Imperial College London

NHS Imperial College Healthcare NHS Trust

Gestational Diabetes and Type 2 Diabetes in Pregnancy

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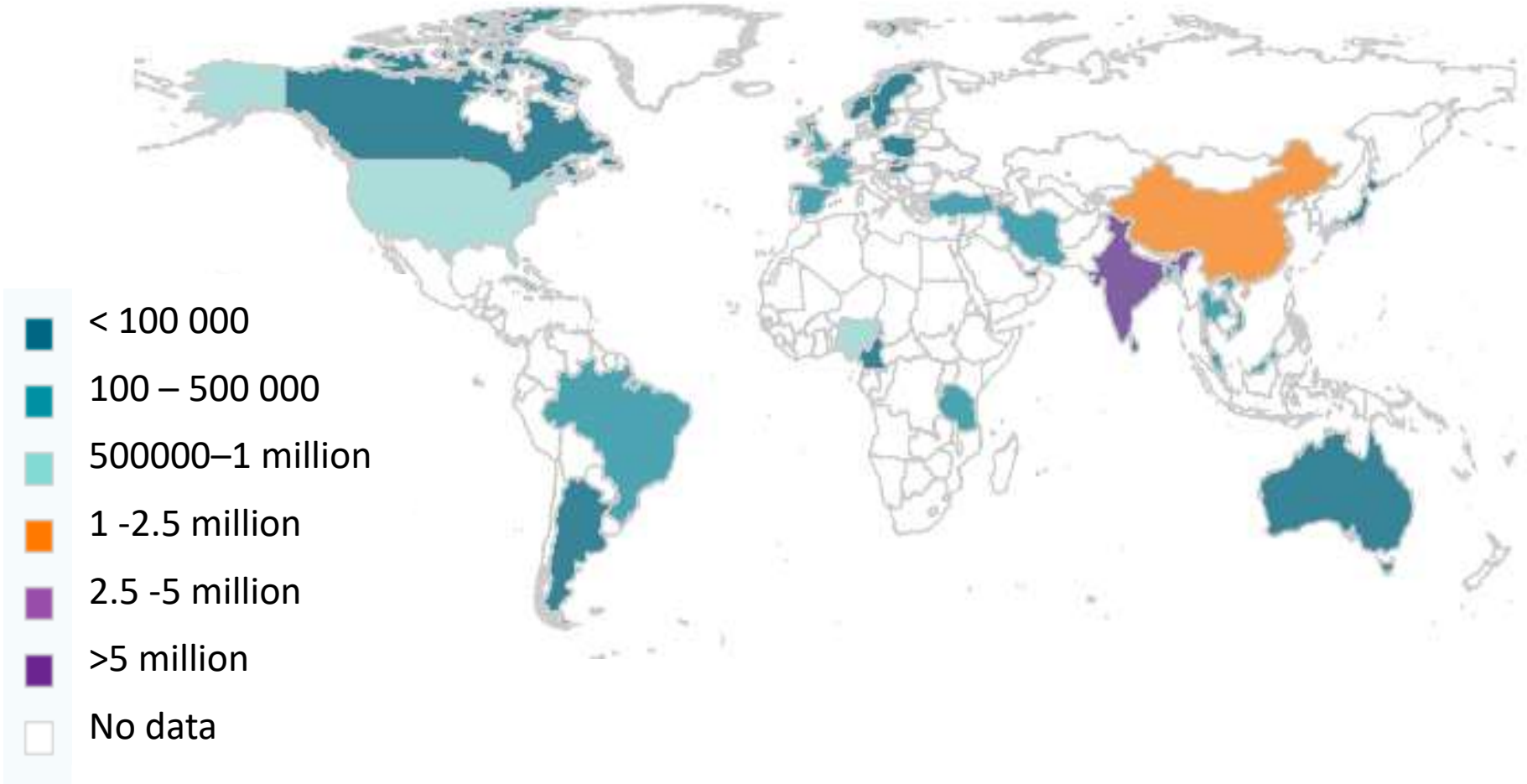
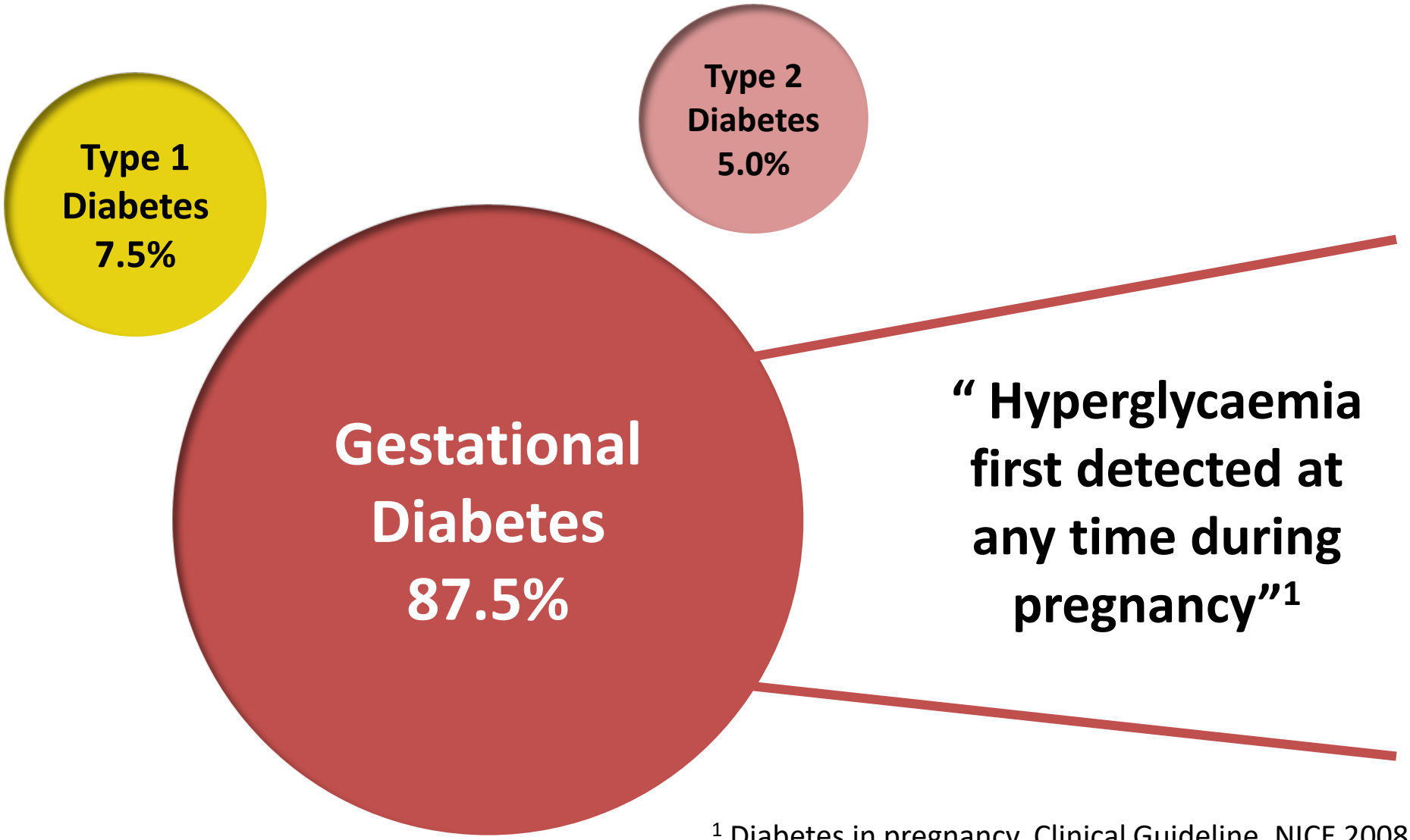
30th October 2019

Number of Live Births affected by Hyperglycaemia in 1000s: IDF Atlas (2017)



