KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

PREGNANCY: THE KIDNEY MARATHON
A training guide for women with diabetes

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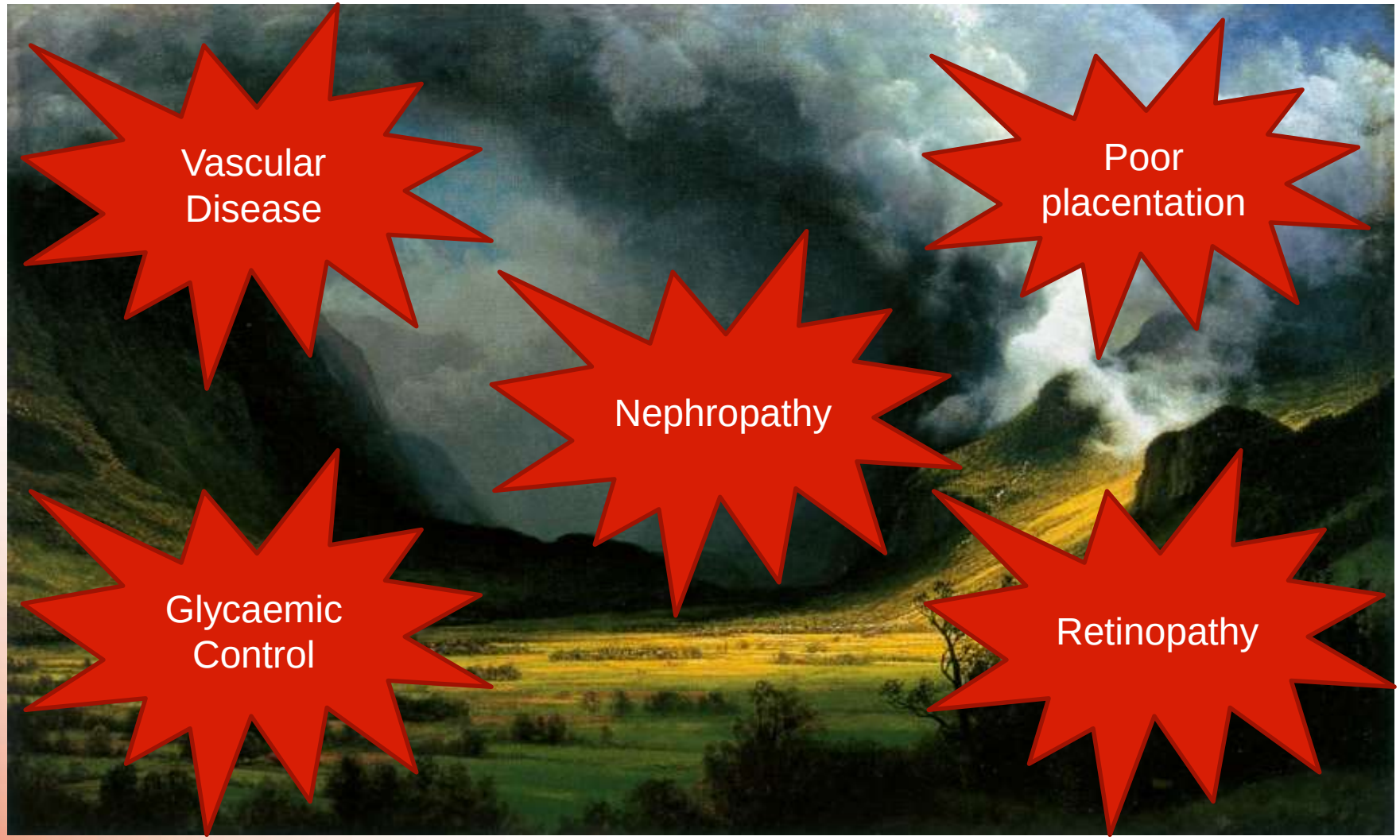
Preparation for the marathon

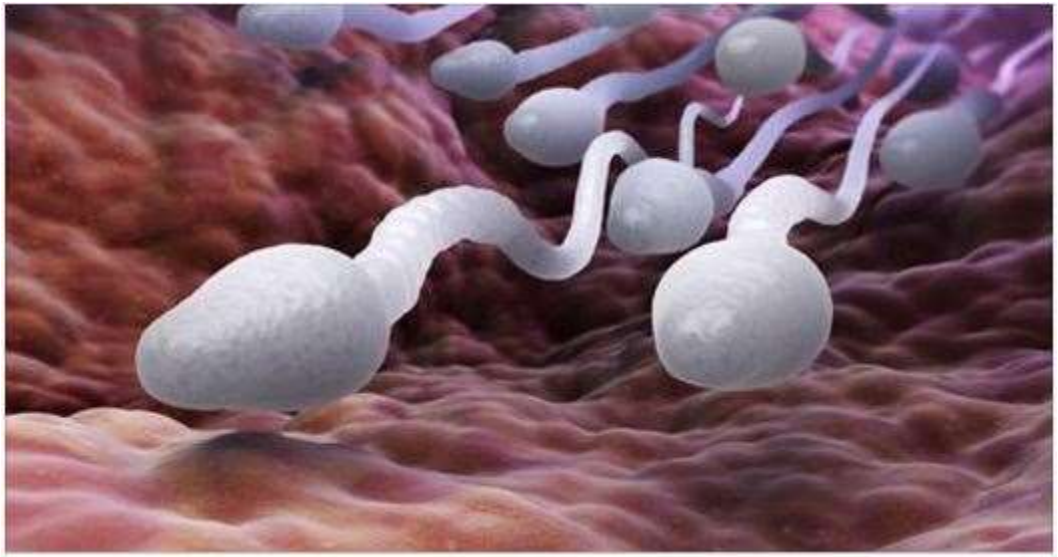
Running the Marathon

Finishing the marathon

Diabetic nephropathy and pregnancy – the perfect storm



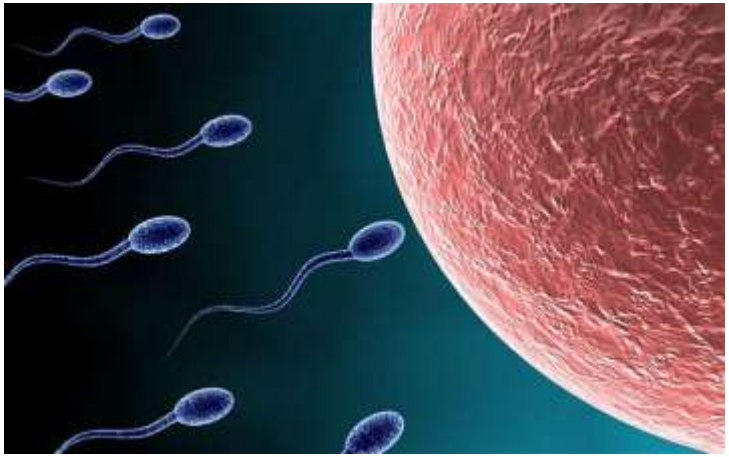
Getting pregnant



Diabetes often has no effect on fertility

Type 1 diabetes

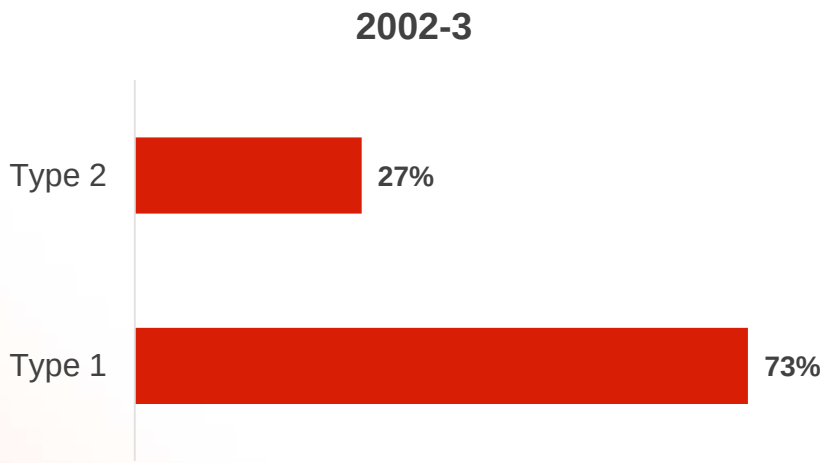
- No reduction in fertility
- Increased menstrual irregularity
- Delayed menarche
- Premature menopause

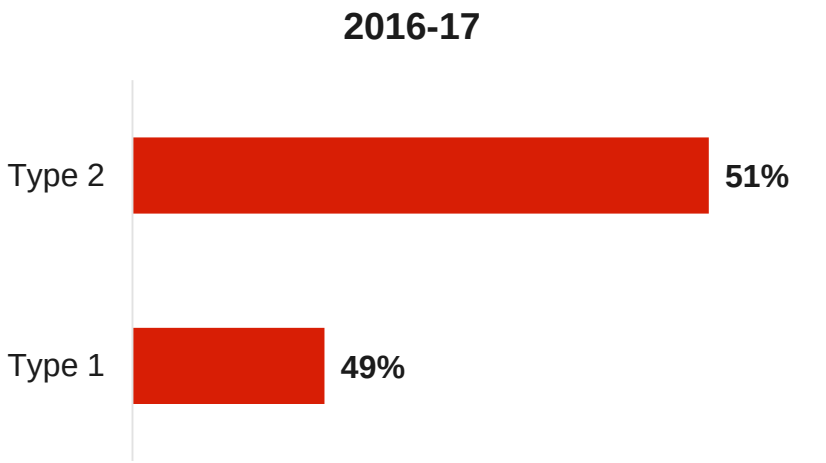


Type 2 diabetes

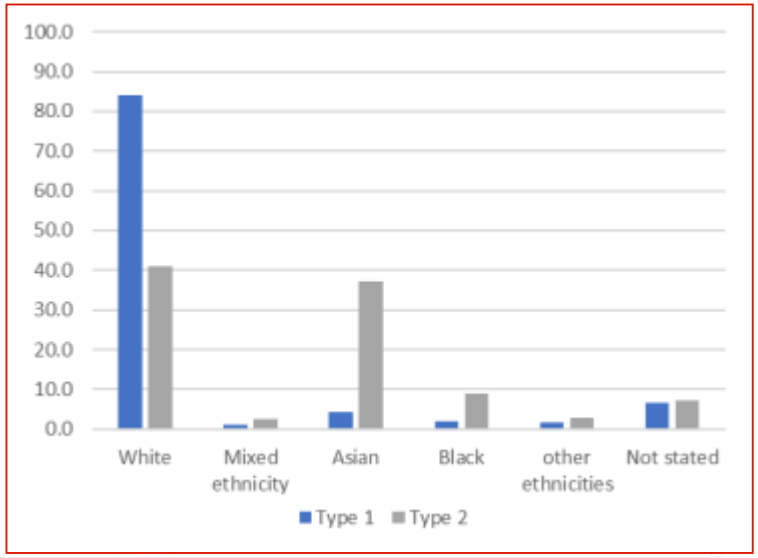
- Association with polycystic ovaries

The proportion of type 2 diabetes is increasing in pregnancy

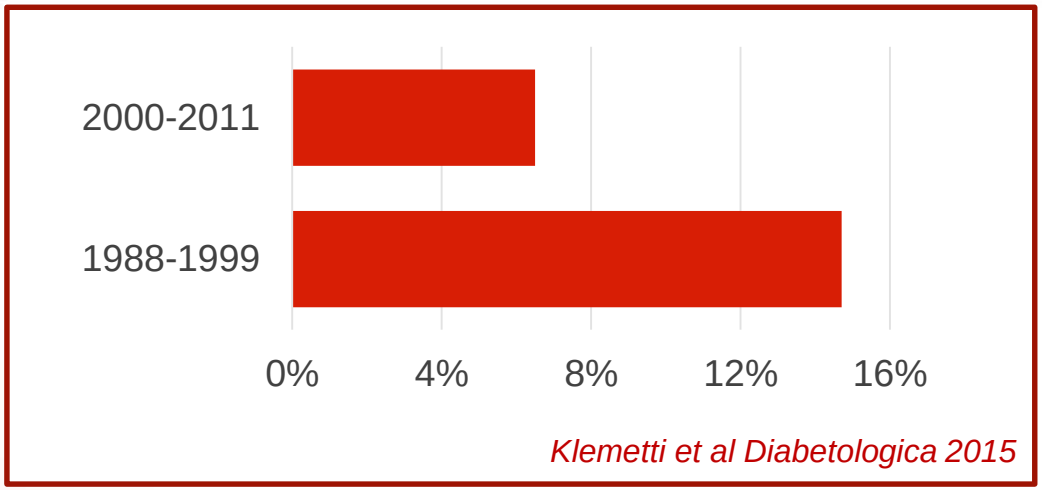




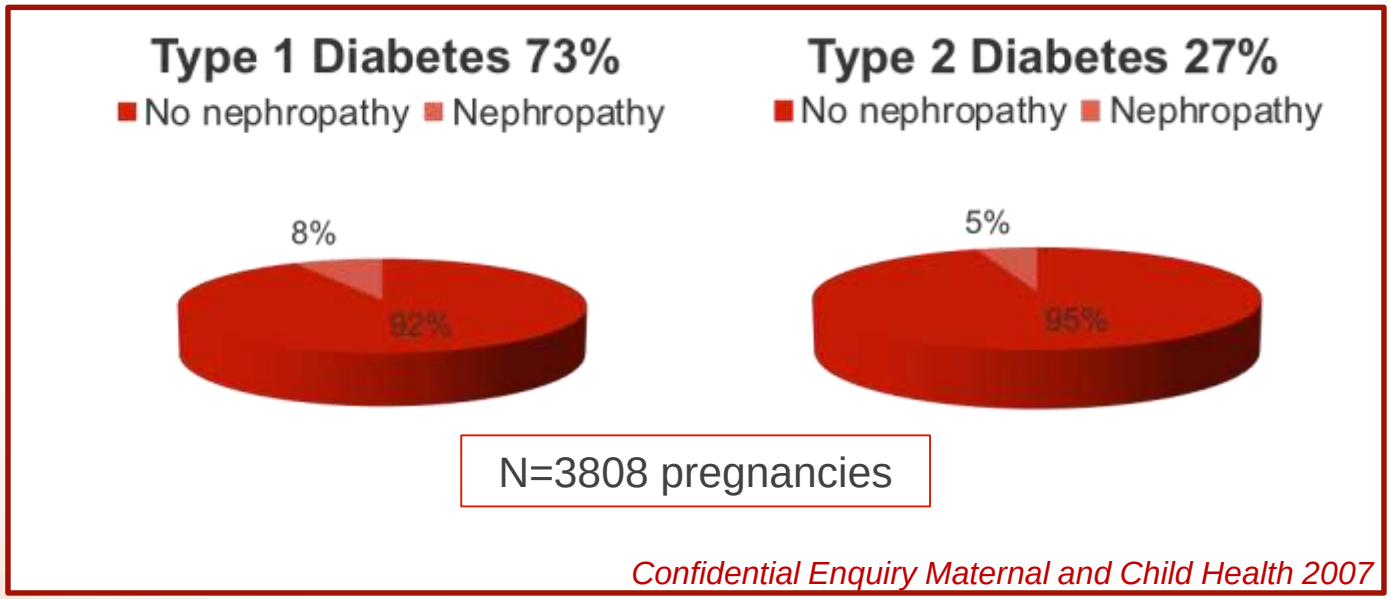
	Type 1 Diabetes	Type 2 Diabetes
Median age (years)	30.0	34.0
Median duration of diabetes (years)	13.0	3.0
Median BMI (kg/m^2)	26.0	32.5



