), n=691	2·4 (1·9), n=691	..	0·14 (−0·06 to 0·34)	0·16
Antenatal	2·9 (2·5), n=65	2·9 (3·5), n=74	..	−0·02 (−0·98 to 0·95)	0·98
Postnatal	2·2 (1·7), n=685	2·3 (1·6), n=684	..	0·08 (−0·09 to 0·25)	0·37
Gestational weight gain (kg)‡	..	..	..	..	..
Total	7·76 (4·6), n=567	7·19 (4·6), n=526	..	−0·55(−1·08 to −0·02)	0·041
Before pregnancy to 27–28 weeks + 6 days	5·40 (3·3), n=664	4·97 (2·9), n=637	..	−0·42(−0·75 to −0·09)	0·013

(Table 2 continues on next page)

	Standard care	Intervention	Effect of intervention		p
			Risk ratio (95% CI)	Mean difference (95% CI)	
Large for gestational age (customised birthweight centiles)	..	..	..	..	..
≥90th	61/751 (8%)	71/761 (9%)	1·15 (0·83–1·59)	1·2% (−1·6 to 4·1)*	0·40
≥95th	32/751 (4%)	39/761 (5%)	1·20 (0·76–1·90)	..	0·43
≤10th	76/751 (10%)	95/761 (13%)	1·24 (0·93–1·64)	..	0·15
≤5th	43/751 (6%)	36/761 (5%)	0·83 (0·54–1·27)	..	0·39
Population birthweight centiles	..	..	..	..	..
≥90th	83/750 (11%)	96/761 (13%)	1·14 (0·87–1·50)	..	0·35
≥95th	42/750 (6%)	51/761 (7%)	1·20 (0·81–1·78)	..	0·37
≤10th	38/750 (5%)	53/761 (7%)	1·38 (0·92–2·06)	..	0·12
≤5th	19/750 (3%)	22/761 (3%)	1·14 (0·62–2·09)	..	0·67
Birthweight (kg)	3450 (580), n=751	3420 (580), n=761	..	−27 (−85 to 31)	0·37
≥4	105/751 (14%)	105/761 (14%)	0·99 (0·77–1·27)	..	0·93
≤2·5	36/751 (5%)	31/761 (4%)	0·85 (0·53–1·36)	..	0·50
≤1·5	9/751 (1%)	7/761 (1%)	0·77 (0·29–2·05)	..	0·60
Gestational age at birth (weeks)	39·5 (2·4), n=751	39·5 (2·0), n=761	..	0·02 (−0·2 to 0·2)	0·89
Delivery ≤37 weeks	48/751 (6%)	45/761 (7%)	0·93 (0·62–1·37)	..	0·70
Delivery ≤34 weeks	16/751 (2%)	15/761 (2%)	0·93 (0·46–1·86)	..	0·83
Hospital admission	..	..	..	..	..
Admission to neonatal unit	57/751 (8%)	65/761 (9%)	1·13 (0·80–1·58)	..	0·49
Time spent in neonatal unit, if admitted (days)	16·8 (30·2), n=52	11·6 (23·5), n=61	..	−0·26 (−9·65 to 9·13)	0·96
Time spent in hospital after birth, if admitted (days)	3·0 (9·0), n=733	2·8 (7·3), n=743	..	−0·06 (−0·86 to 0·74)	0·88
Neonatal death	2/771 (<1%)	3/783 (<1%)	0·98 (0·14–6·97)	..	0·99
Intraventricular haemorrhage, grade 3–4	2/751 (<1%)	0/760	..	..	..
Retinopathy of prematurity	1/751 (<1%)	1/760 (<1%)	0·99 (0·06–15·70)	..	0·99
Discharged home on oxygen	4/751 (1%)	2/760 (<1%)	0·49 (0·09–2·69)	..	0·41
Neonatal hypoglycaemia	12/751 (2%)	27/760 (4%)	2·22 (1·13–4·36)	..	0·020
Confirmed infection	14/751 (2%)	7/760 (1%)	0·49 (0·20–1·22)	..	0·13
Congenital abnormalities	6/751 (1%)	5/760 (1%)	0·82 (0·25–2·69)	..	0·75
Mechanical ventilation	21/751 (3%)	19/760 (3%)	0·89 (0·48–1·65)	..	0·72
Duration of mechanical ventilation (h)	500 (885), n=20	330 (573), n=16	..	−170 (−667 to 327)	0·49
Necrotising enterocolitis	2/751 (<1%)	0/760	..	..	..
Pulmonary haemorrhage	2/751 (<1%)	1/760 (<1%)	0·49 (0·04–5·43)	..	0·56

Data are number of children/total (%) or mean (SD), number of children. Population centiles were calculated with WHO centiles. *For the primary neonatal outcome, the risk difference (95% CI) is presented.