UK Data: 177 800 pregnancies complicated by hyperglycaemia



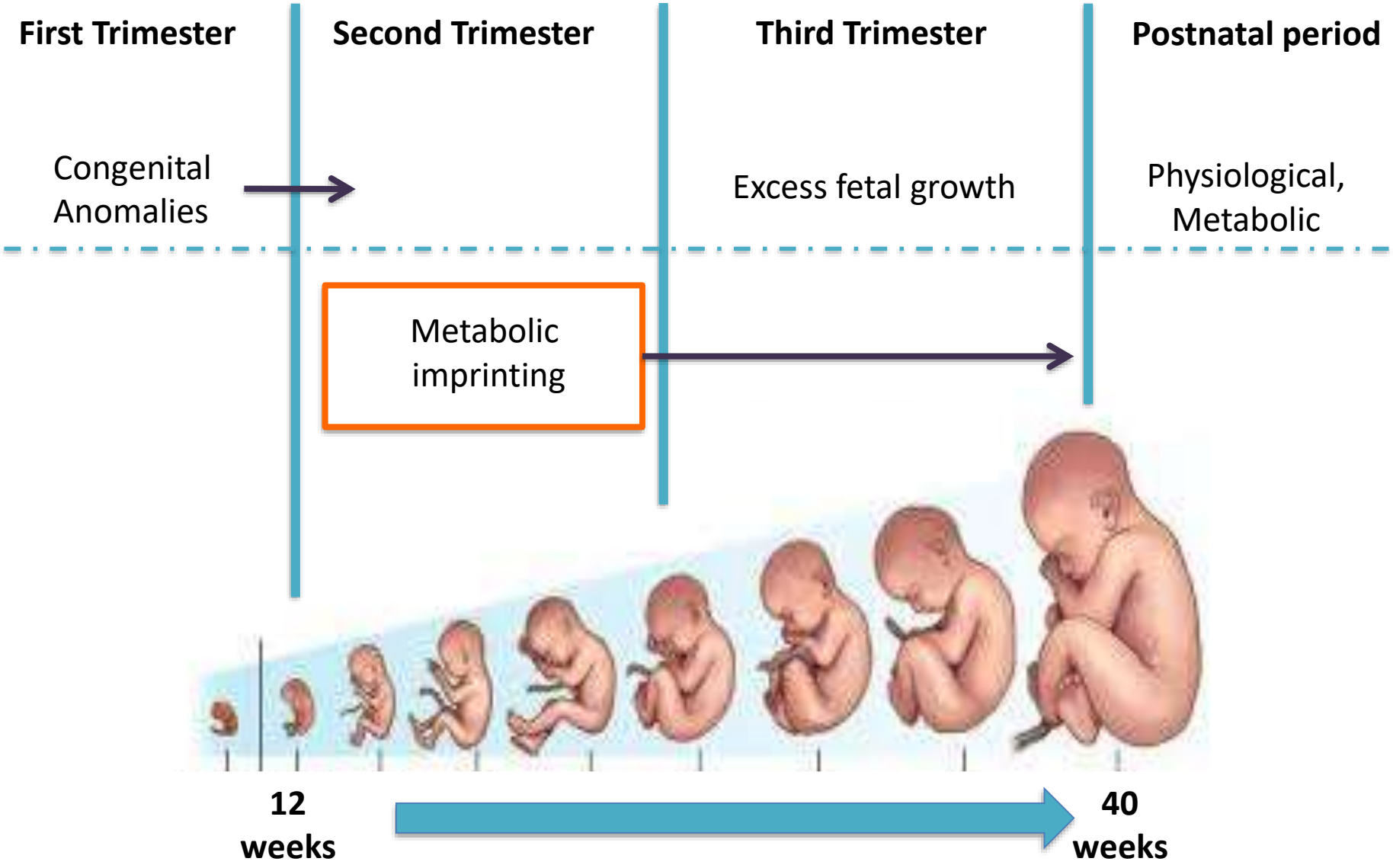
“ Hyperglycaemia first detected at any time during pregnancy”[1]

[1] Diabetes in pregnancy. Clinical Guideline. NICE 2008

Objectives

- Risks associated with development of hyperglycaemia in pregnancy
- Methods for mitigating materno-fetal risk
- Review materno-fetal outcomes in T2DM
- Understand the long-term risks of diabetes in pregnancy for mother and baby
- Long-term effects of in-utero exposure to metformin

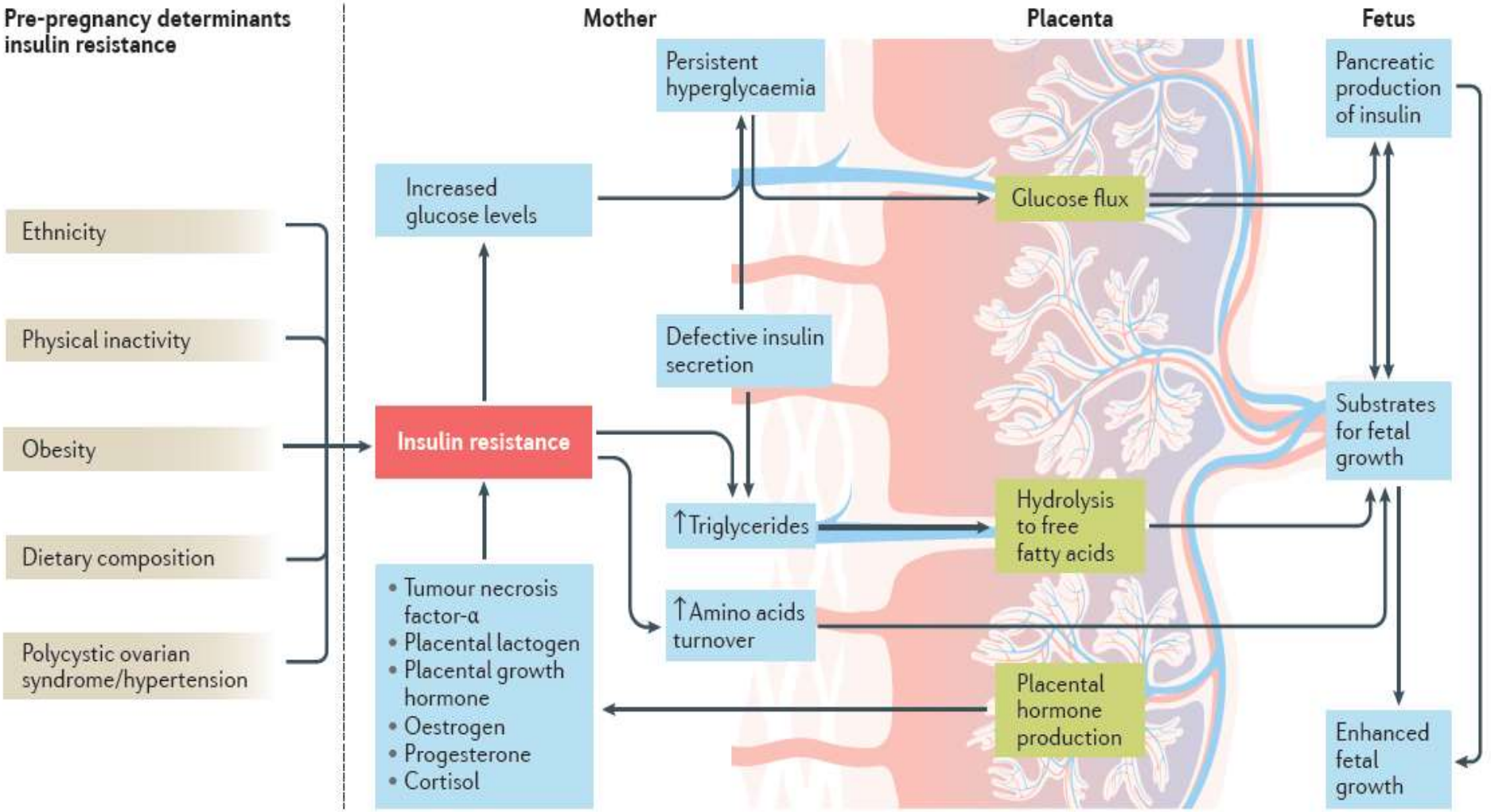
Effects of Exposure to in Utero Hyperglycaemia



Early Fetal development

- Risk congenital malformations 3-5 times higher than background population
- Teratogenic effects of hyperglycaemia and ketonaemia implicated in fetal embryopathy
- “Oxidative stress hypothesis”

Pathophysiology Fetal Macrosomia



Nature Reviews Endocrinology (12): 533-546

Postnatal Complications

Intrauterine Death/ Still Birth

3-5 times higher than background rate

Mechanisms poorly understood

Thought to relate

- fetal hypoxia
- Placental insufficiency

Teramo et al 2004 Diabetologia

Objectives

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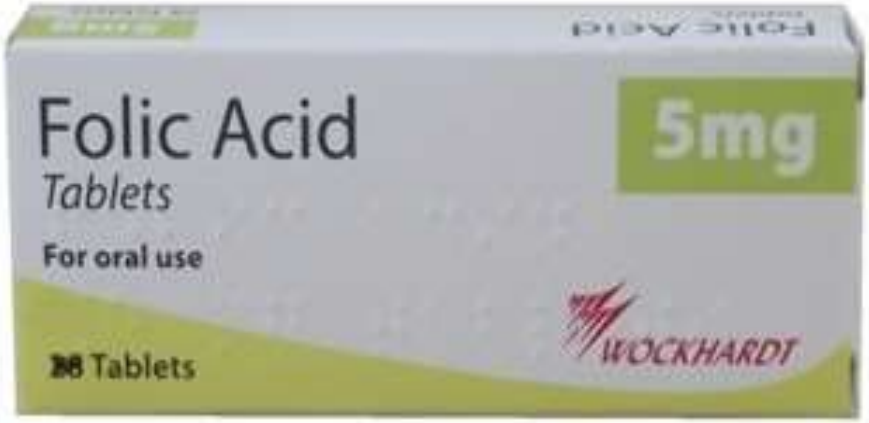
Type 2 Diabetes: Preconception Care



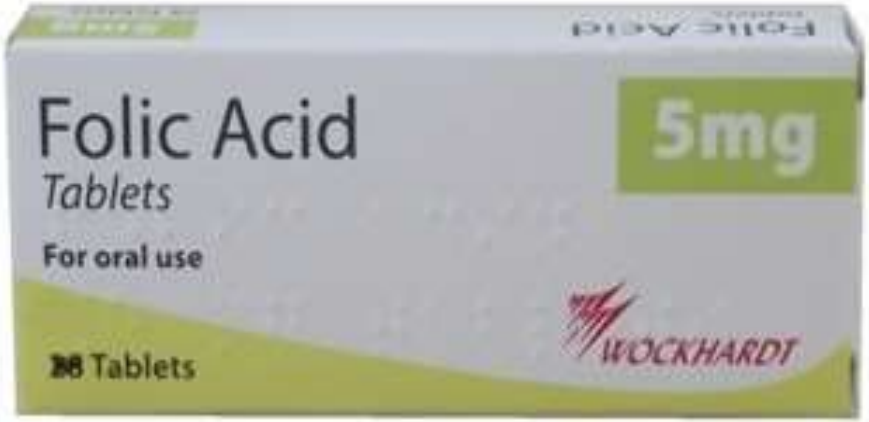
- Well established guidance for women with pre-gestational diabetes
- Evidence base largely exists in women with previous neonate with neural tube defect
- Consider potential vitamin B12 deficiency