Incidence of nephropathy in pregnant women with pre-existing diabetes is falling



Klemetti et al Diabetologica 2015



Confidential Enquiry Maternal and Child Health 2007

Pregnancy outcome is optimised pre-conception

NHS National Institute for Health and Clinical Excellence

Pre-conception counselling is recommended for ALL women with type 1 and type 2 diabetes

	Pre-existing diabetes	General maternity population
Planned Pregnancy	158/384 (41%)	58%
Use of contraception in 12mths before pregnancy	107/392 (27%)	
Pre-pregnancy folic acid	102/380 (27%)	<10-50%
Smoking	107/386 (28%)	35%

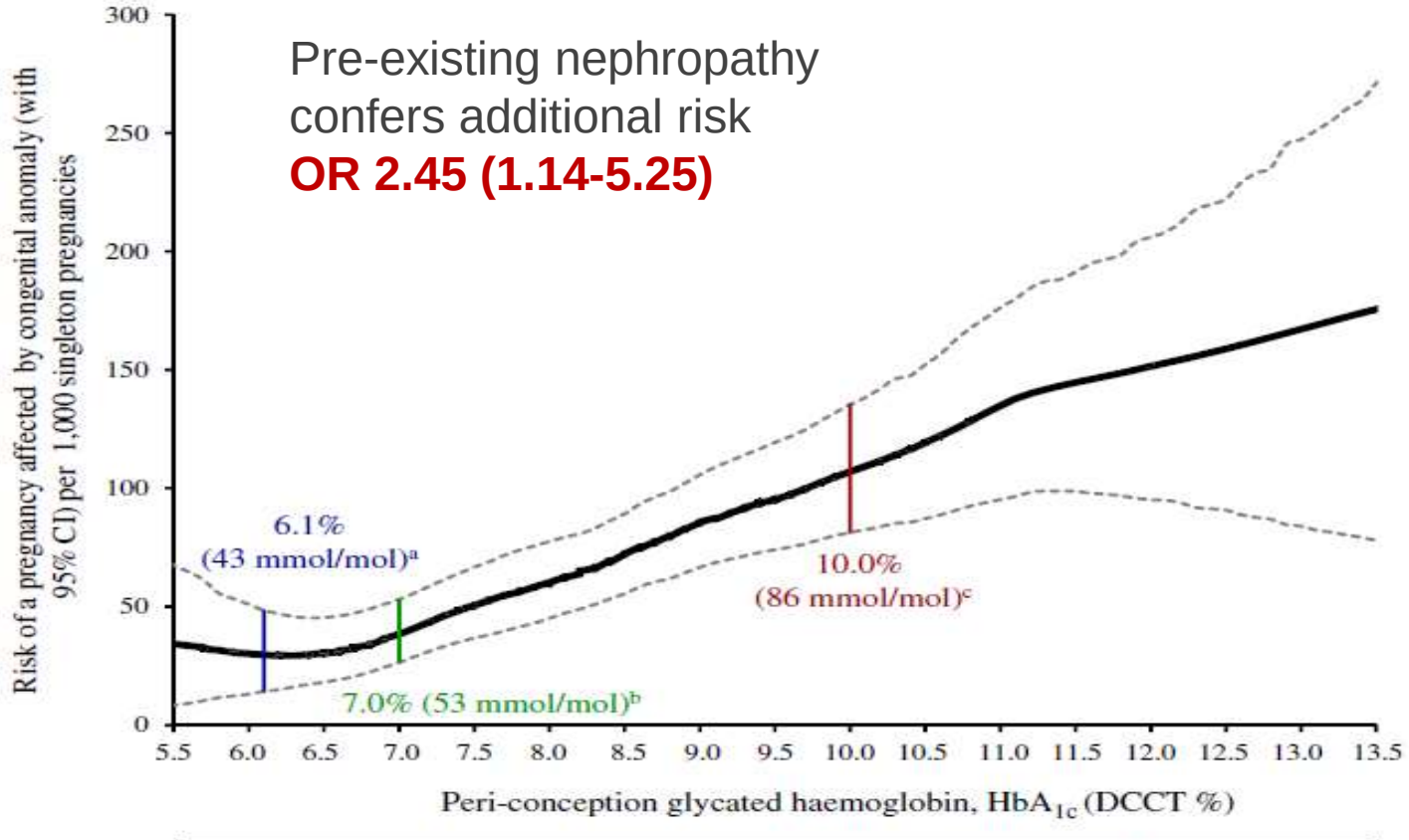
Confidential Enquiry into Maternal and Child Health 2007

Preparation for the marathon

Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

Every 1% rise in pre-conception HbA1c over 6.3% associated with 30% increased odds of birth defects



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

Bell et al Diabetologia 2012

Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

Aim: HbA1c <6.5%

Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

Aim: HbA1c <6.5%

Max RAAS blockade

Treat hypertension

Folic Acid

ACE Inhibitors / ARBs should not be used in pregnancy

Ramipril, Lisinopril, Fosinopril, Enalapril, Quinapril, Perindopril, Trandolapril, Benazepri

Candesartan, Irbesartan, Olmesartan, Losartan, Diovan, Valsartan, Telmisartan, Eprosartan

ndei.org

‘Avoid teratogenic medications in sexually active women of child-bearing potential’

NHS
National Institute for Health and Clinical Excellence

‘Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists should be discontinued before conception or as soon as pregnancy is confirmed.’

THE RENAL ASSOCIATION
founded 1950

‘Women with diabetic nephropathy continue angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive’

First trimester ACEI exposure is considered teratogenic BUT…

Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study

OPEN ACCESS

De-Kun Li *principal investigator*[1], Chunmei Yang *program analyst*[1], Susan Andrade *research associate professor*[2], Venessa Tavares *program analyst*[1], Jeannette R Ferber *program analyst*[1]

1995 – 2008
Northern California

Risk of congenital heart defects:

ACEi v Controls	**Other anti-HT** v Controls
3.9% v 1.6%	2.4% v 1.6%
OR 1.54 (95% CI 0.90 to 2.62). **NS**	OR 1.52 (95% CI 1.04 to 2.21). **P<0.05**

Hypertension is associated with risk of congenital abnormalities NOT ACEI

First trimester ACEI exposure is considered teratogenic BUT…

1,333,624 pregnancies
4,107 (0.31%) exposed to ACE inhibitors

Medicaid Data

	Full Cohort		
	Risk		RR (95% CI)
Congenital Malformations	Exposed (n=4,107)	Unexposed (n=1,329,517)	Unadjusted
Overall	244 (5.94)	43,323 (3.26)	1.82 (1.61–2.06)
Cardiovascular	139 (3.38)	15,272 (1.15)	2.95 (2.50–3.47)
CNS	11 (0.27)	2,433 (0.18)	1.46 (0.81–2.64)

RR, relative risk; CI, confidence interval; CNS, central nervous system.
Data are n (%) unless otherwise specified.
* Cell size less than 11, which cannot be disclosed in accordance with the data use agreement.

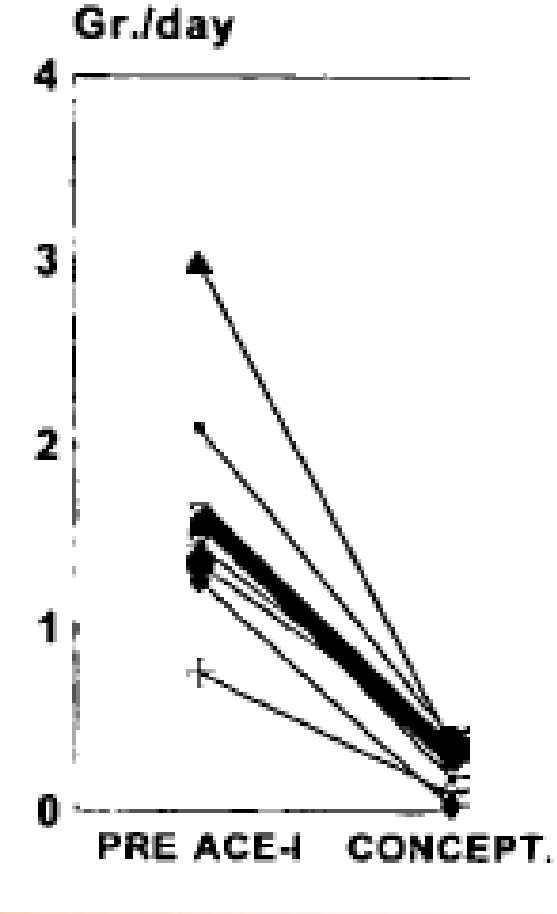
OBSTETRICS & GYNECOLOGY

Bateman Obs Gyn 2017

… the increased risk appears to be attributable to the underlying condition NOT exposure

Hypertension-Restricted Cohort				
Risk		RR (95% CI)		
Exposed (n=2,631)	Unexposed (n=15,884)	Unadjusted	Diabetes-Adjusted	Propensity Score–Adjusted
142 (5.40)	634 (3.99)	1.35 (1.13–1.61)	0.97 (0.79–1.19)	0.89 (0.75–1.06)
77 (2.93)	260 (1.64)	1.79 (1.39–2.30)	1.08 (0.81–1.44)	0.95 (0.75–1.21)
*	45 (0.28)	1.07 (0.51–2.27)	0.68 (0.30–1.54)	0.54 (0.26–1.11)

Continuing RAAS blockade pre-conception in women with diabetic nephropathy



8 women (Cr 0.8±0.05mg/dl)

>6 months until **proteinuria <500mg**

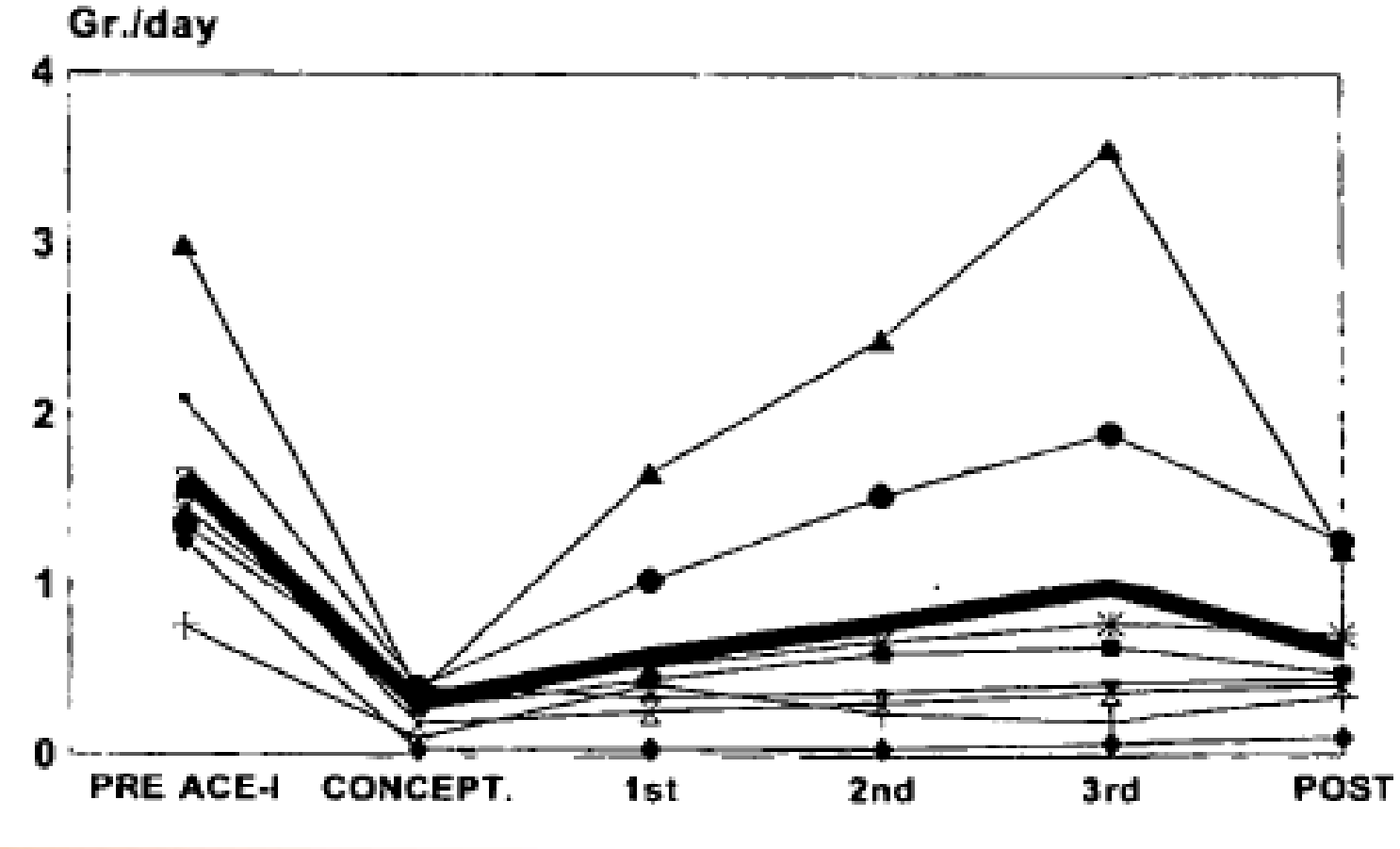
Intensive RAAS blockade
(Captopril – 37.5-75mg daily)

- Pre-ACEI Proteinuria 1633±66mg/24hrs
- Post-ACEI Proteinuria 273±146mg/24hrs

Improved glycaemic control pre-pregnancy

Hod et al NDT 1995

Continuing RAAS blockade pre-conception in women with diabetic nephropathy



Only 2 women had proteinuria >1000mg during pregnancy (1903mg / 3578mg/24hr)

Hod et al NDT 1995

Does pre-pregnacy RAAS blockade improve outcomes?