Table 4: Neonatal outcomes

Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial

Carolyn Chiswick, Rebecca M Reynolds, Fiona Denison, Amanda J Drake, Shareen Forbes, David E Newby, Brian R Walker, Siobhan Quenby, Susan Wray, Andrew Weeks, Hany Lashen, Aryelly Rodriguez, Gordon Murray, Sonia Whyte, Jane E Norman

	Placebo group		Metformin group		Adjusted mean difference or OR (95 % CI)	p value
	Mean (SD) or n (%)	N	Mean (SD) or n (%)	N		
Primary outcome						
Z score of birthweight percentile*	0·2680 (1·0055)	220	0·2464 (1·0179)	214	−0·029 (−0·217 to 0·158)	0·76
Birth outcome (all births)						
Livebirth at ≥24 weeks' gestation	220 (99%)	222	214 (97%)	221	..	..
Stillbirth at ≥24 weeks' gestation, miscarriage, or termination of pregnancy	2 (1%)†	222	7 (3%)‡	221	3·597 (0·739 to 17·504)§	0·11
Birth outcome (liveborn babies at ≥24 weeks' gestation)						
Gestational age at delivery (days)	275·9 (15·9)	220	276·6 (11·7)	214	..	..
Male sex	109 (50%)	220	109 (51%)	214	..	..
Birthweight at delivery (g)	3463 (660)	220	3462 (548)	214	..	..
Birthweight percentile	57·3 (27·9)	220	56·9 (28·6)	214	..	..

OR=odds ratio. *Percentile by gestational age, sex, and parity for livebirths at ≥24 weeks' gestation. †Two terminations of pregnancy, one for fetal abnormality (split hand and foot syndrome) and one after a spontaneous membrane rupture at 18 weeks' gestation. ‡Of the two stillbirths, one was at 31 weeks of a baby with a known cardiac anomaly and severe hydrops fetalis and one was an intrauterine death of a normally formed baby born at 38 weeks with a birthweight less than the third percentile for gestation. Of the four miscarriages, one was after a road traffic accident and three were spontaneous. One termination of pregnancy was done after a diagnosis of trisomy 21. None of the women returned diaries nor provided a blood sample for analysis of metformin. §OR from post-hoc analysis.

Table 2: **Primary and birth outcomes**

	Placebo group		Metformin group	
	Mean (SD) or n (%)	N	Mean (SD) or n (%)	N
(Continued from previous page)				
Subscapular skinfold (mm)	32·0 (12·2)	222	32·6 (11·8)	220
Maternal fat (%)*	46·8 (5·6)	48	48·2 (5·2)	53
Blood tests				
Fasting glucose (mmol/L)	4·39 (0·34)	223	4·41 (0·40)	226
2 h glucose (mmol/L)†	5·50 (1·09)	223	5·20 (1·08)	226
Fasting insulin (pmol/L)	153·35 (70·84)	189	152·44 (85·15)	188
HOMA-IR score‡	4·36 (2·16)	189	4·36 (2·76)	188
C-reactive protein (mg/L)	11·1 (7·4)	221	10·7 (6·9)	223
Cholesterol (mmol/L)	4·87 (1·15)	216	4·88 (1·09)	214
HDL (mmol/L)	1·67 (0·39)	215	1·64 (0·38)	214
LDL (mmol/L)	2·91 (0·78)	194	2·89 (0·86)	191
Triglycerides (mmol/L)	1·51 (0·53)	216	1·43 (0·56)	214
Interleukin-6 (mmol/L)	2·77 (5·50)	189	2·63 (4·37)	188
Leptin (ng/mL)	93·6 (42·1)	189	98·5 (40·3)	188
Serum cortisol (nmol/L)	396·4 (143·6)	189	431·0 (178·8)	188
NEFA (mmol/L)	0·52 (0·20)	189	0·48 (0·18)	188
PAI-1 to PAI-2 ratio	1·48 (1·39)	131	1·77 (5·22)	128
Putative father details				
Height (cm)	178·5 (8·3)	204	177·1 (13·7)	202
Weight (kg)	92·3 (22·5)	187	93·5 (25·8)	188
Ethnic origin				
White	214 (96%)	223	210 (94%)	224
Mixed	4 (2%)	223	4 (2%)	224
Asian	0	223	3 (1%)	224
Black	4 (2%)	223	6 (3%)	224
Chinese	0	223	0	224
Other	1 (<1%)	223	1 (<1%)	224

HOMA-IR= homeostatic model assessment of insulin resistance. NEFA=non-esterified fatty acids. PAI=plasminogen activator inhibitor. *Measured only in Edinburgh participants. †After a 75 g oral glucose challenge. ‡Fasting glucose (mmol/L)×insulin (μIU/L).

Table 1: **Baseline characteristics**

GDM clairvoyance

Diabetes in Pregnancy useful concept

GDM/ hyperglycaemia in pregnancy as a risk factor rather than disease

Risk stratification

University of Glasgow

University of Glasgow

"Sugar Pie, Honey Bunch"

Oooooooooooooooh!
Sugar Pie, Honey Bunch
You know that I love you
I can't help myself
I love you and nobody else

University of Glasgow

Princess Royal Maternity Unit

Fiona Mackenzie
David Carty


University
of Glasgow
VIA VERITAS VITA