Type 2 Diabetes: Preconception Care

- **Statins – potentially teratogenic**
  - Congenital malformation risk Unadjusted RR 1.79 (95% CI 1.43-2.27): Adjusted RR 1.07 (95% CI 0.85-1.37)

- **ACE/ARBs – unclear effects of first trimester exposure**
  - Use in 2nd/3rd trimester contraindicated due to damaging effects on kidneys

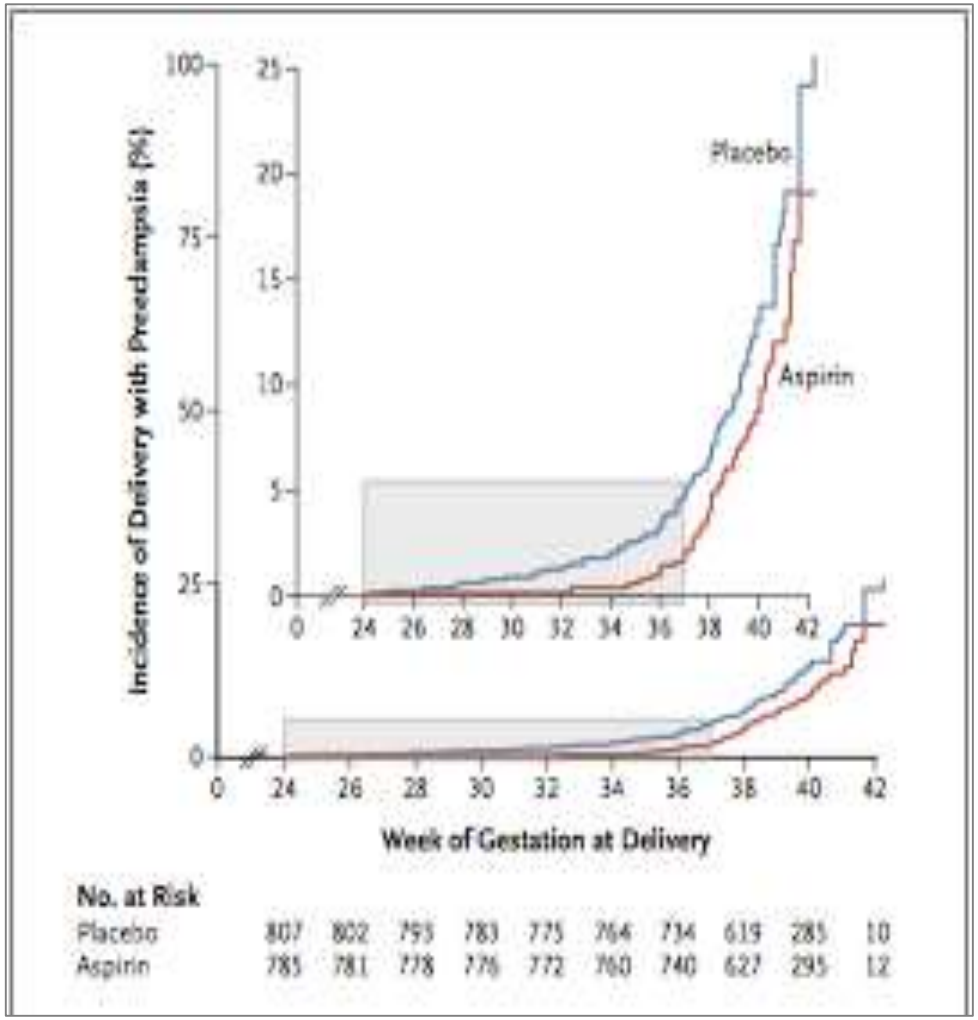
Type 2 Diabetes: Preconception Care



Target HbA1c
≤ 48mmol/mol

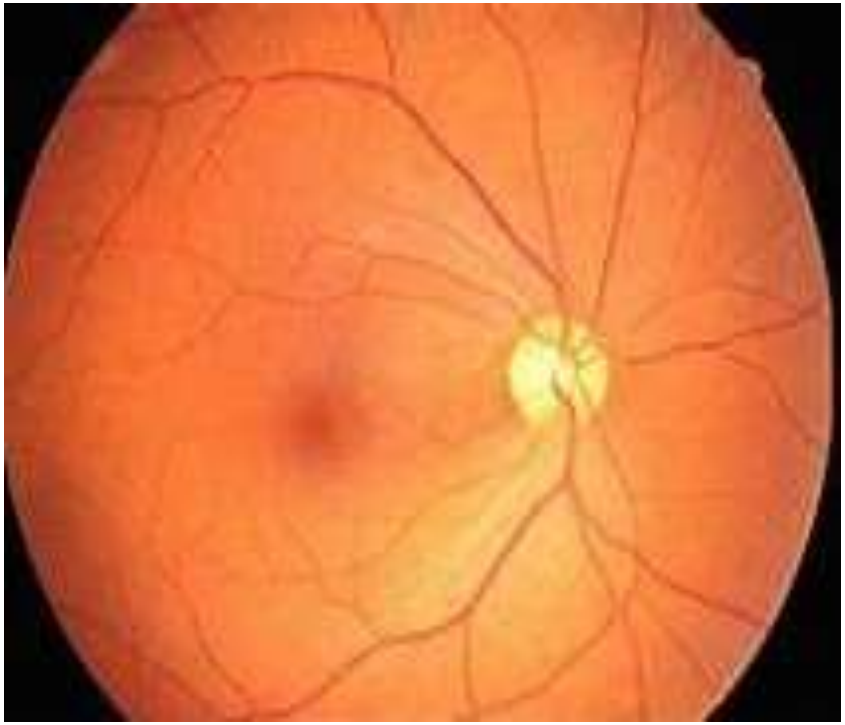
Type 2 Diabetes Antenatal Considerations: Pre-eclampsia Prevention

- N=1776
- High risk for pre-term PET
- Randomised 150mg aspirin versus placebo from 12 weeks gestation
- NOT specifically diabetes



Rolnik et al 2017 NEJM 377:613

Antenatal Care: Further Considerations



Retinal screening recommended at least twice (booking and 28 weeks)

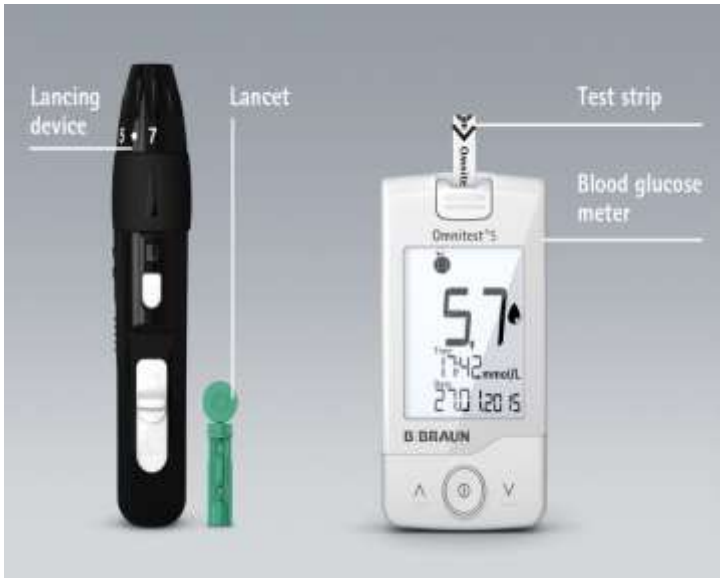
Risk progression retinopathy not as high as Type 1 diabetes

- occurred in 14%

Reduction in HbA1c from baseline to 34 weeks significantly higher in those with progression

Rasmussen K.L. et al. Diabetologia 2009

Glucose Monitoring in Type 2/ GDM

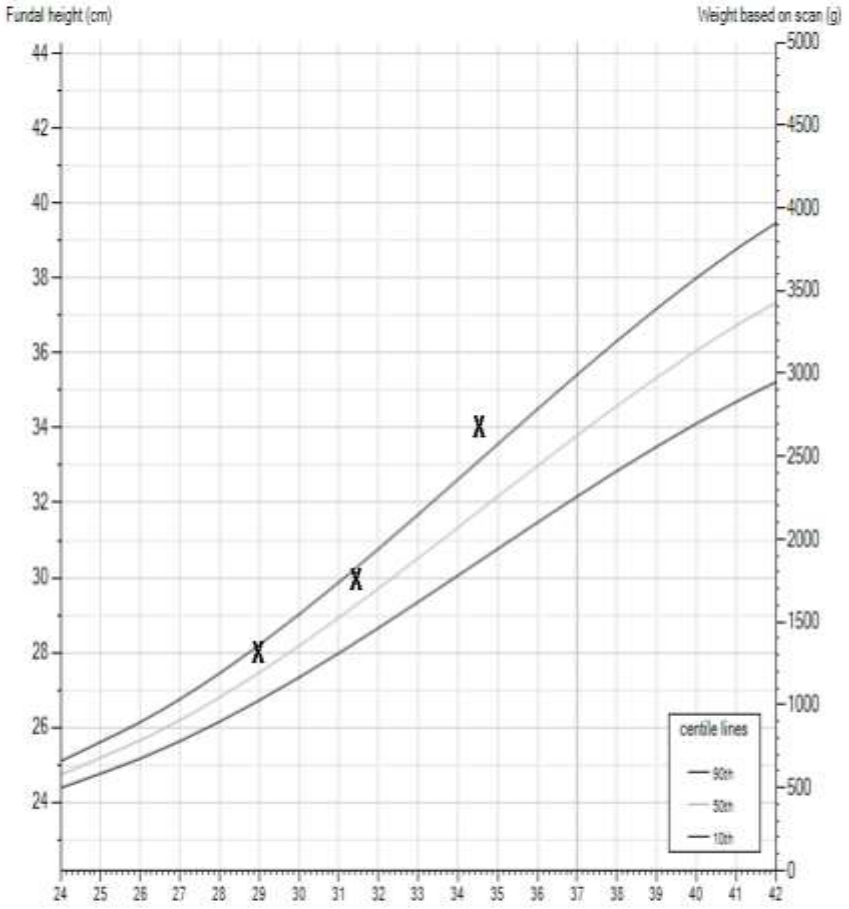


FPG
< 5.5 mmol/L

One hour
Post-prandial glucose
< 7.8mmol/L

- HbA1c monitoring should be used second line
- No evidence base for use continuous glucose monitoring in Type 2 Diabetes/ GDM