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

Antihypertensive Therapy Strategy	Ekbom *et al.*, 2001 (25)	Nielsen *et al.*, 2006 (54)	Nielsen *et al.*, 2009 (2)
	Pre-Eclampsia Diastolic BP >95 mmHg	BP >140/90 mmHg UAE >2 g/24 h ACE Inhibitor before Pregnancy	BP >135/85 mmHg UAE ≥300/24 h ACE Inhibitor before Pregnancy
Number	26	20	10
Duration of diabetes (yr)	19±5	18±8	15±10
HbA1c at inclusion (%)	8.1±0.9	6.8±0.5	7.3±1.5
Week of onset of antihypertensive therapy	29 (20–34)	13 (Before-34)	Before (Before-14)
Patients on antihypertensive therapy during pregnancy	9 (35)	10 (50)	5 (50)
ACE inhibitor before pregnancy	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)
Pre-eclampsia	11 (42)	4 (20)	0
Preterm delivery before 34 wk	6 (23)	0	0
Preterm delivery before 37 wk	16 (62)	8 (40)	2 (20)
Birth weight (g)	3124±767	3279±663	3471±670
Perinatal mortality	1 (4)	0	0
Major congenital malformations	1 (4)	0	0

We definitely need to ensure early detection of pregnancy

Recommend continue Angiogensin Converting Enzyme Inhibitors until conception

Test frequently for pregnancy

Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

Aim: HbA1c <6.5%

Max RAAS blockade

Treat hypertension

Folic Acid

Regular pregnancy testing

If BMI >27kg/$m^{2:}$

Dietary review
Weight loss

Pre-pregnancy Counselling Guidelines

Avoid pregnancy if >86mmol/mol (10%)

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Max RAAS blockade

Treat hypertension

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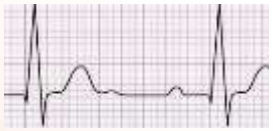
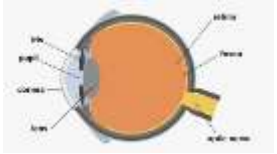




Things to do when you see a positive pregnancy test

Involve the **MDT**

Retinal assessment if non within 3 months

Confirmation of **viability and gestational age** <9weeks

HbA1c to assess risk

I'M PREGNANT!

Review **medications**

Advice regarding **nausea and vomiting** and glucose control

Start **aspirin 75mg** OD

Start **vitamin D**

Over the start line: What's needed now?!

Antenatal care

Multi-disciplinary Care:

Midwives
Obstetricians
Diabetologist
Nephrologist
Nurses
Dieticians
Ophthalmologists …

Continuity of appropriate carers must be a primary aim

"Continuity of carer is even more important particularly for women with pre-existing health… conditions who are being cared for by multidisciplinary team maternity professionals."

RCM (2019)

'The right people with the right skills at the right time'

Sandall (2011)

'Intuitive knowledge'

Berg, (2005)

Antenatal care – running the marathon!

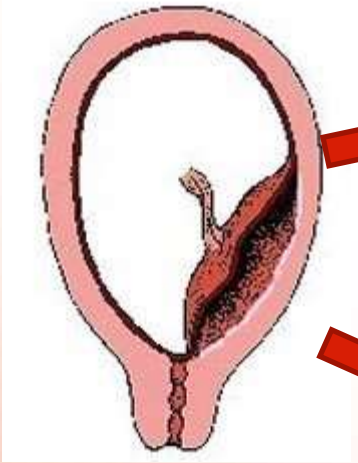
Control

blood sugar

Multi-disciplinary Care:

Midwives
Obstetricians
Diabetologist
Nephrologist
Nurses
Dieticians
Ophthalmologists
…

Glycaemic control during normal pregnancy is challenging



Cortisol

Glucagons

Lactogen

Placental Insulinases

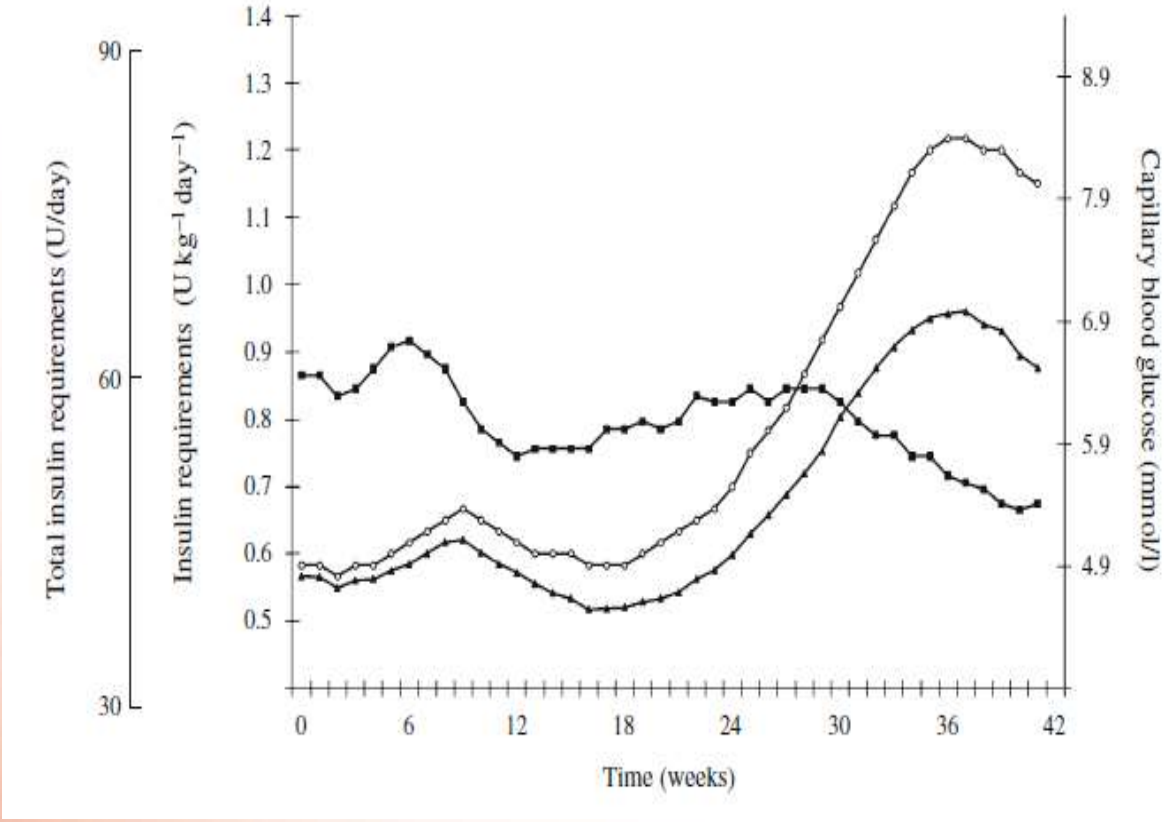
Insulin resistance

Safety of Medications in Pregnancy

Drug	FDA	Human Teratogenicity	Fetal/neonatal effects	Comments
Isophane (NHP) insulin	B	×	×	First choice long acting insulin
Rapid-acting insulin analogues e.g aspart, lispro	B	×	×	May be preferable to start pre-pregnancy
Longer-acting insulin analogues e.g. detemir, glargine	C	×	×	Increasing evidence to suggest safety
Metformin	B	×	×	GFM or Type 2 only
Glibenclamide	C	×	×	Doses <20mg/day less likely to cause neonatal hypoglycamia
Thiazolidinediones e.g. Rosiglitazline	C	None reported but	Unknown	Stop at conception

Insulin requirements in pregnancy will fluctuate and are unpredictable

63 women with type 1 diabetes



Total insulin requirement

Insulin

Capillary blood glucose

Garcia-Paterson et al Diabetologica 2012

Frequent glucose monitoring is recommended for women with type 1 and type 2

Time	NICE 2015 (mmol/l)	ADA 2015 (mmol/l)
Fasting	<5.3	3.3-5.4
1 hour post meal	<7.8	5.4-7.1
2 hours post meal	<6.4	<6.4

If on insulin or glibenclamide – advise to maintain plasma glucose >4mmol/l

NHS National Institute for Health and Clinical Excellence

- Increase risk of hypoglycamia and impaired awareness in first trimester

HbA1C is not accurate during pregnancy

- Increased red cell turnover
- Changes in glycaemic range

Trimester	Healthy Pregnancy Range
First	<5.3%
Second	<7.8%
Third	<5.6%

NHS National Institute for Health and Clinical Excellence

- DO not use HbA1C in second or third trimester to assess control

ndei.org NATIONAL DIABETES EDUCATION INITIATIVE™

- Target <6.0%

Ketonaemia testing is recommended more readily

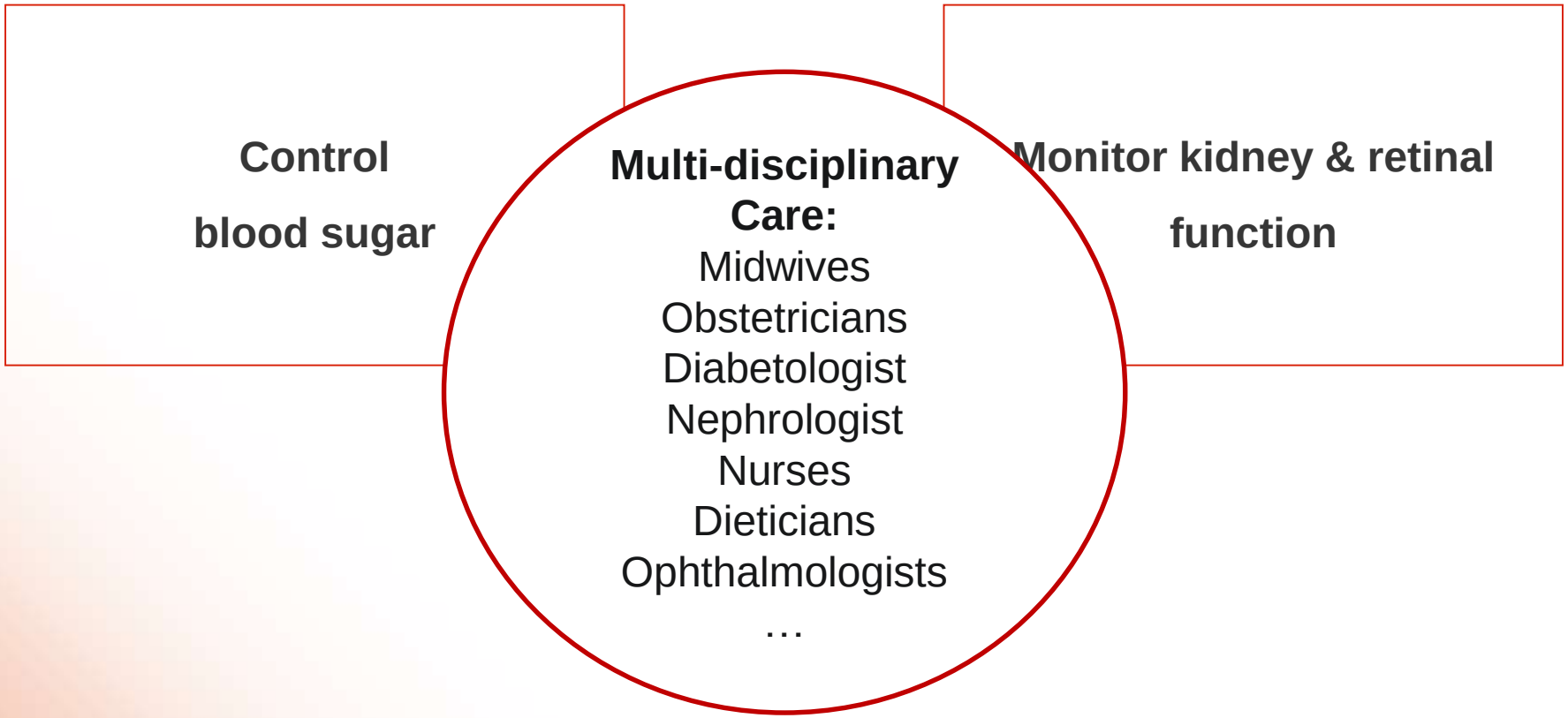
	Time Interval	Incidence, % (No.)	Perinatal Mortality Rate, % (No.)
Lufkin et al. (1)	1950–1979	7.9 (18/228)	27.8 (5/18)
Kilvert et al. (2)	1971–1990	1.7 (11/635)	22
Montoro et al. (3)	1972–1987	3.9 (22/560)	35 (7/20)
Chauhan et al. (4)	1976–1981	22	35
	1986–1991	3	10
Cullen et al. (5)	1985–1995	2 (11/520)	9 (1/11)

Diabetic Ketoacidosis is associated with increased perinatal mortality

NHS
National Institute for
Health and Clinical Excellence

Women with type 1 diabetes should be advised to test for ketonaemia if they become hyperglycaemic or unwell

Antenatal care – running the marathon!



OVER TO DR BRAMHAM!!!!

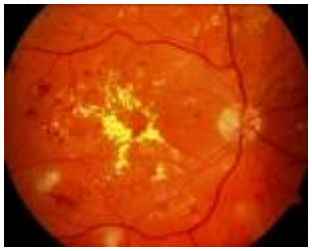
Diabetic retinopathy – Progression in pregnancy

Table 3—*Comparison of incidences of short-term progression of any retinopathy between pregnant and nonpregnant women**

	Not pregnant		Pregnant				
Group	Total	With worse retinopathy	Total	With worse retinopathy	OR†	95% CI	*P*
Intensive							
Unadjusted	2,950	693 (23)	124	39 (31)	1.62	1.01–2.59	<0.05
Adjusted‡	—	—	—	—	1.63	1.01–2.64	<0.05
Conventional							
Unadjusted	5,605	1,742 (31)	73	37 (51)	2.54	1.59–4.03	<0.001
Adjusted	—	—	—	—	2.48	1.56–3.94	<0.001

Data are *n* or *n* (%), unless otherwise indicated. *Progression is relative to the pregnancy-free ETDRS level 6 and 12 months prior; †OR obtained from a GEE logistic regression model; ‡model adjusted for the prepregnancy retinopathy status, the recent change in HbA_{1c} from the prior visit, and time of visit during study.