Fetal Monitoring



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metformin versus Insulin for the Treatment of Gestational Diabetes

- RCT metformin vs insulin in 751 women with GDM
- Trial designed to rule out 33% increase in composite of the following
  - Neonatal hypoglycaemia/ RDS/ need for phototherapy/ birth trauma/ APGAR <7/ prematurity
- Improved satisfaction in women receiving metformin
  - 46.3% required supplemental insulin

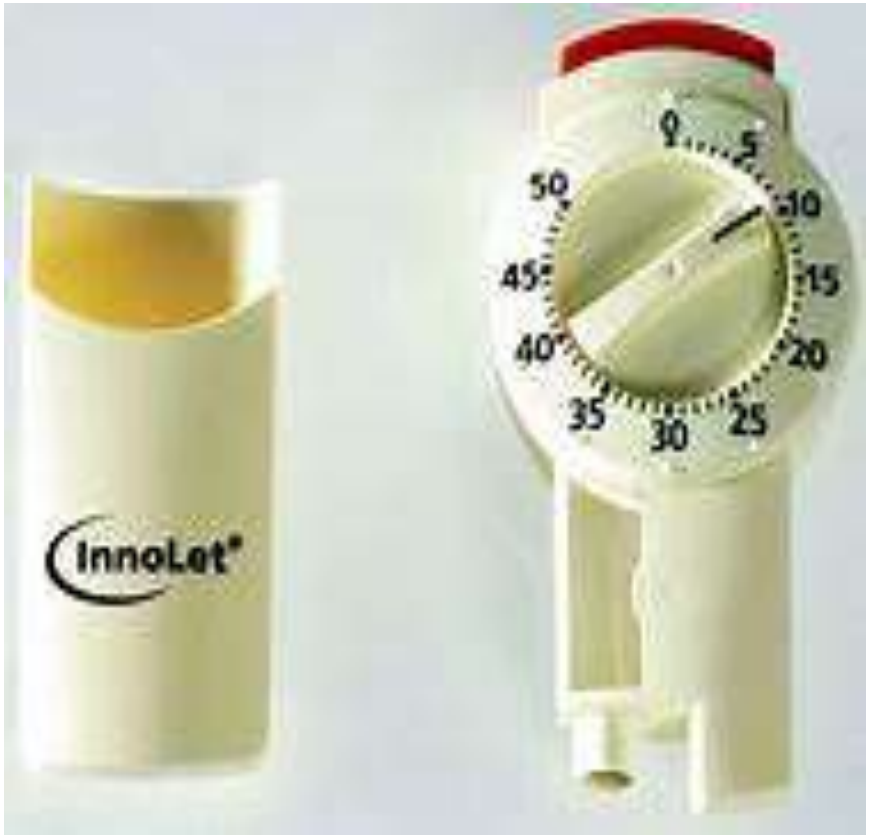
Metformin versus Insulin for the Treatment of Gestational Diabetes

Table 2. Primary Outcome and Additional Neonatal Complications.*

Outcome	Metformin Group (N=363)	Insulin Group (N=370)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary composite outcome	116 (32.0)	119 (32.2)	0.99 (0.80–1.23)	0.95
Recurrent blood glucose level <46.8 mg/dl†	55 (15.2)	69 (18.6)	0.81 (0.59–1.12)	0.21
Any blood glucose level <28.8 mg/dl	12 (3.3)	30 (8.1)	0.41 (0.21–0.78)	0.008
Weight change — kg				
Loss from enrollment to postpartum visit ¶¶¶		8.1±5.1	6.9±5.3	0.006
Gain from early pregnancy to enrollment‖‖‖		7.0±5.4	6.4±5.5	0.20
Gain from enrollment to 36 or 37 wk of gestation****		0.4±2.9	2.0±3.3	<0.001

Metformin versus insulin for treatment of Gestational Diabetes. NEJM 2008(358)
Metformin in Gestational Diabetes: the offspring follow-up (MiG TOFU). DC. 2011(34)


Humulin
KwikPen 100 IU/ml
Suspension for Injection
Human Insulin
Isophane Insulin


InnoLet
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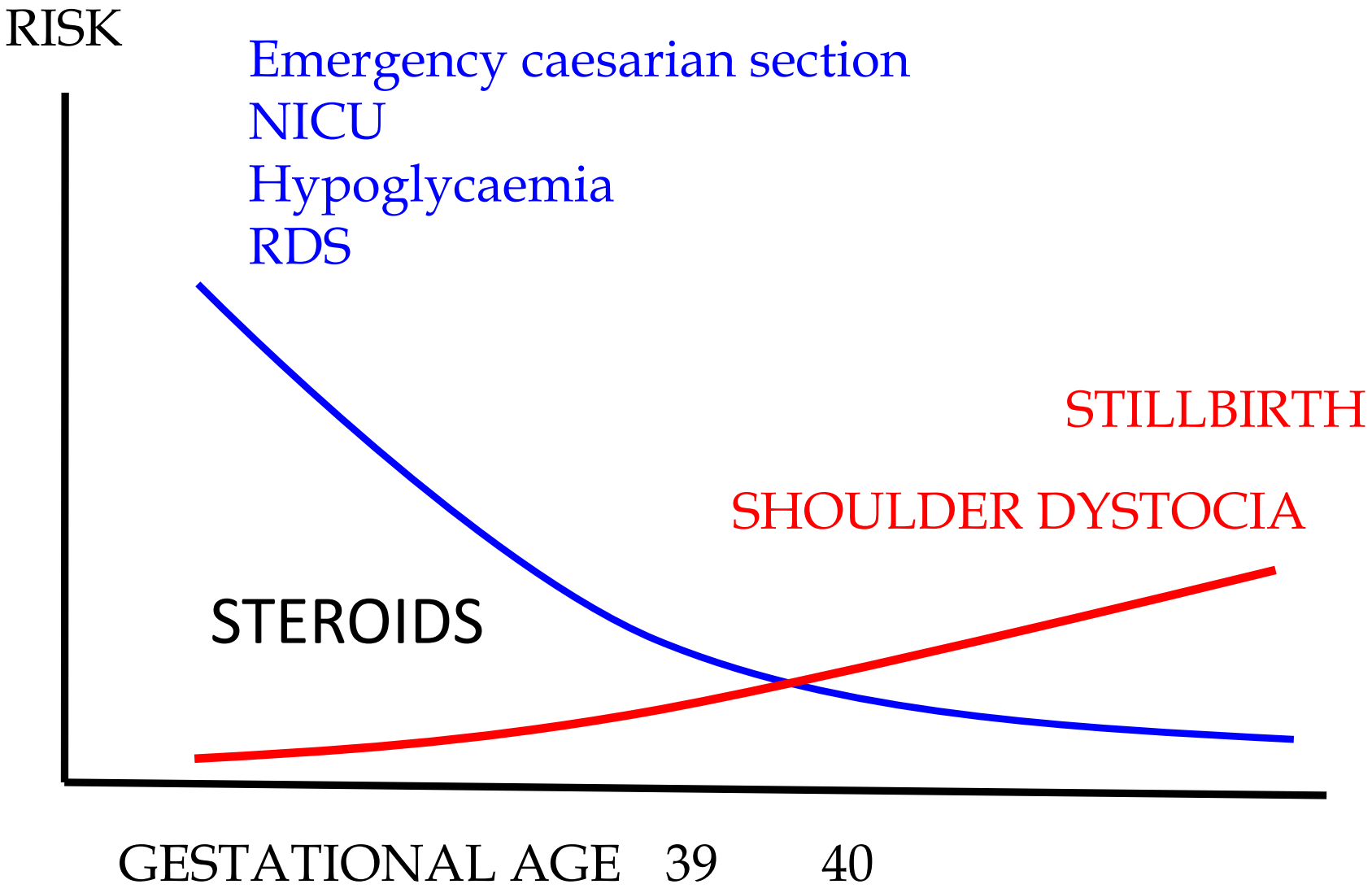
Timing of Delivery



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National Pregnancy in Diabetes Audit Report (2016)

NICE Guideline:

- Keep HbA_{1c} <48 mmol/mol where achievable without causing problematic hypoglycaemia
- Use a folic acid supplement prior to pregnancy
- Suspend use of statins and ACE inhibitors/ARBs

Only one in twelve women (8 per cent) were well prepared for pregnancy

Adverse Pregnancy Outcomes

Key Finding:
Stillbirth rate

Stillbirth rates were more than twice, and neonatal death rates nearly four times the general population rate.

Key Finding:
HbA_{1c}

Higher first trimester HbA_{1c} was related to congenital anomaly rates and in women with Type 1 diabetes to stillbirth and neonatal death.

Perinatal Outcomes in T2DM

- East Anglia Study Group for Improving Pregnancy Outcomes in women with Diabetes (EASIPOD)
- 682 consecutive T1DM and T2DM (2006-2009)
  - 59.8% T1DM: 40.2% T2DM
  - HbA1c: 63mmol/mol T1DM vs 52 mmol/mol T2DM
  - No difference combined congenital anomaly and perinatal mortality rates 67/1000 T1DM vs 50/1000 T2DM

Hewapathirana NM, Murphy HR Current Diabetes Reports 2014

Further Challenges Associated with T2DM

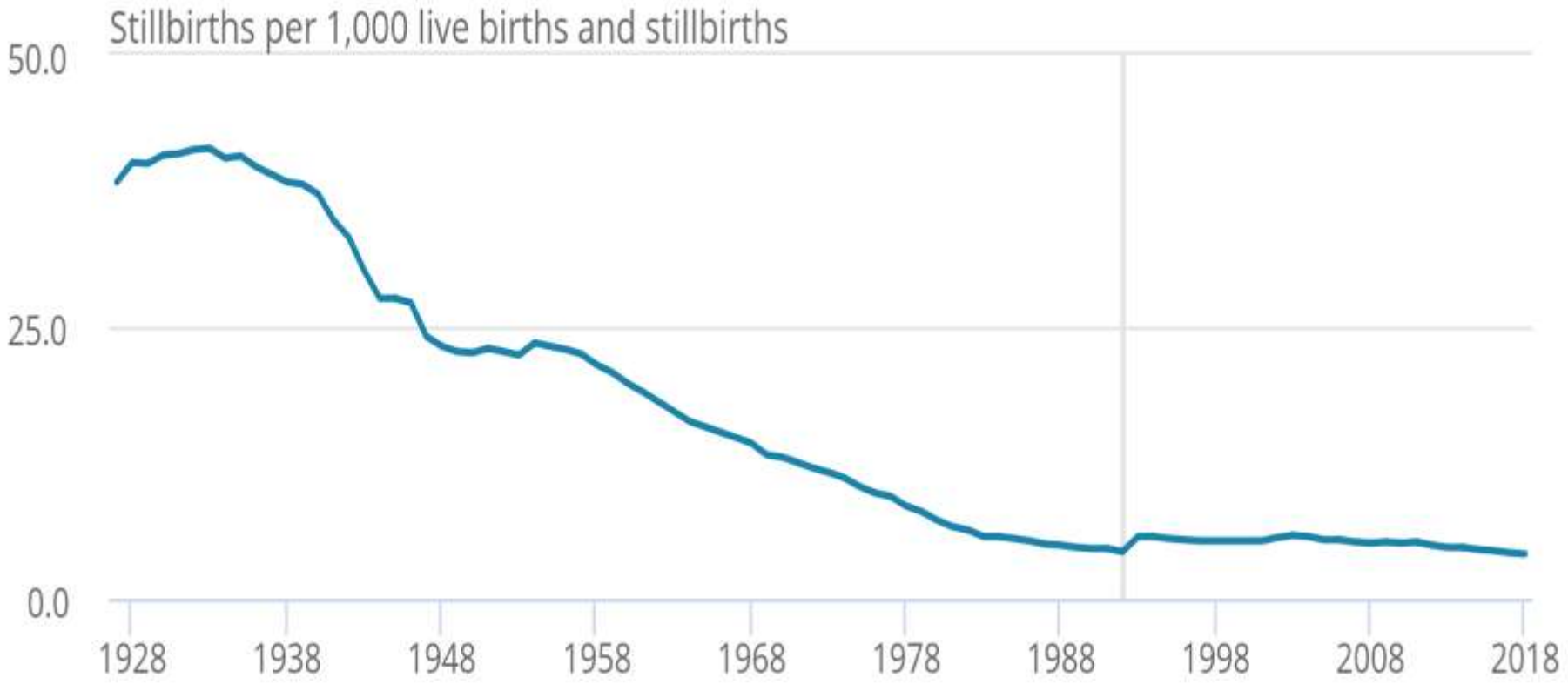
	Type 1 diabetes	Type 2 diabetes
Median age[a] (years)	30.0	34.0
Median duration[b] of diabetes (years)	14.0	4.0
Median Body Mass Index (kg/m^2)	26.1	32.6

[a] Age at completion of pregnancy.
[b] Duration of diabetes at start of pregnancy.

Non-white ethnicity: 59.4% versus 23% T1DM

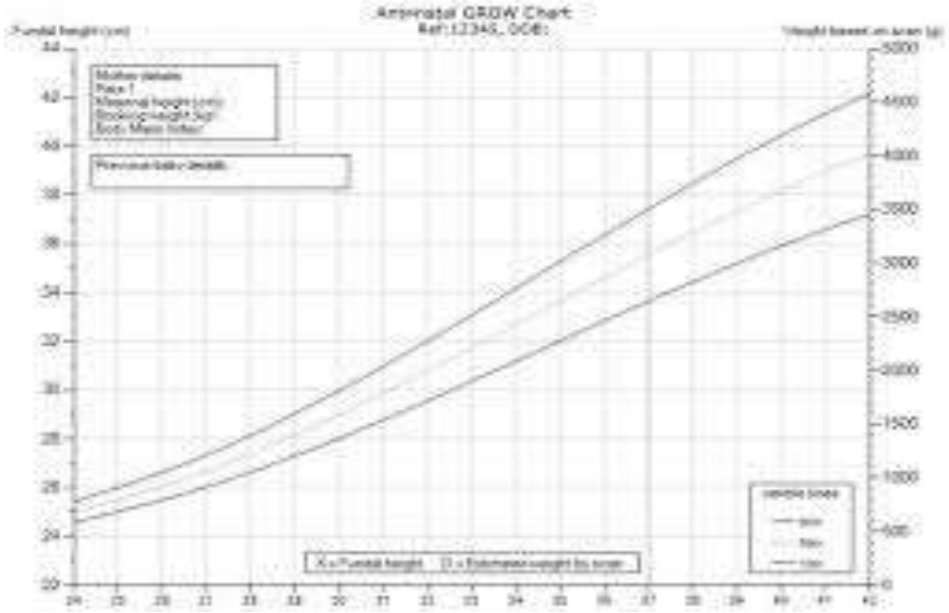
Social deprivation quintile 5: 41.5% versus 24.0% T1DM

Stillbirth Rates, England and Wales: 1927 to 2018



Still Birth Rates

- UK has one of the highest still birth rates in high income studies
- Overall rate 4.7 per 1000 births



MBRRACE-UK

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

Saving Babies' Lives

A care bundle for reducing stillbirth

An Early Pregnancy $HbA_{1c} \geq 5.9\%$ (41 mmol/mol) Is Optimal for Detecting Diabetes and Identifies Women at Increased Risk of Adverse Pregnancy Outcomes

Diabetes Care 2014;37:2953–2959 | DOI: 10.2337/dc14-1312

- HbA1c measured at 47 days in 16,122 women: New Zealand 2008-2010
- HbA1c assessed against OGTT <20 wks
  - Women invited for OGTT if HbA1c >5.6%

Table 2—Pregnancy outcomes stratified according to HbA_{1c} measurement at ≤20 weeks' (140 days') gestation, excluding women treated for GDM

	HbA_{1c} 5.9–6.4% (41–46 mmol/mol) *n* = 200 *n* (%)	HbA_{1c} <5.9% (<41 mmol/mol) *n* = 7,987 *n* (%)	RR (95% CI)
Delivery gestation			
<37 weeks	16 (8.0)	392 (4.9)	1.66 (1.01–2.74)*
<32 weeks	3 (1.5)	71 (0.9)	1.67 (0.55–5.10)
Induction of labor	35 (17.5)	1,016 (12.7)	1.44 (1.01–2.06)*
Caesarean delivery			
Total	65 (32.5)	2,428 (30.4)	1.10 (0.82–1.47)
Emergency	33 (16.5)	1,529 (19.1)	0.84 (0.58–1.21)
Major congenital anomalies		*n* = 7,992	
	7 (3.5)	103 (1.3)	2.67 (1.28–5.53)*
Preeclampsia	11 (5.5)	181 (2.3)	2.42 (1.34–4.38)*
Perinatal death	4 (2.0)	38 (0.5)	3.96 (1.54–10.16)*
Shoulder dystocia	5 (2.5)	79 (1.0)	2.47 (1.05–5.85)*
Birth weight	*n* = 199		
Mean (SD)	3,480.2 (597.0)	3,483.8 (571.0)	*P* = 0.93
>4,000 g	34 (17.1)	1,240 (15.5)	1.12 (0.78–1.61)
Population birth weight centiles†	*n* = 199		
Small for gestational age	22 (11.1)	1,202 (15.1)	0.71 (0.46–1.10)
Large for gestational age	26 (13.1)	655 (8.2)	1.66 (1.11–2.48)*
Customized birth weight centiles‡	*n* = 199		
Small for gestational age	23 (11.6)	1,173 (14.7)	0.76 (0.50–1.17)
Large for gestational age	21 (10.1)	641 (8.0)	1.34 (0.86–2.09)

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2019.1593959

ORIGINAL ARTICLE

Hyperglycemia recognised in early pregnancy is phenotypically type 2 diabetes mellitus not gestational diabetes mellitus: a case control study