DCCT Study Diabetes Care 2000



Risk factors for retinopathy progression

- Established disease
- Anaemia
- Diastolic hypertension

Assess at

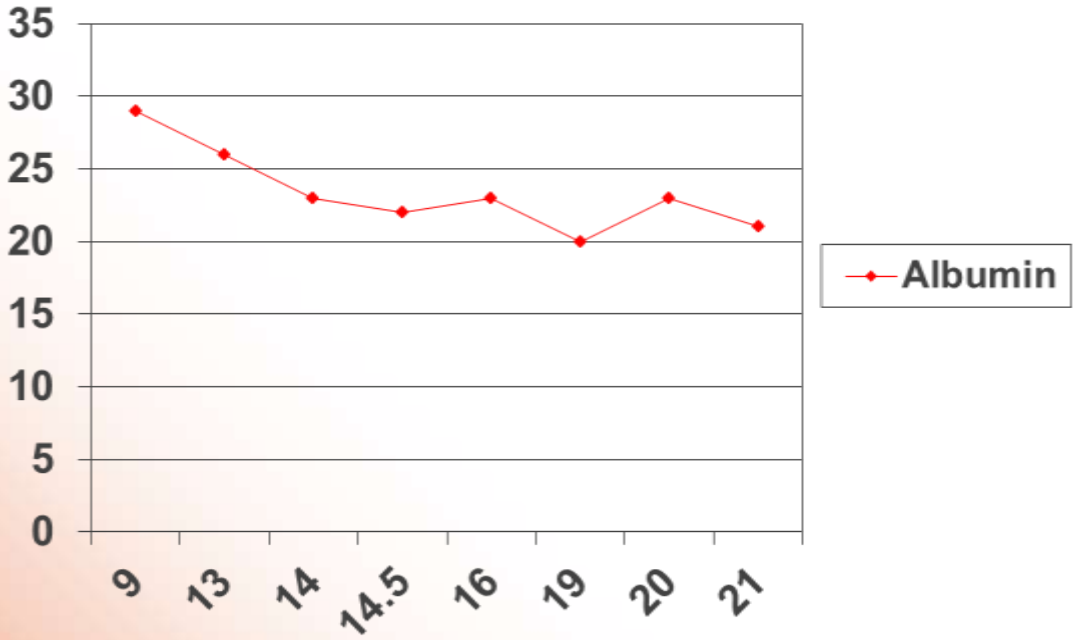
a) First visit (if not done within last 3 months)
b) At 28 weeks
c) If present at first antenatal visit additional assessment at 16-20 weeks

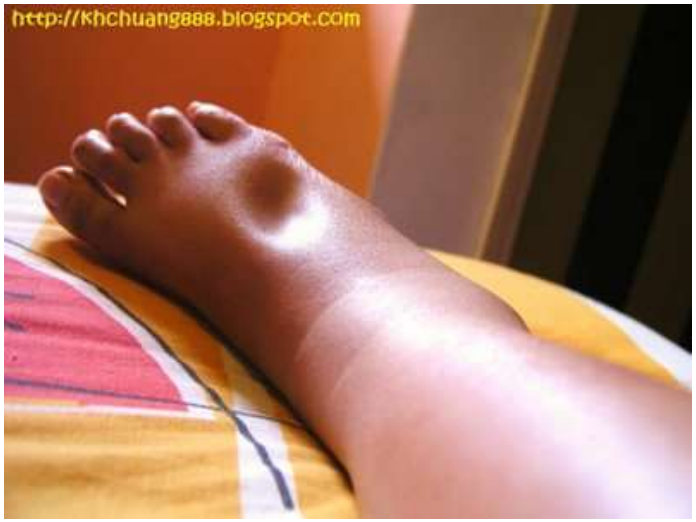
- Retinopathy is not a contraindication to a vaginal delivery
- Lazer treatment is safe in pregnancy

Management of Proteinuria

Case 1

23 year old Type 1 Diabetes (HbA1C 9.8%)
Protein: Creatinine Ratio 1240mg/mmol at 20 weeks'





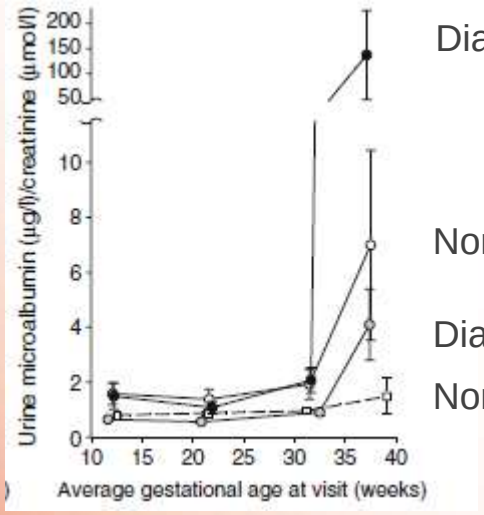
Thromboprophylaxis: recommended by NICE for proteinuria >5g/24 hours
Should be considered in context of other risk factors
Frusemide 20mg od

Proteinuria

Progression of Proteinuria

- N=11 Cr range 1.8-2.5mg/dl (159-221µmol/l)
  - Early pregnancy 18% nephrotic range (Median 2.4g/24hrs (0.2-8.0)
  - Late pregnancy 72% nephrotic range (Median 5.6g/24hrs (0.2-14.4)
- Worsening proteinuria in 82%

Purdy et al Diabetes Care 1996



Diabetic pre-eclampsia n= 26

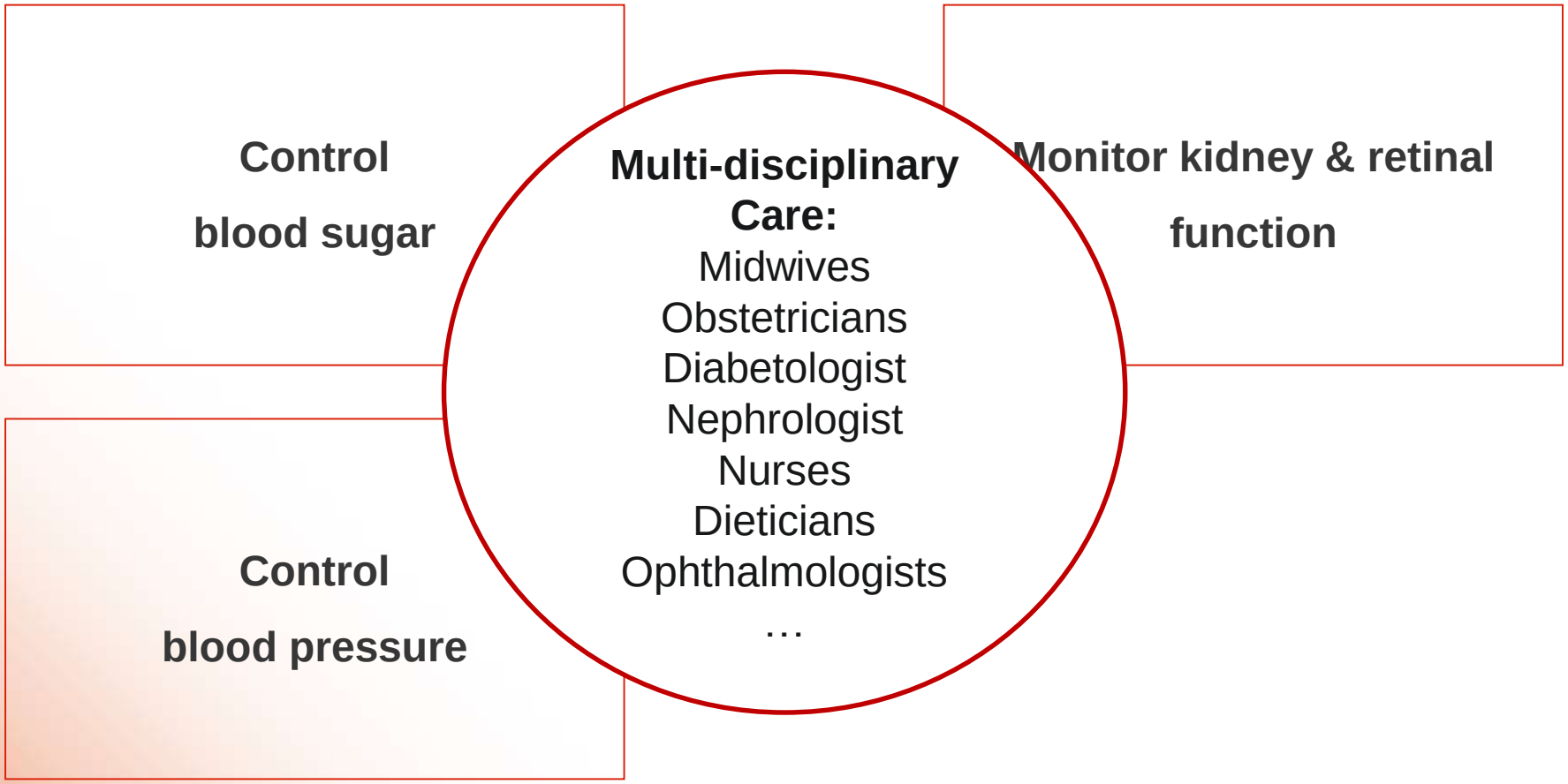
Non diabetic pre-eclampsia n= 3

Diabetic normotensive n= 95

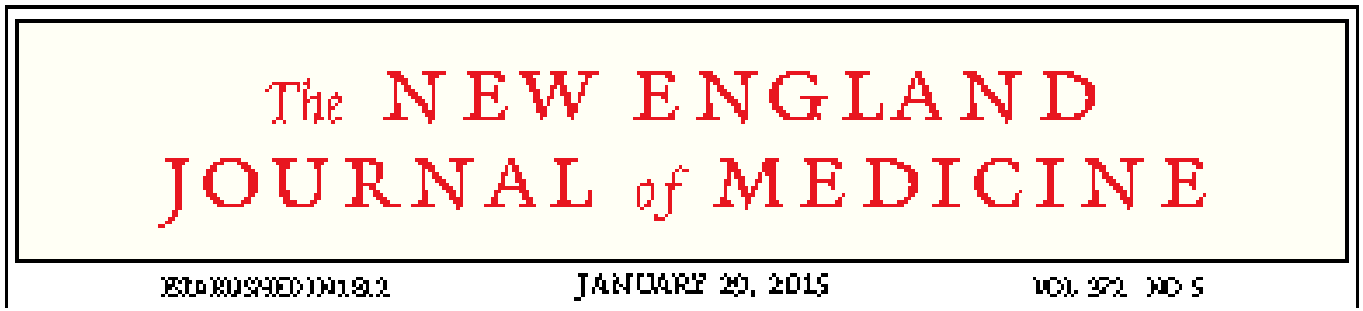
Non diabetic normotensive n= 21

Yu et al Diabetologica 2009

Antenatal care – running the marathon!



Blood pressure targets



Less-Tight versus Tight Control of Hypertension in Pregnancy

Laura A. Magee, M.D., Peter von Dadelszen, M.B., Ch.B., D.Phil., Evelyne Rey, M.D., Susan Ross, M.B.A., Ph.D., Elizabeth Asztalos, M.D., Kellie E. Murphy, M.D., Jennifer Menzies, M.Sc., Johanna Sanchez, M.I.P.H., Joel Singer, Ph.D., Amiram Gafni, D.Sc., Andrée Gruslin, M.D., Michael Helewa, M.D., Eileen Hutton, Ph.D., Shoo K. Lee, M.D., Ph.D., Terry Lee, Ph.D., Alexander G. Logan, M.D., Wessel Ganzevoort, M.D., Ph.D., Ross Welch, M.B., B.S., D.A., M.D., Jim G. Thornton, M.B., Ch.B., M.D., and Jean-Marie Moutquin, M.D.

CHIPS

Tight blood pressure control (Diastolic <85 mmHg) better maternal outcomes and no adverse impact on babies