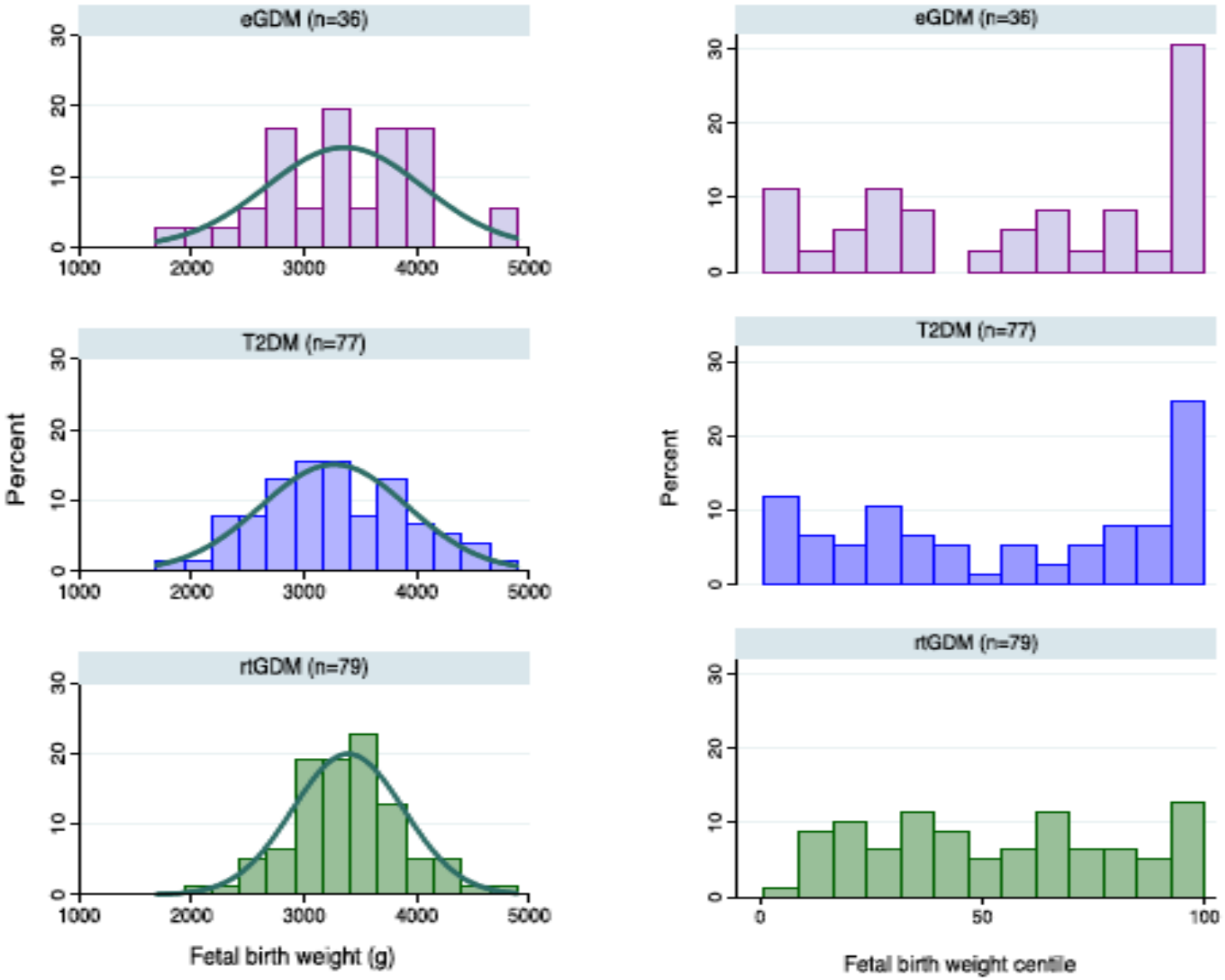
- Case control study (n=200)
- Women with hyperglycaemia diagnosed early in pregnancy (eGDM n=40) compared to two separate weight and age-matched control groups
  - Recognised Type 2 diabetes (T2DM, n=80)
  - GDM (rtGDM, n=80)

R Agha-Jaffar et al, JMFNM 2019

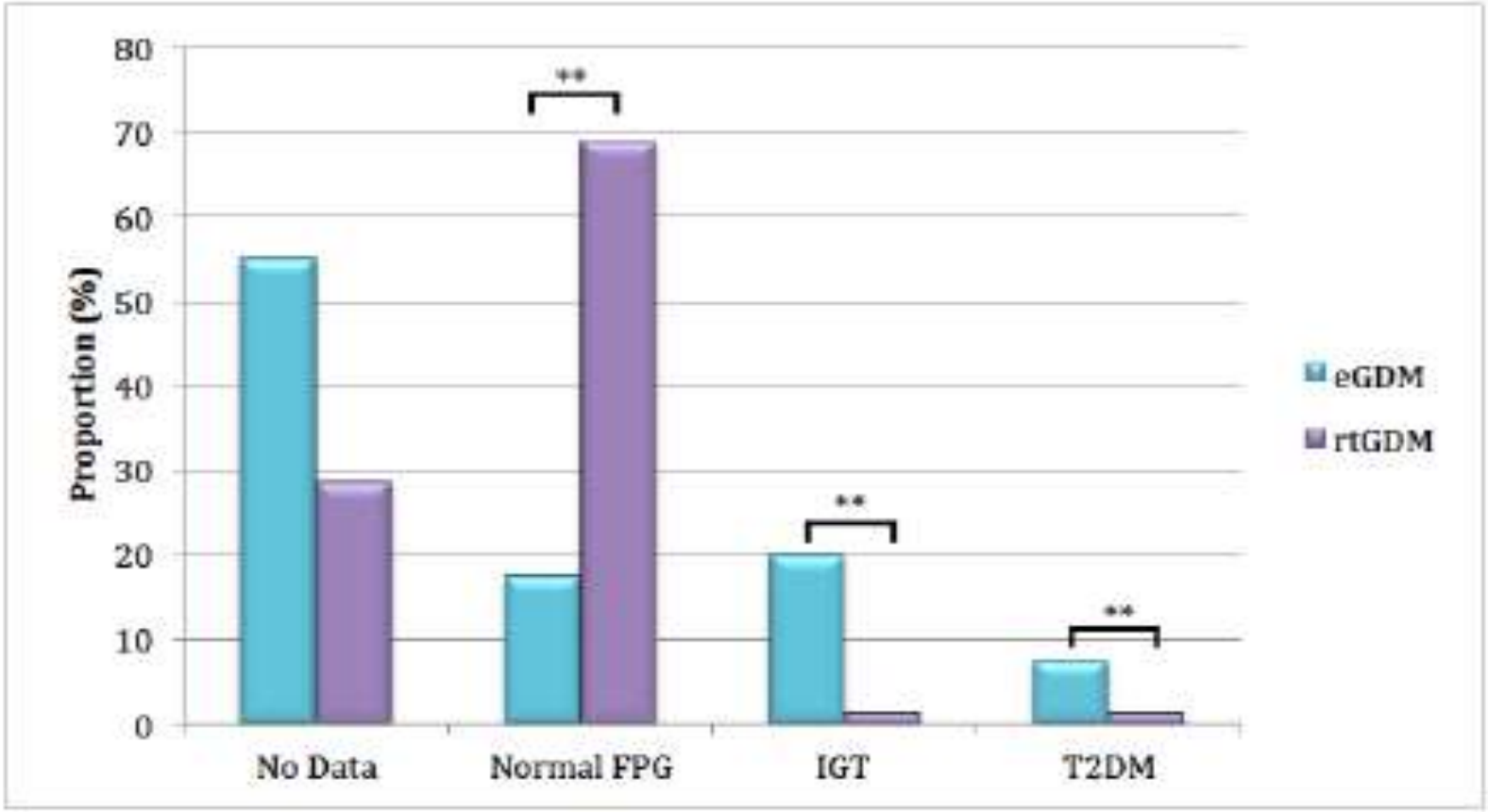
Maternal baseline demographics and biochemical data

	eGDM ($n=40$)	T2DM ($n=80$)	rtGDM ($n=80$)	Significance
Mean (SD) Age (years)	33.9 (±4.5)	34.2 (±5.1)	33.7 (±5.5)	.35
Mean (SD) Height (cm)	161.7 (±7.3)	161.5 (±7.2)	160.8 (±6.0)	.79
Mean (SD) Weight (kg)	83.6 (±15.8)	84.1 (±19.2)	78.8 (±12.5)	.14
Median (IQR) BMI (kg/m^2)	32.0 (27.0–35.0)	31.0 (28.0–35.9)	30.4 (27.9–33.9)	.50
Non-White ethnicity % (n)	80.0 (32)	86.2 (69)	76.3 (61)	.27
Black African–Caribbean	25.0 (10)	26.2 (21)	22.5 (18)	
Arab/North African	20.0 (8)	15.0 (12)	7.5 (6)	
South Asian	25.0 (10)	37.5 (30)	18.8 (15)	
Other	10.0 (4)	7.5 (6)	27.5 (22)	
Parity				
Primigravida % (n)	17.5 (7)	18 (22.5)	37 (46.3)	<.001
Multiparous % (n)[a]	25.0 (10)	11 (13.8)	4 (5.0)	
History previous pregnancy complicated by GDM % (n)	71.8 (28)	38.5 (30)	0.0 (0)	<.001
Diagnosis	20.0	23.4	3.8	.001
Hypertension % (n)[b]	(8)	(18)	(3)	
Median (IQR) HbA1c (%)	6.4 (6.1–7.3)	6.8 (6.1–7.8)	5.6 (5.3–5.8)	<.001
Median (IQR) HbA1c (mmol/mol)	46 (43–56)	51 (43–62)	38 (34–40)	<.001

Variations in Fetal Birth Weight and Adjusted Birth Weight Centile



Postpartum Glucose Assessments



Footnotes: ** Denotes significance level <0.05.
Abbreviations: ***eGDM*** women diagnosed with hyperglycaemia <20 weeks gestation, ***rtGDM*** women diagnosed with gestational diabetes 24-28 weeks gestation, ***FPG*** Fasting plasma glucose, ***IGT*** Impaired glucose tolerance, ***T2DM*** Type 2 diabetes mellitus.

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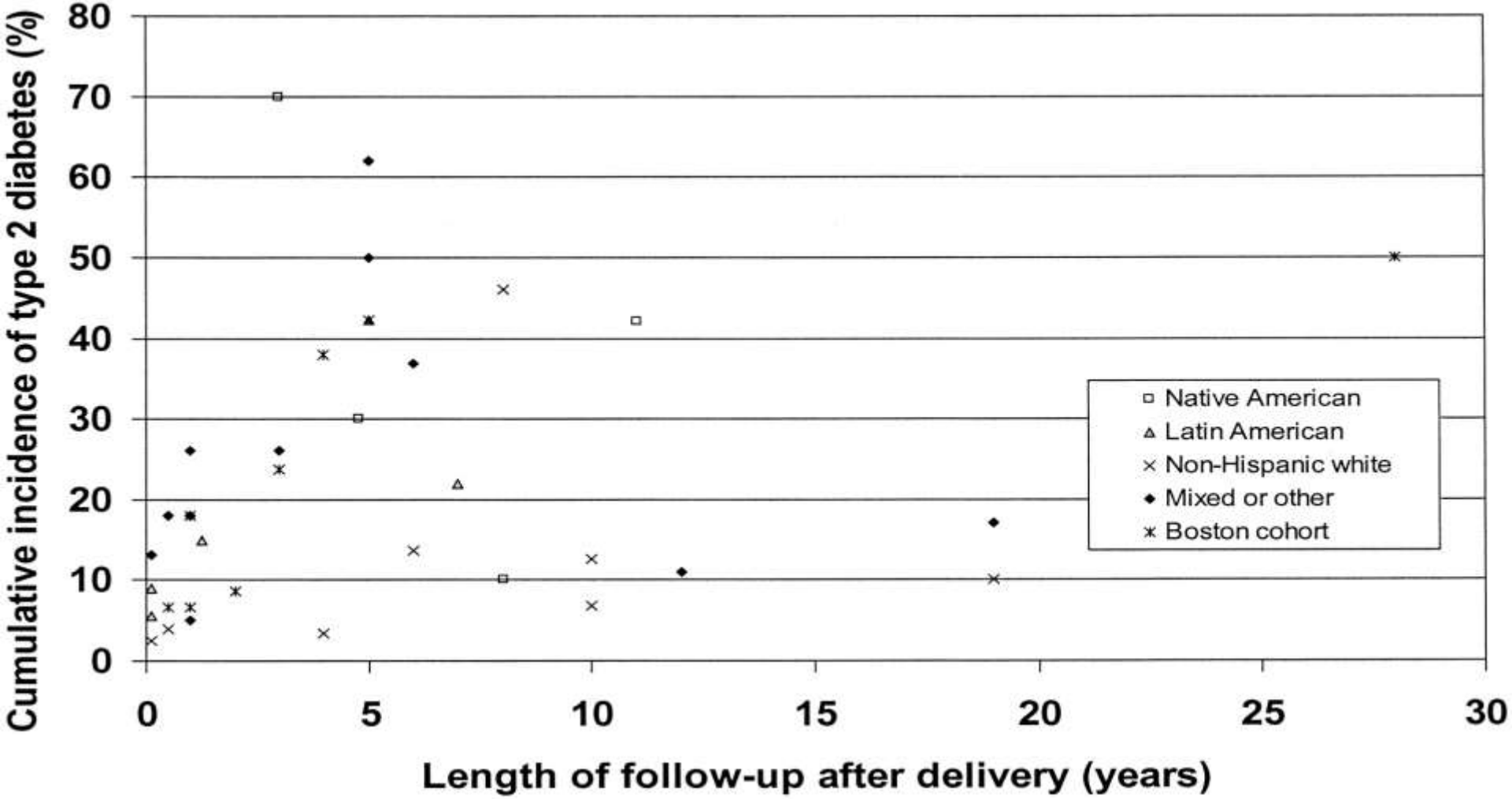
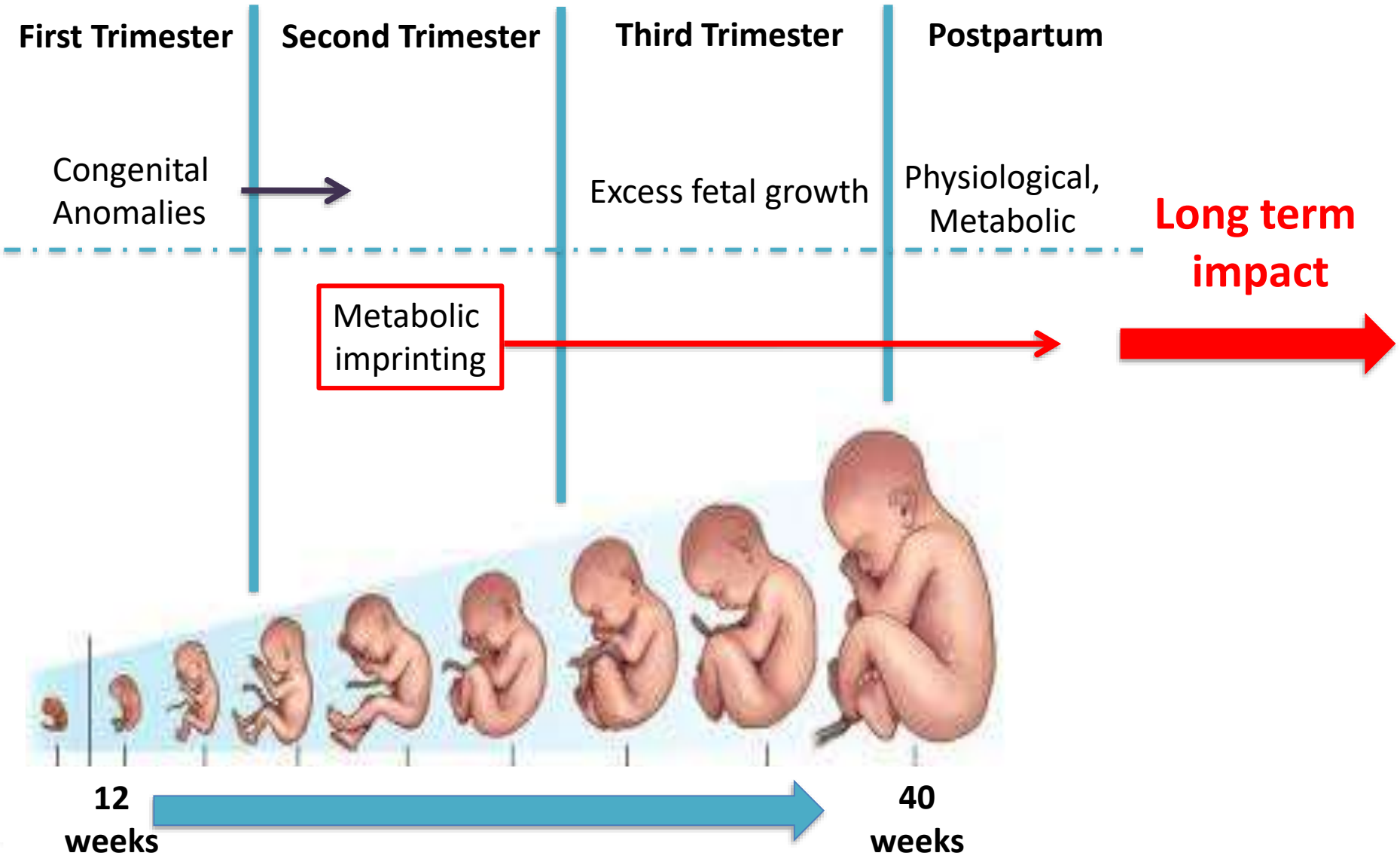
- Long-term effects of in-utero exposure to metformin