Magee NEJM 2015

Target blood pressure for women with diabetes

Target Blood Pressure - Controversial

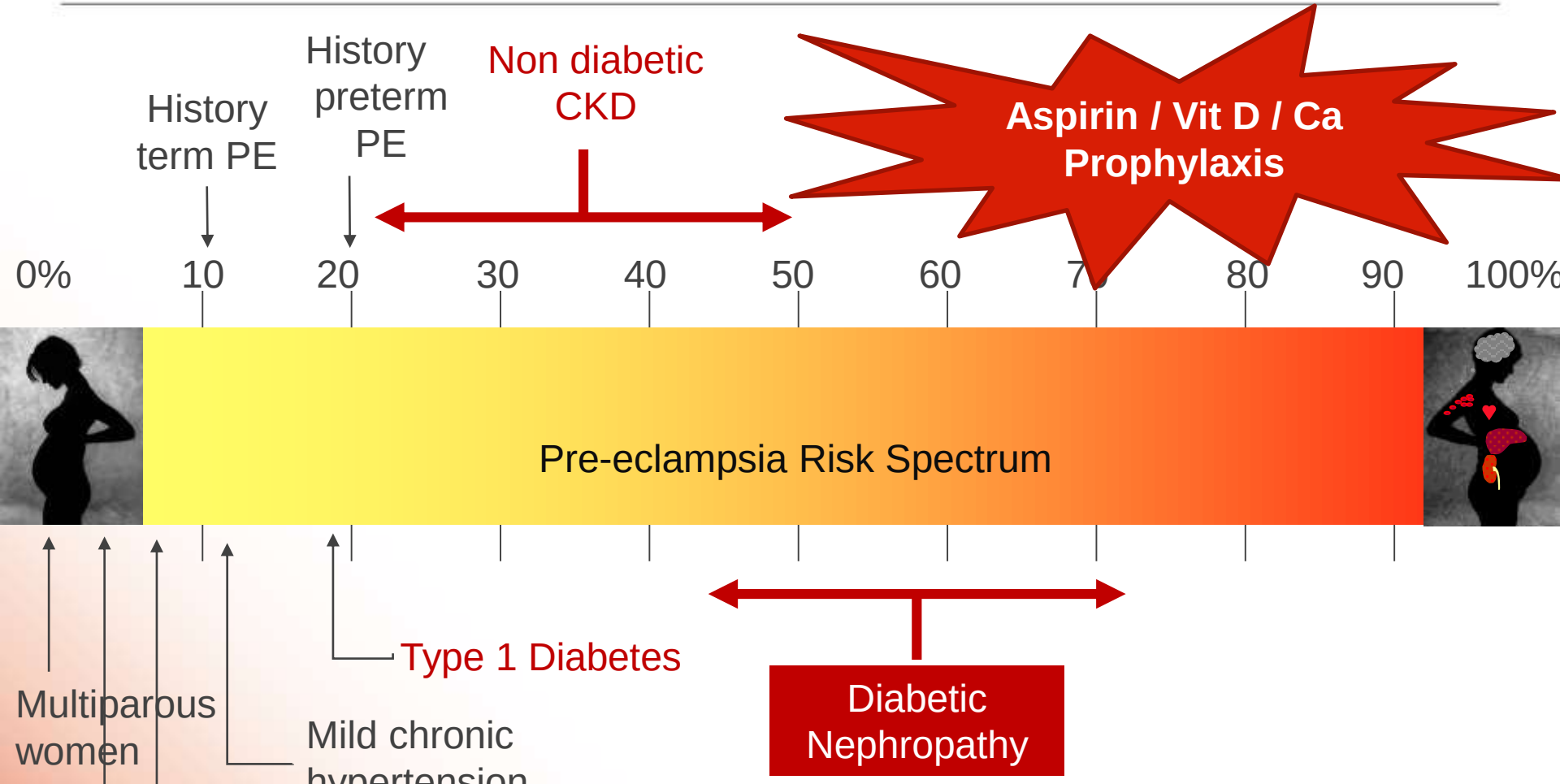
ADA Guidelines

- Systolic 110-129mmHg
- Diastolic 65-79mmHg

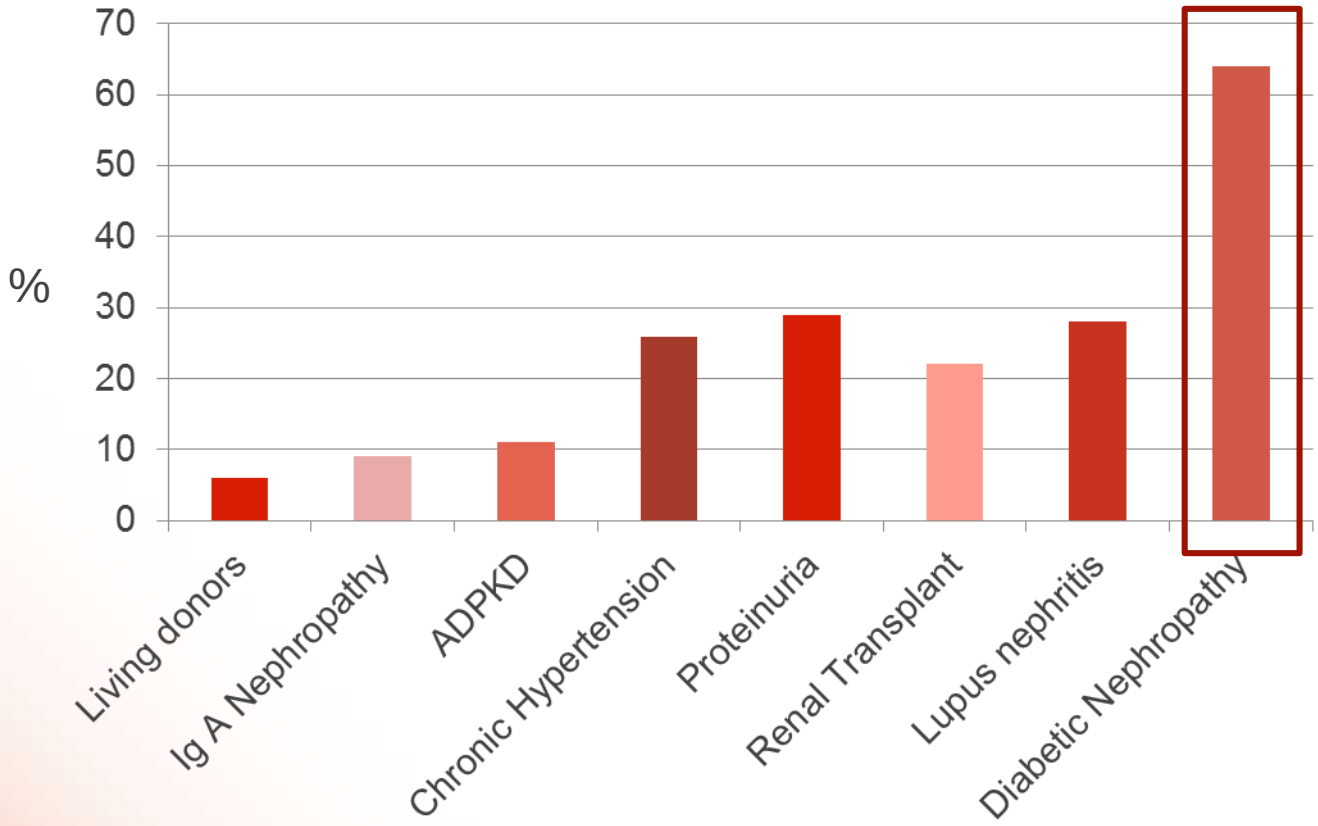
Canadian Guidelines

- Systolic 130-139mmHg
- Diastolic 80-89mmHg’

Pre-eclampsia Risk

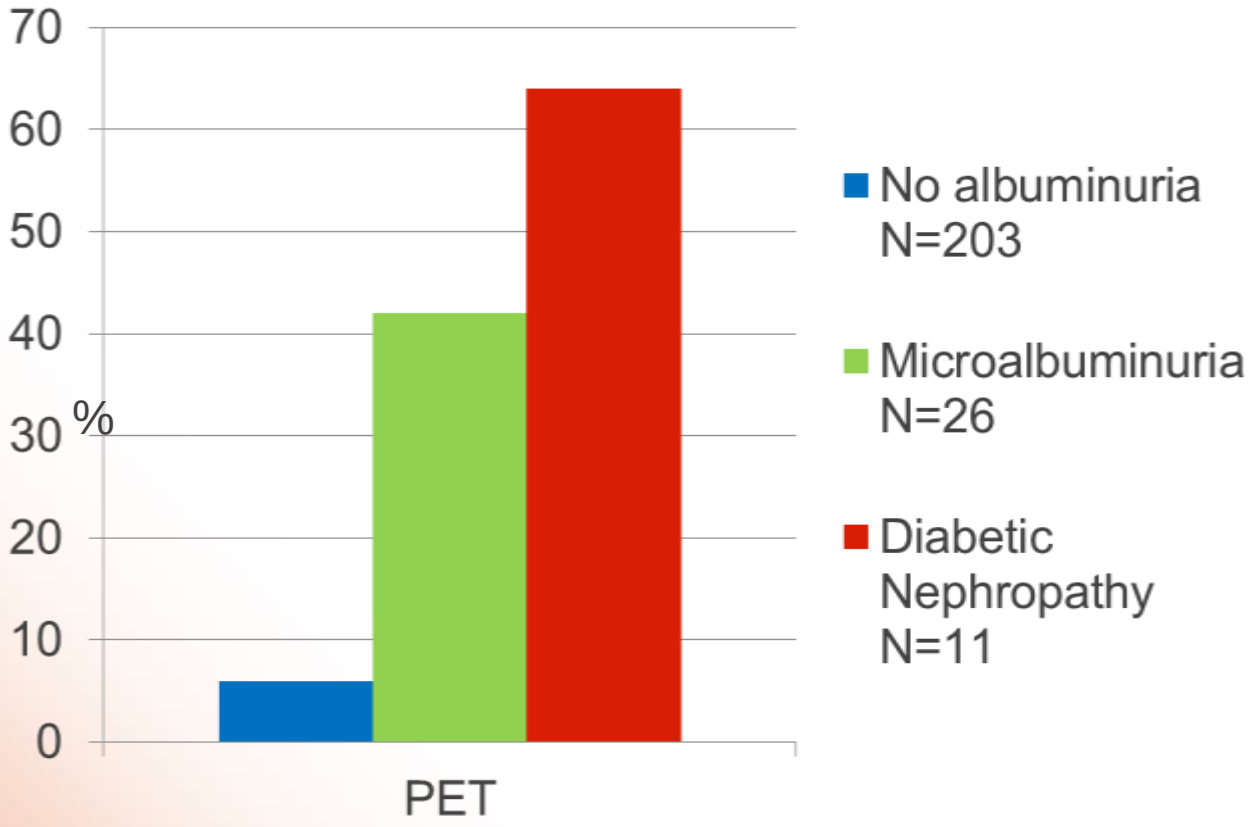


Rate of pre-eclampsia according to renal aetiology



Garg et al NEJM 2015; Liu et al AJKD 2014, ; Chapman et al J Am Soc Nephrol 1984; Bramham et al BMJ 2014, Stetler AJOG 1992, Bramham et al CJASN 2013, Ekbom et al Diabetes Care 2001; Bramham et al J Rheum 2011

Pregnancy Outcomes – Diabetic Nephropathy



Danish Prospective Cohort Study

Ekbom et al Diabetes Care 2001

Pregnancy outcomes: Normoalbuminuria v microalbuminura

Table 1—*Maternal and fetal characteristics in 846 normoalbuminuric and microalbuminuric women with type 1 diabetes*

	Normoalbuminuria	Microalbuminuria	*P*
n	762	84	
Age (years)	28 (25–32)	27 (24–31)	0.34
BMI (kg/m^2)	23 (21–25)	24 (22–26)	0.002
Duration of diabetes (years)	10 (4–17)	15 (10–20)	<0.001
Nulliparity	452 (59)	57 (68)	0.12
Prepregnancy insulin dose (IU/day)	44 (32–54)	47 (40–58)	<0.001
Blood pressure ≥140/90 mmHg at first visit	5 (1)	3 (4)	<0.001
Proliferative retinopathy	25 (3)	9 (11)	<0.001
First-trimester A1C (%)	7.1 (6.4–8.0)	7.6 (6.8–8.5)	0.007
Third-trimester A1C (%)	6.6 (6.0–7.3)	6.8 (6.2–7.5)	0.14
Hypertension during second trimester*	11 (1.5)	11 (13)	<0.001
Preeclampsia	92 (12)	34 (41)	<0.001
Gestational age (days)	260 (252–266)	260 (250–266)	0.2
Gestational age <34 weeks	45 (6)	11 (13)	0.02
Gestational age <37 weeks	284 (37)	30 (36)	0.78
Birth weight (g)	3,650 (3,162–4,060)	3,335 (2,900–3,650)	<0.001
Large-for-gestational-age infant	483 (63)	42 (50)	0.02

Data are medians (interquartile range) or *n* (%). *Blood pressure ≥140/90 mmHg.

Danish population study 1993-1999

Independent predictors of pre-eclampsia

- Microalbuminuria OR 4.0 (95% CI 2.2-72)
- Nulliparity OR 3.1 (95% CI 1.9-5.3)
- Third trimester HbA1C increase by 1% OR 1.3 (95% CI 1.1-1.5)

Excluded

- Urine albumin >300mg/24 hrs
- Women taking antihypertensives

Jensen et al Diabetes Care 2012

Aspirin for Pre-eclampsia

Daily aspirin dose could lower pre-eclampsia risk in pregnant women

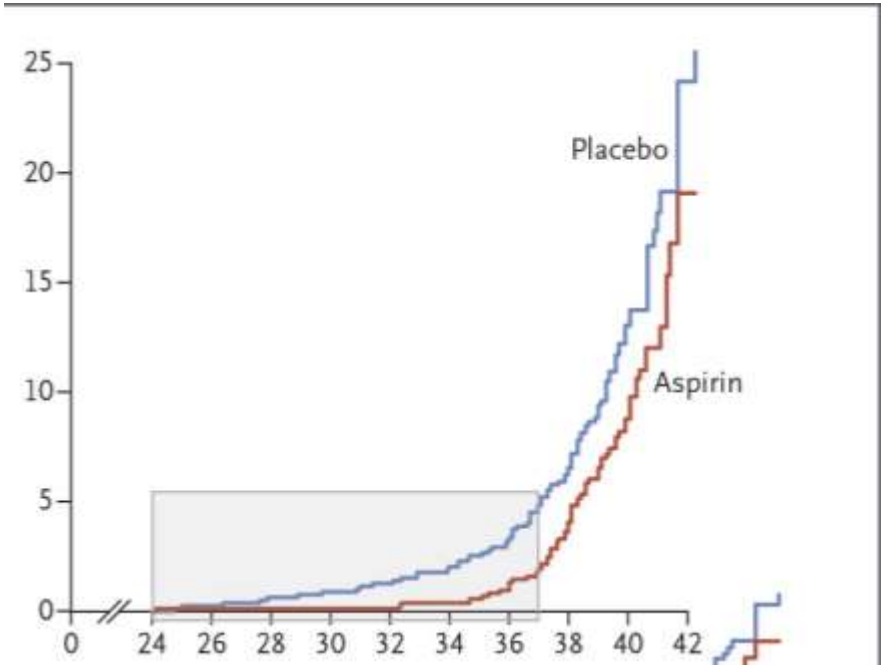
Low dose taken by women at risk of pre-eclampsia throughout pregnancy more than halves chances of premature birth, finds study

- Used screening test algorithm that combines 17 variables to stratify risk then randomised to 150 mg aspirin or placebo