Long Term Risks for the Mother

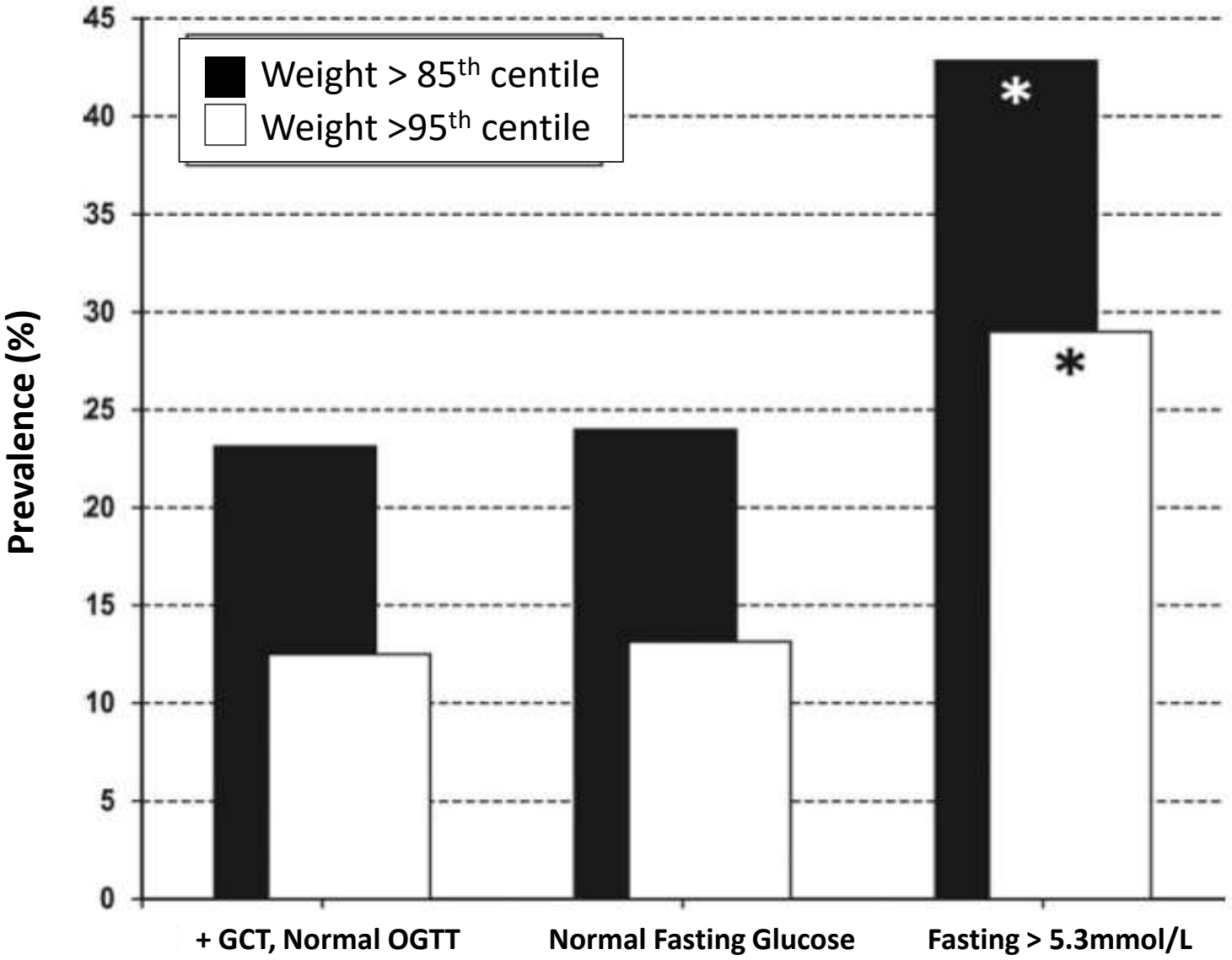


Kim et al Diabetes Care 2002

Effects of Exposure to in Utero Hyperglycaemia



Maternal Hyperglycaemia and Childhood Obesity



Childhood Obesity and Metabolic Imprinting: the ongoing effects of childhood obesity. Diabetes Care. 2007; 30 (9): 2287- 2292

Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark

Damm P., Houshmand-Oeregaard A., Kelstrup L., et al.
Diabetologia (2016) 59:1396-1399

- Follow up offspring born to women in one of three groups: GDM, T1DM, background population
- Pre-diabetes/ diabetes was present in 21%, 11% and 4% offspring aged 18-27 years respectively
- 8-fold and 4-fold increase in prediabetes/ diabetes risk in GDM and T1DM offspring

Mild Gestational Diabetes Mellitus and Long-Term Child Health

Landon M.B., Rice M.M., Varner M.W., et al: Diabetes Care 2015;38:445–452

- Follow up study of children enrolled in an RCT of “mild GDM” treatment versus no treatment (n=500)
- Maternal demographics similar in two groups
- BMI ≥95th and ≥85th percentiles similar in treated versus non-treated groups: 20.8% vs. 22.9% and 32.6% versus 38.6% respectively
- No difference in metabolic dysfunction

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PLOS | MEDICINE

RESEARCH ARTICLE

Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis

- Meta-analysis of nineteen studies (3723 neonates)

- Neonates born to metformin treated mothers had
  - Lower birth weights (mean difference -107.7g)
  - Lower OR macrosomia and LGA (OR 0.59 and 0.78 respectively) relative to insulin treated mothers
  - Significantly higher BMI in metformin treated group

Table 1. Childhood adiposity indices.

Adiposity index	Study details	Mean difference (fixed)	95% CI	Significance	Heterogeneity test
Total fat mass (DEXA)	Adelaide ($n = 61$) Auckland ($n = 98$)	0.20	−0.11, 0.51	$p = 0.25$	$p = 0.15$, $I_2 = 52\%$
Abdominal fat mass (DEXA)	Adelaide ($n = 61$) Auckland ($n = 98$)	79.80	−59.32, 218.92	$p = 0.26$	$p = 0.11$, $I_2 = 60\%$
Abdominal fat volume (MRI)	Adelaide ($n = 12$) Auckland ($n = 92$)	0.44	0.06, 0.82	**$p = 0.02$**	$p = 0.84$, $I_2 = 0\%$
Abdominal subcutaneous fat volume (MRI)	Adelaide ($n = 12$) Auckland ($n = 92$)	0.29	−0.07, 0.65	$p = 0.11$	$p = 0.95$, $I_2 = 0\%$
Visceral fat volume (MRI)	Adelaide ($n = 12$) Auckland ($n = 92$)	0.41	0.05, 0.77	**$p = 0.03$**	$p = 0.85$, $I_2 = 0\%$
Thigh fat mass (DEXA)	Adelaide ($n = 61$) Auckland ($n = 98$)	90.77	−148.68, 330.23	$p = 0.46$	$p = 0.46$, $I_2 = 61\%$
Arm fat mass (DEXA)	Adelaide ($n = 61$) Auckland ($n = 98$)	102.57	−73.34, 278.47	$p = 0.25$	$p = 0.09$, $I_2 = 65\%$
Bicep skinfold thickness	Adelaide ($n = 109$) Auckland ($n = 98$)	0.53	−0.60, 1.66	$p = 0.35$	$p = 0.21$, $I_2 = 36\%$
Tricep skinfold thickness	Adelaide ($n = 109$) Auckland ($n = 98$)	0.64	−0.76, 2.04	$p = 0.83$	$p = 0.37$, $I_2 = 70\%$
Subscapular skinfold thickness	Adelaide ($n = 109$) Auckland ($n = 98$)	1.05	−0.70, 2.79	$p = 0.24$	$p = 0.32$, $I_2 = 0\%$

Strategies to Prevent GDM

Dietary intervention

- Results conflicting

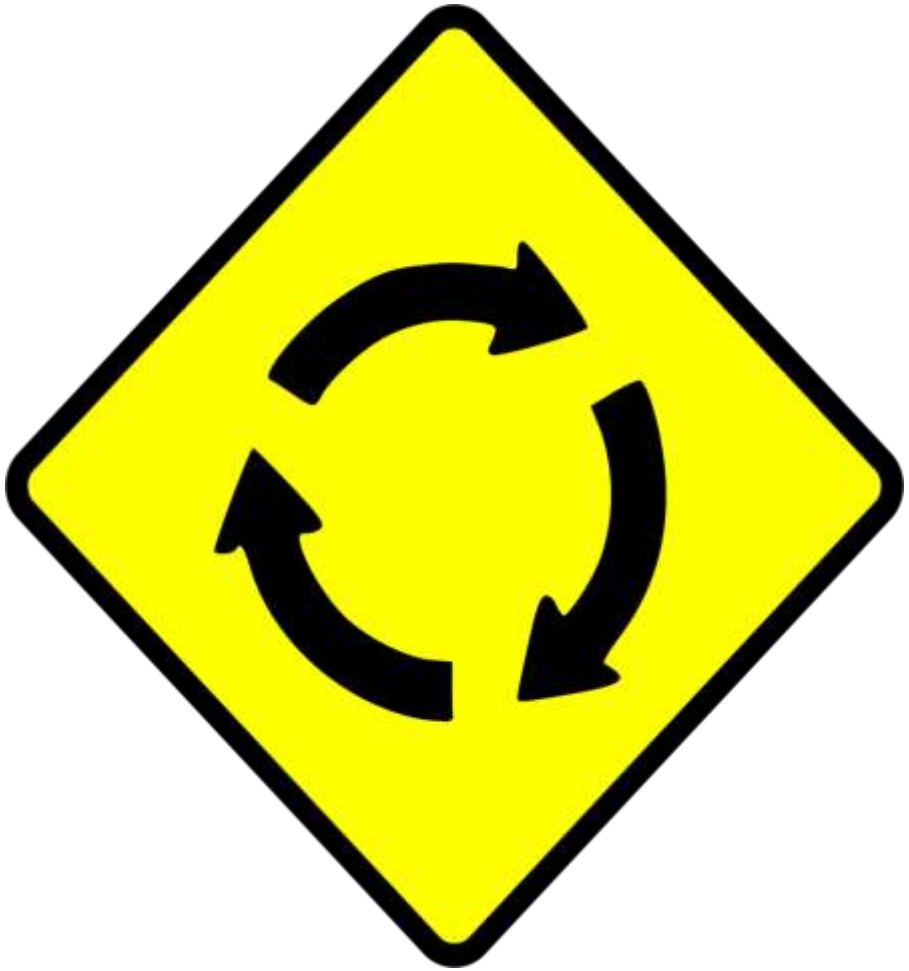
Increased physical activity

- No benefit with intervention

Combined lifestyle interventions

- Improved materno-fetal outcomes in absence of improving maternal hyperglycaemia


Environment Special:
The oceans—why 70% of our planet is in danger
The Facebook Movie:
The secret history of social networking
TIME
How the first nine months shape the rest of your life
The new science of fetal origins
BY ANNIE MURPHY PAUL



Thank you!

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