The NEW ENGLAND JOURNAL of MEDICINE

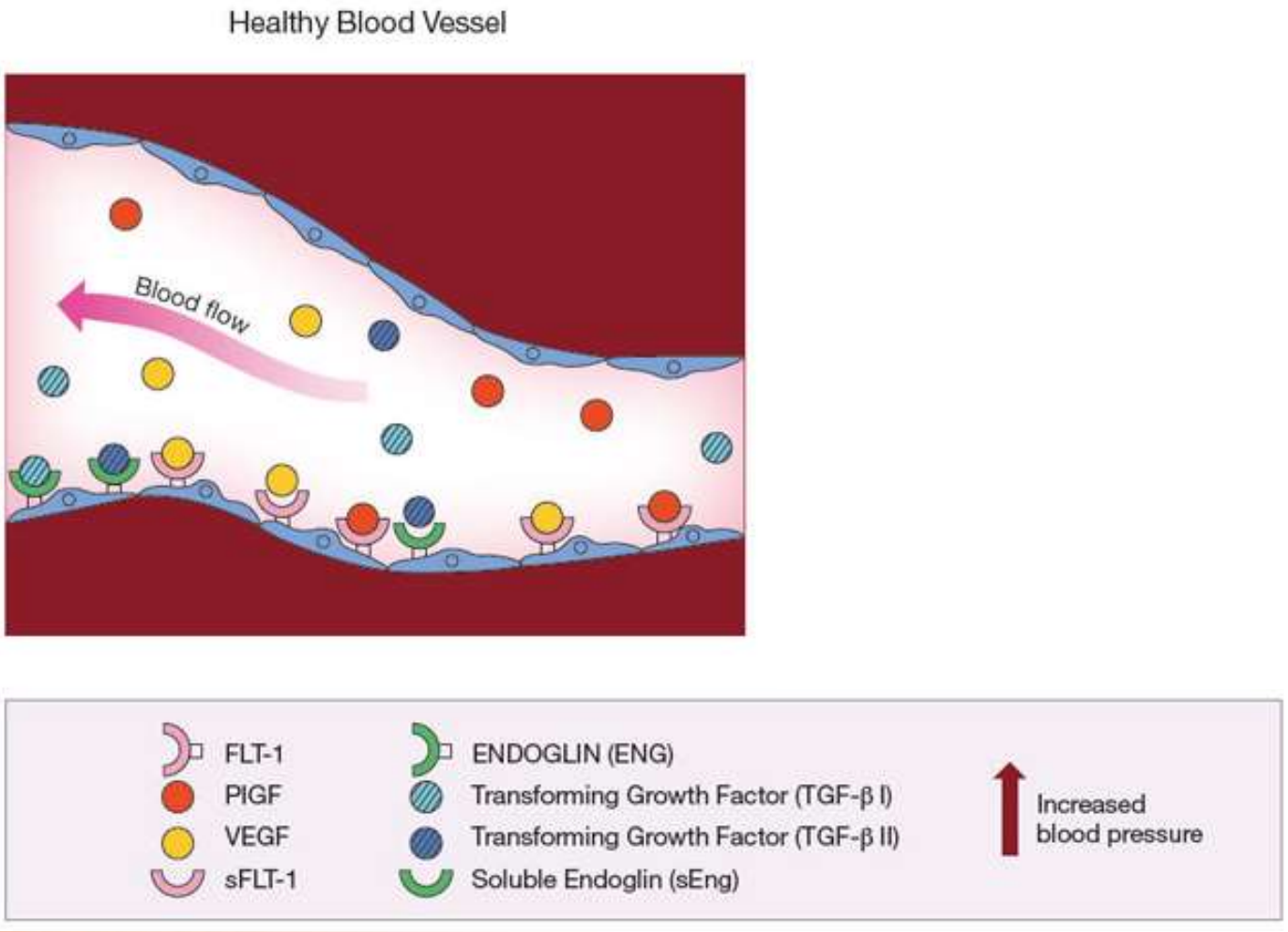
ORIGINAL ARTICLE

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

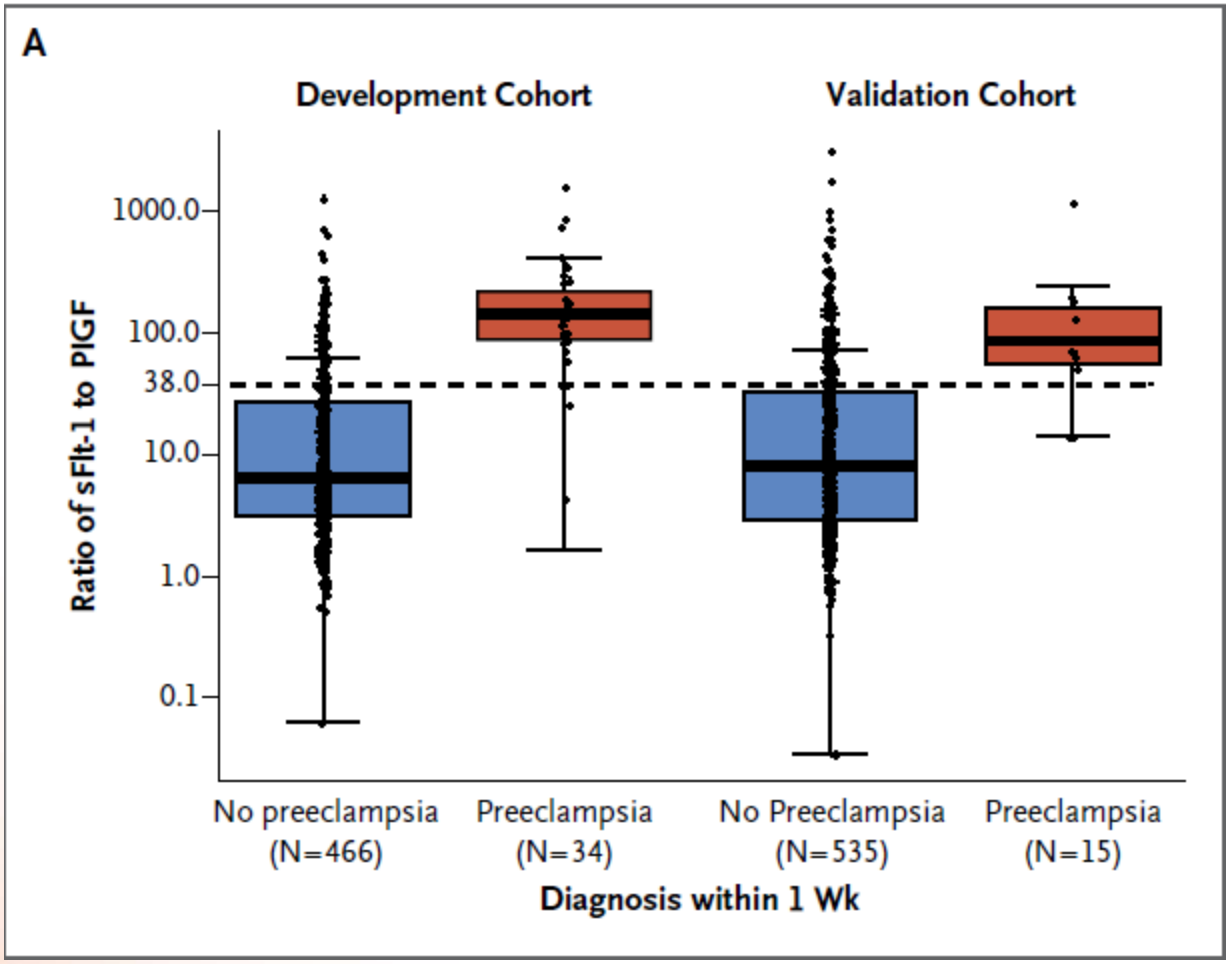


Rolnik NEJM 2017

Pre-eclampsia – Novel biomarkers



PROGNOSIS – Prospective International Cohort Study



Zeisler NEJM 2016

PROGNOSIS – Prospective International Cohort Study

Table 2. Validation of a Cutoff Point of 38 for the sFlt-1:PlGF Ratio in Predicting Preeclampsia.*

Preeclampsia	Development Cohort	Validation Cohort
	percent (95% CI)	
Within 1 wk		
Negative predictive value: rule out	98.9 (97.3–99.7)	99.3 (97.9–99.9)
Sensitivity	88.2 (72.5–96.7)	80.0 (51.9–95.7)
Specificity	80.0 (76.1–83.6)	78.3 (74.6–81.7)
Within 4 wk		
Positive predictive value: rule in	40.7 (31.9–49.9)	36.7 (28.4–45.7)
Sensitivity	74.6 (62.5–84.5)	66.2 (54.0–77.0)
Specificity	83.1 (79.3–86.5)	83.1 (79.4–86.3)

Placental Growth Factor in Clinical Practice

Hypertension in Pregnancy NICE Guidelines
with additional diagnostic test for the PARROT trial

Mild hypertension
BP up to 149/99 mmHg

- **Do not admit to hospital.**
- BP up to 149/99 mmHg
- **Do not treat** hypertension.
- **Measure BP no more than** x1/wk
- **Test for proteinuria** at each visit
- **Carry out routine** antenatal blood tests.
- **If presenting before** 32/40, or at high risk of pre-eclampsia, test for proteinuria and measure BP x2/ wk.

Moderate hypertension
BP 150/100–159/109 mmHg

Do not admit to hospital.

- **Treat hypertension** to keep BP <150/80–100 mmHg.
- **Measure BP at least** x2/ wk.
- **Test for proteinuria** at each visit
- **Test kidney function,** electrolytes, FBC, transaminases, bilirubin.
- **No further blood tests** if no subsequent proteinuria.
- Arrange fetal USS

Severe hypertension
BP ≥ 160/110 mmHg

- **Admit to hospital until** BP *≤159/109 mmHg* and **treat hypertension** to keep BP < 150/80–100 mmHg.
- **Measure BP at least** x4/ day
- **Test for proteinuria** daily
- **Test kidney function,** electrolytes, FBC, transaminases, bilirubin at presentation & then weekly.
- Arrange fetal USS

Continue care as in guidelines pathway; integrate additional information from PlGF test as shown below

PlGF >100 NORMAL	PlGF 12-100 LOW	PlGF <12 VERY LOW
CONTINUE WITH USUAL MANAGEMENT	CONSIDER INCREASED SURVEILLANCE	ASSESS AS PRE-ECLAMPSIA

Algorithm version 3.0 Jan 2016

Placental Growth Factor in Clinical Practice

PARROT

Stepped-wedge cluster randomised controlled trial
11 UK maternity units (3000-9000 deliveries per annum)
Women presenting to maternity services with suspected pre-eclampsia

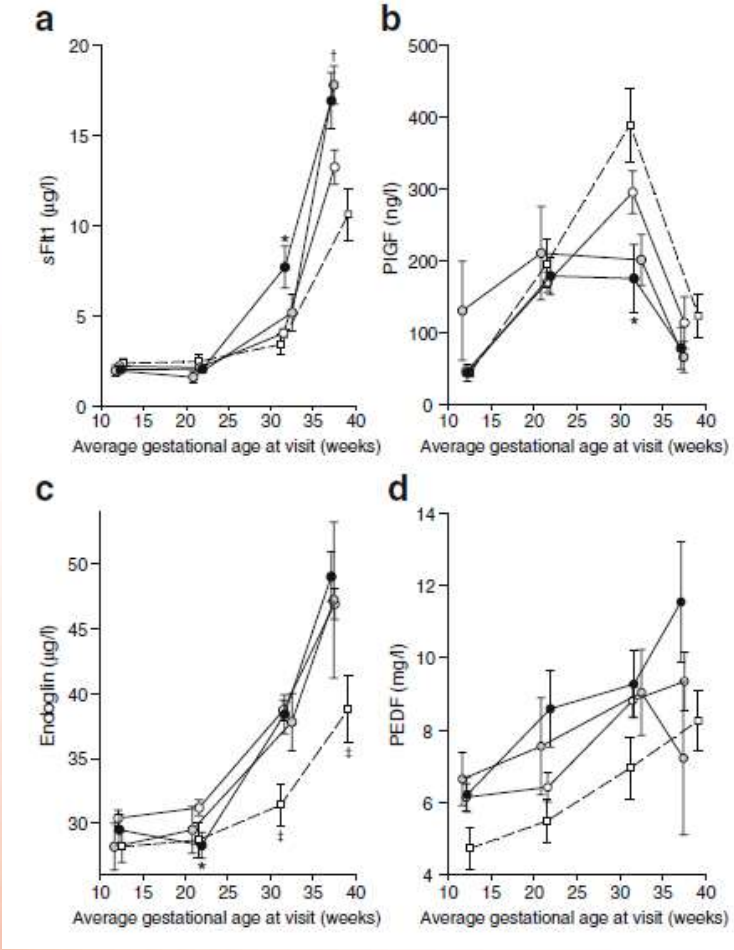
Primary Outcome	Revealed Group	Concealed Group	Effect size
Number of women diagnosed with pre-eclampsia n (%)	**N= 205 (36.8%)**	**N= 155 (34.8%)**	
Time to diagnosis of pre-eclampsia (for those diagnosed) (days) **Median (IQR)**	1.9 (0.5, 9.2)	4.1 (0.8, 14.7)	0.39* (0.17-0.91)

**adjusted ratio of means*

Maternal Adverse Outcome	Revealed Group N= 573	Concealed Group N= 446	Effect size
Maternal adverse outcomes n of women (%) *	22 (3.8%)	24 (5.4%)	aOR 0.32 (0.11-0.96)

**As defined by the fullPIERS consensus*

Diagnosis of Pre-eclampsia – Anti angiogenic factors



Diabetic pre-eclampsia n= 26

Non diabetic pre-eclampsia n= 3

Diabetic normotensive n= 95

Non diabetic normotensive n= 21

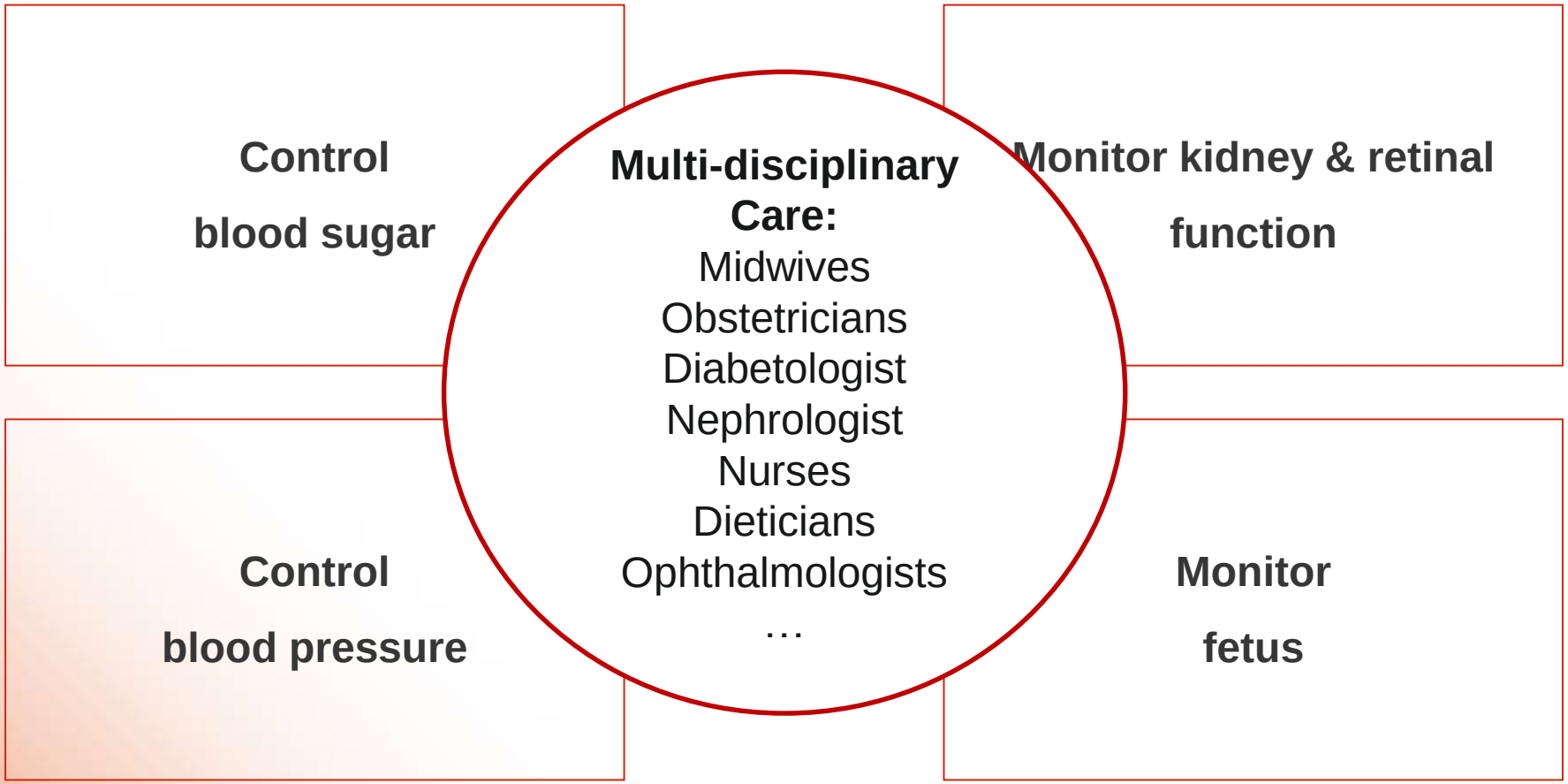
Elevated sFlt-1, Low PLGF and elevated sFLt-1:PlGF precede pre-eclampsia in women with type 1 diabetes

BUT endoglin is elevated in women with type 1 diabetes regardless of onset of pre-eclampsia

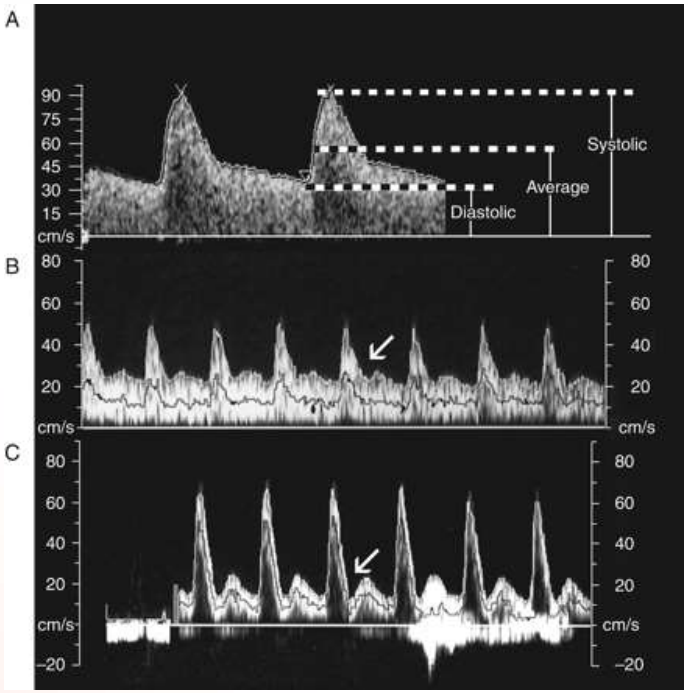
? Contributes to increase risk

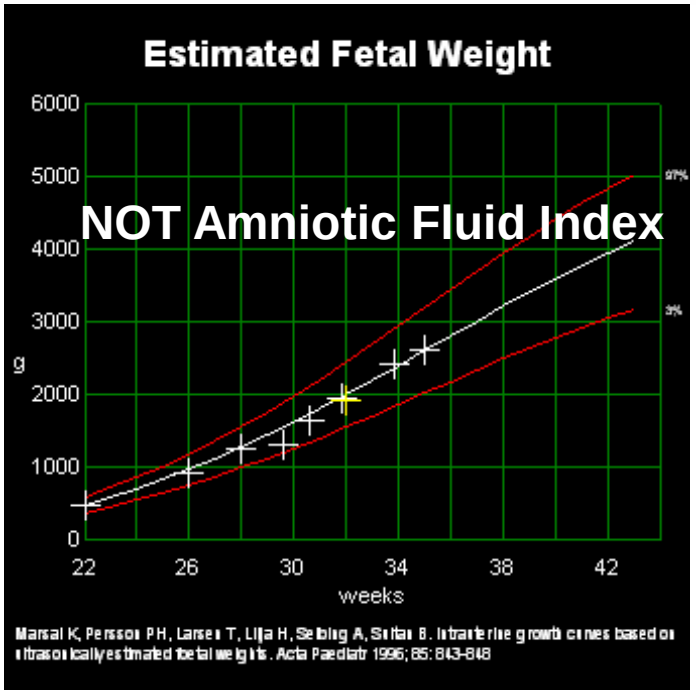
Yu et al Diabetologica 2009

Antenatal care – running the marathon!



Placental / Fetal imaging





Umbilical Artery		L. Middle Cerebral A.	
PI	2.93	PI	1.13
RI		RI	
TAMX [cm/s]		TAMX [cm/s]	
SD ratio		S/D ratio	
EDF	reverse flow	Vmax [cm/s]	62.6

Reliable in CKD, *Piccoli et al NDT 2013, Bramham et al Kidney Int 2016*

Finishing the marathon

Diabetic Nephropathy Pregnancy Outcomes - Summary

+

=

Pre-eclampsia

Caesarean Section

Fetal loss

Preterm delivery

Low Birth Weight

Intrapartum care

NHS
National Institute for
Health and Clinical Excellence

- Diabetes is not a contraindication to antenatal steroids for fetal lung maturity – will need increased insulin and close monitoring
- Not for betamimetic tocolytics
- Anaesthetic assessment in third trimester if obese or autonomic neuropathy
- Aim for plasma glucose 4-7mmol/l during labour
- Intravenous insulin and dextrose recommended after onset of established labour
- **Offer delivery between 37^{+0} – 38^{+6} weeks' if no complications**
- **Consider delivery before 37 weeks if maternal or fetal complications**

Neonatal Outcomes

Neonatal care

Hospital delivery recommended

Blood glucose monitoring 2-4 hours

Complications
- Polycythaemia
- Hyperbilirubinaemia
- Hypocalcaemia
- Hypomagnesiaemia

Vigilance for undiagnosed congenital heart disease

Breastfeeding Compatible Medication
- Metformin
- Glibenclamide
- Insulins

ENALAPRIL *Redman Eur J Clin Pharm1990*

BUT Reduced insulin requirements postpartum

Neonatal Outcomes

Neonatal outcomes in women with pre-existing diabetes

1548 pregnancies with pre-existing diabetes compared 393, 844 without 1996-2008

Table 1 RR of a fetal or infant death (in normally formed singleton offspring) associated with maternal pre-existing diabetes in the North of England during 1996–2008

Outcome	Without pre-existing diabetes		With pre-existing diabetes		RR (95% CI)	*p* value
	Cases (n = 395,844[a]/ 393,262[b])	Prevalence (95% CI) per 1,000 deliveries[c]/live births[d]	Cases (n = 1,548[a]/ 1,502[b])	Prevalence (95% CI) per 1,000 deliveries[c]/live births[d]		
Fetal or infant death	3,988	10.1 (9.8, 10.4)	56	36.2 (27.4, 46.7)	3.59 (2.77, 4.65)	<0.0001
Fetal death[e]	2,582	6.5 (6.3, 6.8)	46	29.7 (21.8, 39.4)	4.56 (3.42, 6.07)	<0.0001
Late miscarriage[f]	796	2.0 (1.9, 2.2)	5	3.2 (1.0, 7.5)	1.61 (0.67, 3.86)	0.25[g]
Stillbirth[h]	1,786	4.5 (4.3, 4.7)	41	26.5 (19.1, 35.8)	5.87 (4.32, 7.97)	<0.0001
Antepartum stillbirth[i]	1,593	4.0 (3.8, 4.2)	38	24.5 (17.4, 33.5)	6.10 (4.44, 8.38)	<0.0001
Intrapartum stillbirth[j]	193	0.5 (0.4, 0.6)	3	1.9 (0.4, 5.7)	3.97 (1.27, 12.41)	0.042[g]
Infant death[k]	1,406	3.6 (3.4, 3.8)	10	6.7 (3.2, 12.2)	1.86 (1.00, 3.46)	0.046
Neonatal death[l]	904	2.3 (2.1, 2.5)	6	4.0 (1.5, 8.7)	1.74 (0.78, 3.87)	0.17[g]
Postneonatal death[m]	502	1.3 (1.2, 1.4)	4	2.7 (0.7, 6.8)	2.09 (0.78, 5.57)	0.13[g]

Tennant et al Diabetologica 2014

Improvement in outcomes from 2002 to 2015

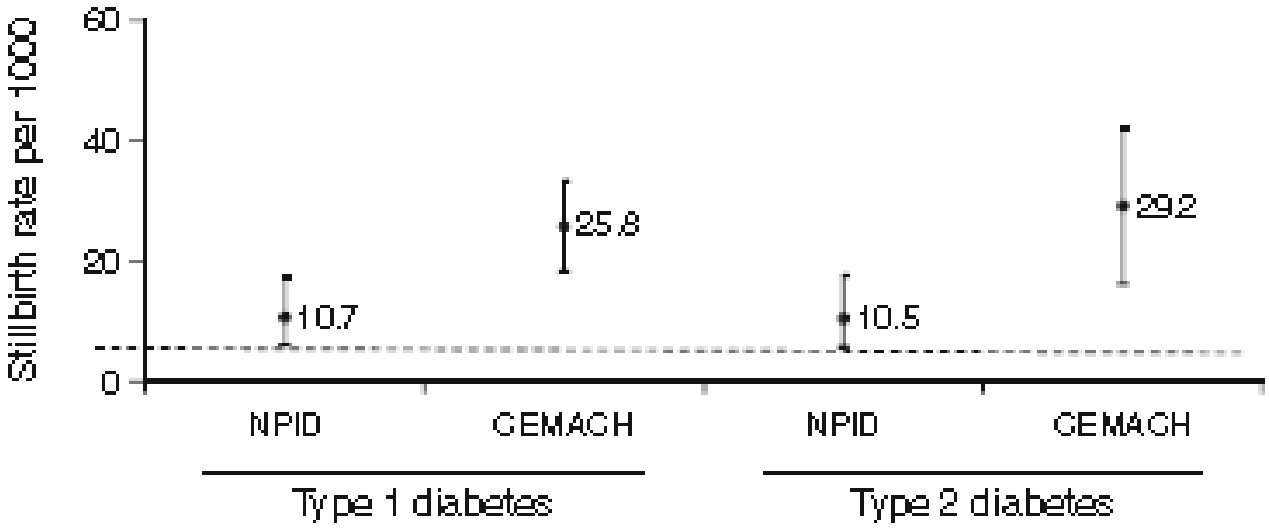


Fig. 3 Stillbirth rate during the NPID audit 2015 compared with CEMACH 2002/2003 for women with type 1 and type 2 diabetes. Data presented are stillbirth rates per 1000 births with 95% CI. Dashed line, stillbirth rate for the general maternity population for 2015 (based on data from the Office for National Statistics [12])

Glycaemic Control and Outcomes

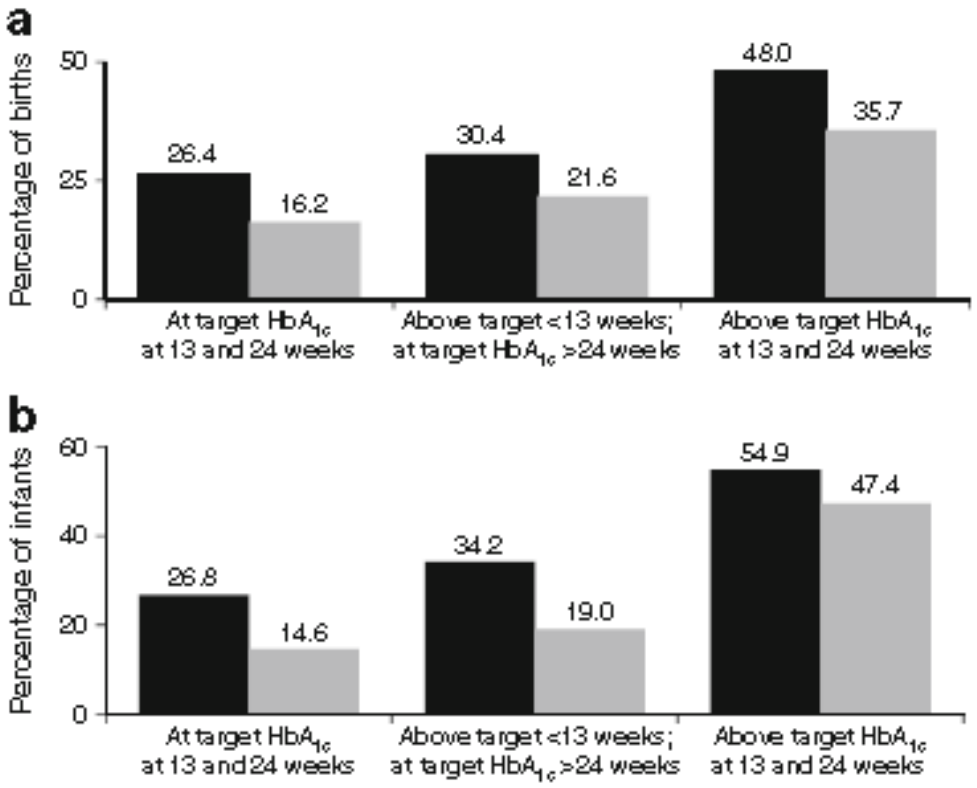


Fig. 2 Relationships for achievement of glycaemic control targets (HbA_{1c} < 6.5% [48 mmol/mol]) with (a) preterm delivery before 37 weeks' gestation and (b) rates of LGA in infants (customised birthweight >90th percentile). Black bars, type 1 diabetes; grey bars, type 2 diabetes

Preterm Birth <37 weeks

Large for Gestational Age

Pregnancy outcomes – Type 1 v Type 2 diabetes

	Type 2 diabetes	Type 1 diabetes	P
n	61	240	
Complications in pregnancy			
Pregnancy-induced hypertension	6 (10)	12 (5)	0.22
Preeclampsia	4 (7)	30 (13)	0.26
Caesarean delivery	22 (36)	123 (51)	0.04
Perinatal outcome			
Congenital malformations	4 (6.6)	7 (2.9)	0.24
Perinatal mortality	4 (6.7)	4 (1.7)	0.05
Gestational age (weeks)*	38.0 (37–39)	37.3 (36–38)	0.03
Birth <34 weeks' gestation*	8 (14)	17 (7)	0.19
Birth <37 weeks' gestation*	18 (31)	87 (38)	0.29
Birth weight (g)*	3,600 (3,095–3,990)	3,595 (3,064–3,925)	0.79
Large for gestational age*	33 (56)	117 (51)	0.54
Small for gestational age*	1 (2)	9 (4)	0.35
Birth weight >4,500 g*	5 (8)	11 (5)	0.27
Neonatal jaundice*	13 (22)	40 (18)	0.35
Respiratory difficulties*	12 (20)	52 (23)	0.79

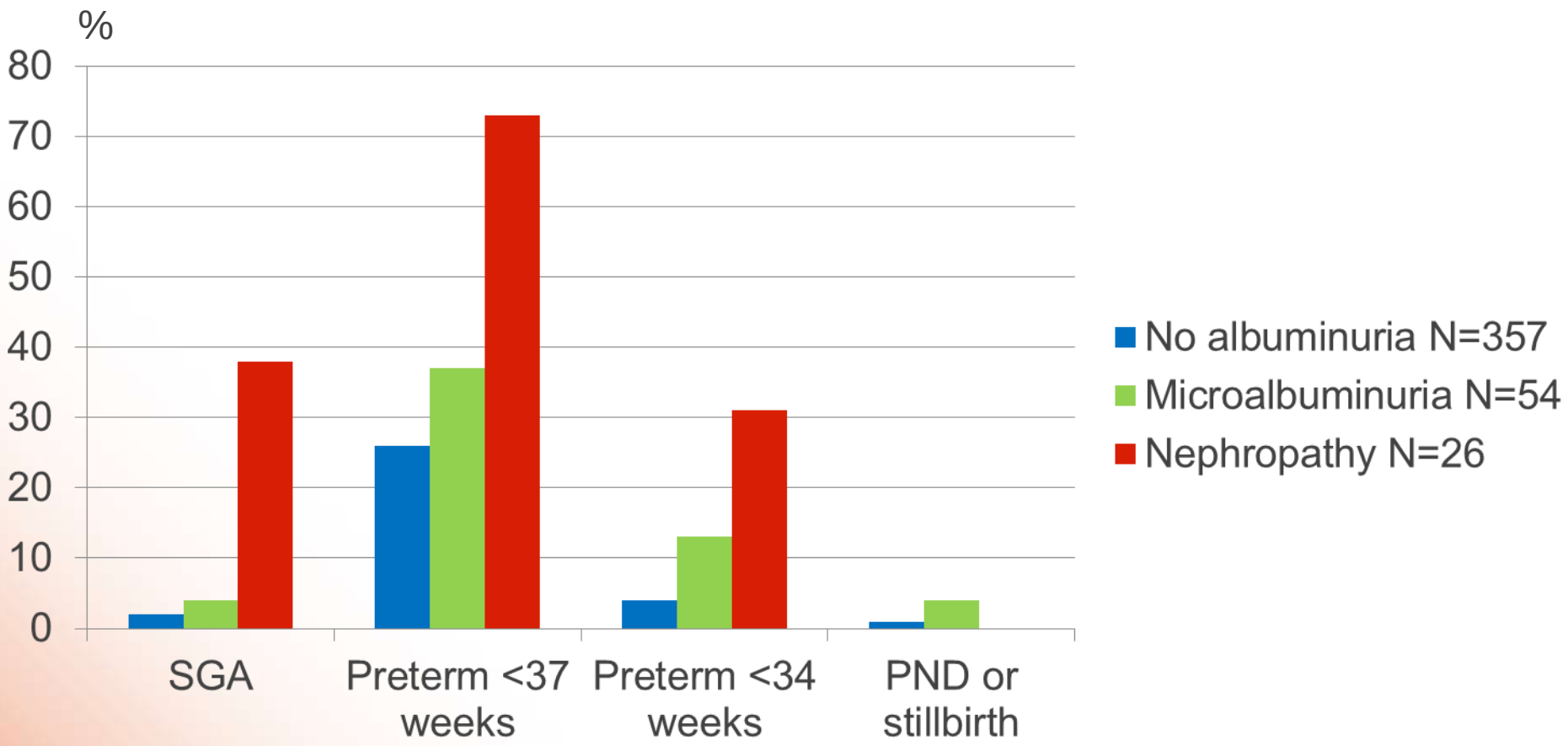
Data are medians (interquartile range) or *n* (%). *The total of live-born singleton infants was 59 for type 2 diabetes and 228 for type 1 diabetes.

Clausen et al Diabetes Care 2005

Comparable pregnancy outcomes between women with nephropathy Type 1 v 2

Damm et al Diabetes Care 2014

Neonatal Outcomes – Diabetic Nephropathy



Piccoli et al Diabetes Studies Rev 2013

Combined data from Themeli et al 2012, Nielsen 2009, Ekbom 2001

Factors influencing pregnancy outcomes in women with diabetic nephropathy

Independent predictors of preterm delivery <37 weeks'

- First trimester blood pressure <130/80mmHg
- First trimester proteinuria >1g/24hrs or 2 or 3+ protein on urinalysis
- Last HbA1c before delivery

Klemmeti et al Diabetologica 2015

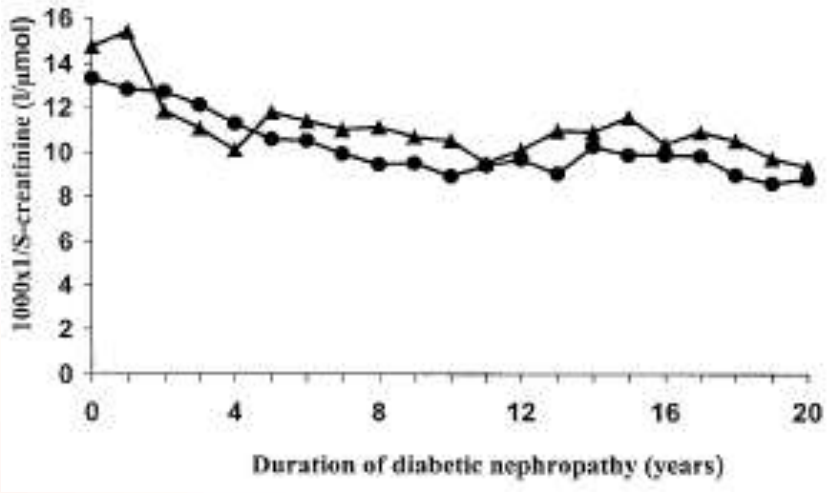
But – small cohort studies – possibly?

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

Antihypertensive Therapy Strategy	Ekbom *et al.*, 2001 (25)	Nielsen *et al.*, 2006 (54)	Nielsen *et al.*, 2009 (2)
	Pre-Eclampsia Diastolic BP >95 mmHg	BP >140/90 mmHg UAE >2 g/24 h ACE Inhibitor before Pregnancy	BP >135/85 mmHg UAE ≥300/24 h ACE Inhibitor before Pregnancy
Number	26	20	10
Duration of diabetes (yr)	19±5	18±8	15±10
HbA1c at inclusion (%)	8.1±0.9	6.8±0.5	7.3±1.5
Week of onset of antihypertensive therapy	29 (20–34)	13 (Before-34)	Before (Before-14)
Patients on antihypertensive therapy during pregnancy	9 (35)	10 (50)	5 (50)
ACE inhibitor before pregnancy	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)
Pre-eclampsia	11 (42)	4 (20)	0
Preterm delivery before 34 wk	6 (23)	0	0
Preterm delivery before 37 wk	16 (62)	8 (40)	2 (20)
Birth weight (g)	3124±767	3279±663	3471±670
Perinatal mortality	1 (4)	0	0
Major congenital malformations	1 (4)	0	0

Long term maternal outcomes

Pre-existing nephropathy Progression



Rossing et al Diabetologica 2002

No difference in rate of decline between women with and without pregnancies over 16 years

	Non-pregnant ($n = 67$)	Pregnant ($n = 26$)	p
Duration of follow-up (years)[a]	16 (3–28)	16 (10–26)	NS
Systolic blood pressure (mmHg)	139 (14)	136 (13)	NS
Diastolic blood pressure (mmHg)	85 (7)	83 (7)	NS
Albuminuria (mg/24 h)[b]	882 (706–1100)	786 (474–1303)	NS
HbA_{1c} (%)	9.4 (1.1)	9.4 (1.2)	NS
Slope of 1/S-creatinine ($1000 \cdot l \cdot \mu mol^{-1} \cdot year^{-1}$)			
– During entire follow-up	–0.41 (0.70)	–0.39 (0.40)	NS
– Post partum		–0.32 (0.52)	NS[d]
Decline in creatinine clearance (ml/min/year)	3.2 (5.1)	3.2 (3.4)	NS
Doubling of baseline creatinine[c] (%)	33 (22–44)	31 (13–49)	NS
Development of ESRD[c] (%)	24 (14–34)	23 (7–39)	NS

Renal Disease Progression: Postpartum – 3 months

Adaptation to pregnancy N=6 (5 women)
- Pre-pregnancy Cr Cl 80mls/min/1.73m^2 (Range 70-91)
- Postpartum Cr Cl 78mls/min/1.73m^2 (Range 70-92)

No adaptation to pregnancy N=8 (7 women)
- Pre-pregnancy Cr Cl 61mls/min/1.73m^2
- (Range 37-73)
- Postpartum Cr Cl 39mls/min/1.73m^2 (Range 22-68) ~ 36% decline

Risk factors for progression
- BP during pregnancy tended to be higher in non adapters
- BP significantly higher in week before delivery

? Role for tight hypertensive control / ? Contribution from placental disease

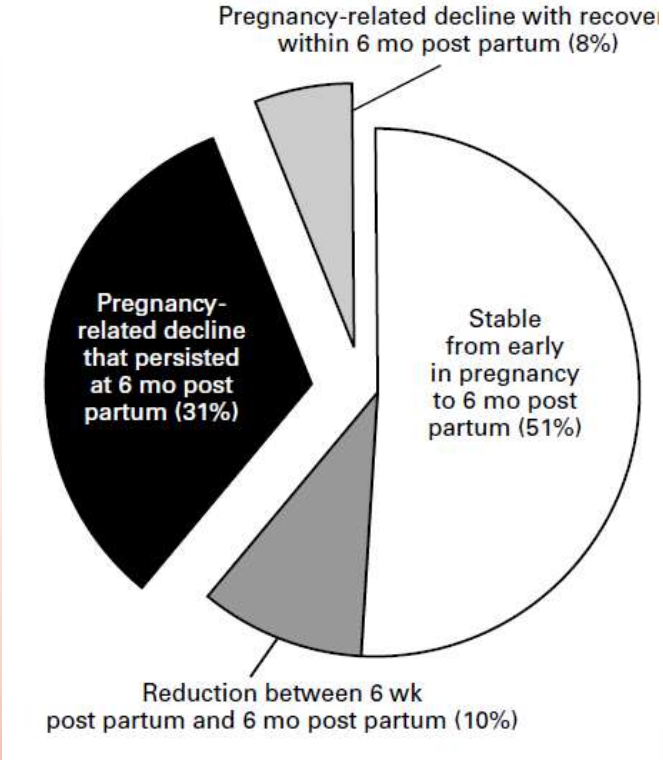
7/11 (64%) progressed to End Stage in 6-57 months after delivery

Biesenback et al J of Nephrology 1999

Comparison of progression with other CKD

82 pregnancies in 62 women

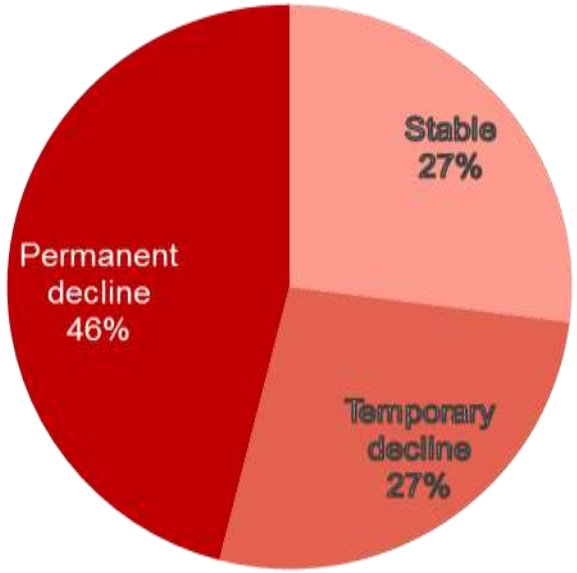
Mean Cr 1.9±0.8mg/dl (168±71µmol/l)



Jones and Hayslett NEJM 2006

11 pregnancies in 11 women

Cr range 1.8-2.5mg/dl (159-221µmol/l)

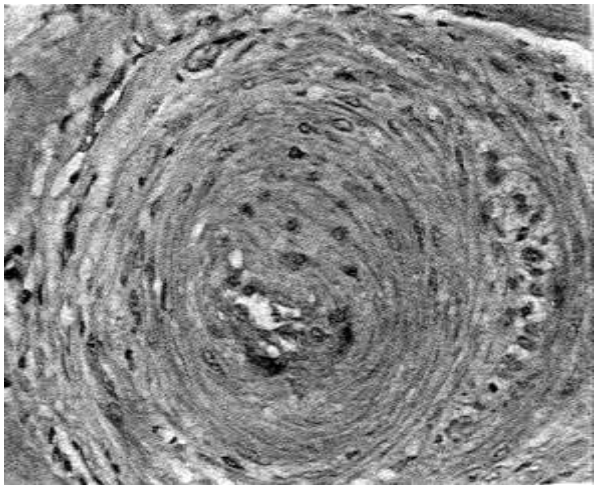


Purdy et al Diabetes Care 1996

Maternal Morbidity and Mortality

Table 3. Causes of death in women with Type I diabetes and diabetic nephropathy

	Non-pregnant (n = 67)	Pregnant (n = 26)	*p*
Cardiovascular	7 (10%)	4 (15%)	
ESRD	8 (12%)	5 (19%)	
Accident	1 (2%)	0 (0%)	
Unknown	4 (6%)	0 (0%)	
Total	23 (34 (23–45)%)[a]	9 (35 (17–53)%)[a]	NS



35% of the cohort had died during the 16 year follow-up period

Rossing et al Diabetologica 2002

Cardiovascular morbidity

•8/14 women with diabetic nephropathy had significant atherosclerotic disease (Bagg et al 2003)

Summary

- Multidisciplinary team work is essential

- Pre-pregnancy counselling
  - Aggressive treatment before conception
  - Avoidance of unplanned pregnancy

- Hypertensive control during pregnancy
- Glycaemic control during pregnancy

- Risk of disease progression at higher GFR than CKD

Thank you

How to optimise outcomes: Hypertension

Suboptimal blood pressure associated with preterm delivery and nephrotic range proteinuria

MAP <110mmHg

Table 2. Comparison of pregnancy and neonatal outcomes between groups

	Below Target (*N* = 22)	Above Target (*N* = 21)	*P*	Crude OR
Nephrotic range proteinuria, *n* (%)	5/15 (33.3)	13/18 (72.2)	.02	5.2 (1.25, 21.66)
Preeclampsia, *n* (%)	6 (27.3)	9 (42.9)	.3	2.0 (0.52, 7.74)
Fetal demise, *n* (%)	2 (9.1)	2 (9.5)	1.0	1.05 (0.14, 8.07)
Delivery gestational age (wk)	35.1 ± 0.5	32.8 ± 0.9	.02	
Delivery <32 weeks' gestation, *n* (%)	1 (4.6)	8 (38.1)	.02	12.92 (1.54, 108.61)
Cesarean delivery, *n* (%)	14 (63.4)	16 (76.2)	.4	1.83 (0.52, 6.45)
Birth weight (kg)	2.52 ± 0.15	1.88 ± 0.2	.01	—
Birth weight percentile	40.8 (9.3–99.1)	20.9 (3.9–99.3)	.07	—
Small-for-gestational age, *n* (%)	2 (9.1)	6 (28.6)	.1	4.0 (0.73, 21.83)

But above target group had:

- Higher Creatinine1.23 +/- 0.17 v 0.85 +/- 0.06 mg/dL
- Higher proteinuria 4.69 +/- 1.08 v 1.65 +/- 0.43 g/24 h

Carr et al Am J Hyperten 2006

How to optimise outcomes: Hypertension

Intensive treatment in 41 women microalbuminuria or nephropathy

Type 1: N=15, Type 2: N=26

- Blood pressure target <135/85mmHg
- Proteinuria target <300mg/24hrs

More women with type 1 diabetes required antihypertensives

Achieved median BP in early and late pregnancy 128/70mmHg

Only 1/41 women developed nephrotic proteinuria / Stable serum creatinine

But – no differences in preterm delivery and birth weight compared with historic data

Damm et al Diabetes Care 2014

How to optimise outcomes: Hypertension

Retrospective Swedish cohort study – 108 pregnancies – Type 1 diabetes 1988-1999 compared with 2000-2011

More antihypertensive use pre-pregnancy and during pregnancy – but frequently discontinued in early pregnancy

Variable	1988–1999 (n=65)	2000–2011 (n=43)	p value
RAS inhibitor used before pregnancy	16 (26.2) [61]	24 (55.8)	0.002
Pre-eclampsia	34 (52.3)	18 (41.9)	0.29
Proteinuria (g/24 h)			
Prepregnancy	1.50 (0.45–7.70) [13]	0.80 (0.34–4.03) [13]	0.42
1st trimester	1.55 (0.40–11.50) [28]	1.77 (0.33–10.40) [17]	0.59
2nd trimester	2.53 (0.58–22.20) [40]	2.44 (0.42–18.50) [29]	0.63
3rd trimester	5.90 (0.37–22.70) [58]	4.22 (0.45–19.80) [40]	0.17

Klemetti et al Diabetologica 2015

Antenatal care

Control blood sugar

Tight targets

Avoiding hypo's

Unpredictably increasing requirements (5% per week)

Caution with HbA1c

Monitor kidney and retinal function

Repeat retinopathy assessment at 28 weeks

Monitor proteinuria

Monitor serum creatinine

NOT eGFR

Multi-disciplinary Care:

Midwives
Obstetricians
Diabetologist
Nephrologist
Nurses
Dieticians
Ophthalmologists …

Control blood pressure

SBP 110-130mmHg

DBP 70-80mmHg

Think PRE-ECLAMPSIA

Monitor fetus

Usual monitoring regime

PLUS…fetal cardiac scan

Uterine artery dopplers

Additional fetal growth scans