LA GRAVIDANZA NELLA PAZIENTE CON NEFROPATIA DIABETICA

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ASST – PAPA GIOVANNI XXIII, BERGAMO

La nefropatia diabetica: le “buone” e le “cattive” notizie

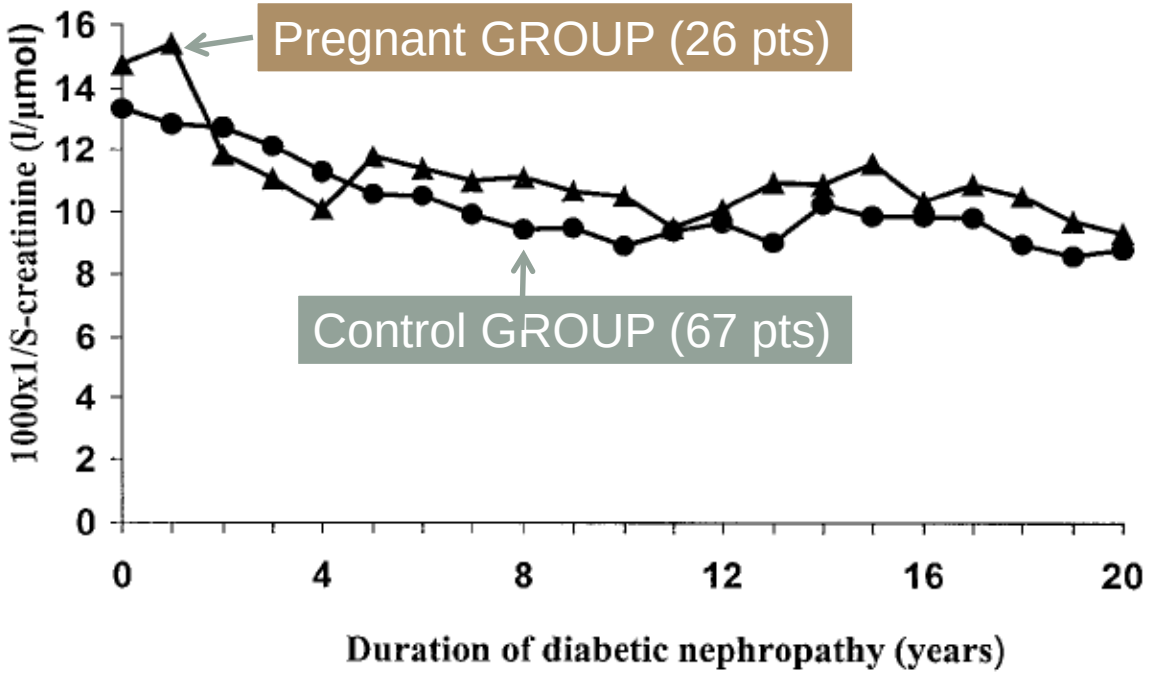
The **GOOD** news

- DN incidence is declining in T1DM.
- DN treatment improves prognosis reducing disease progression.

The **BAD** news

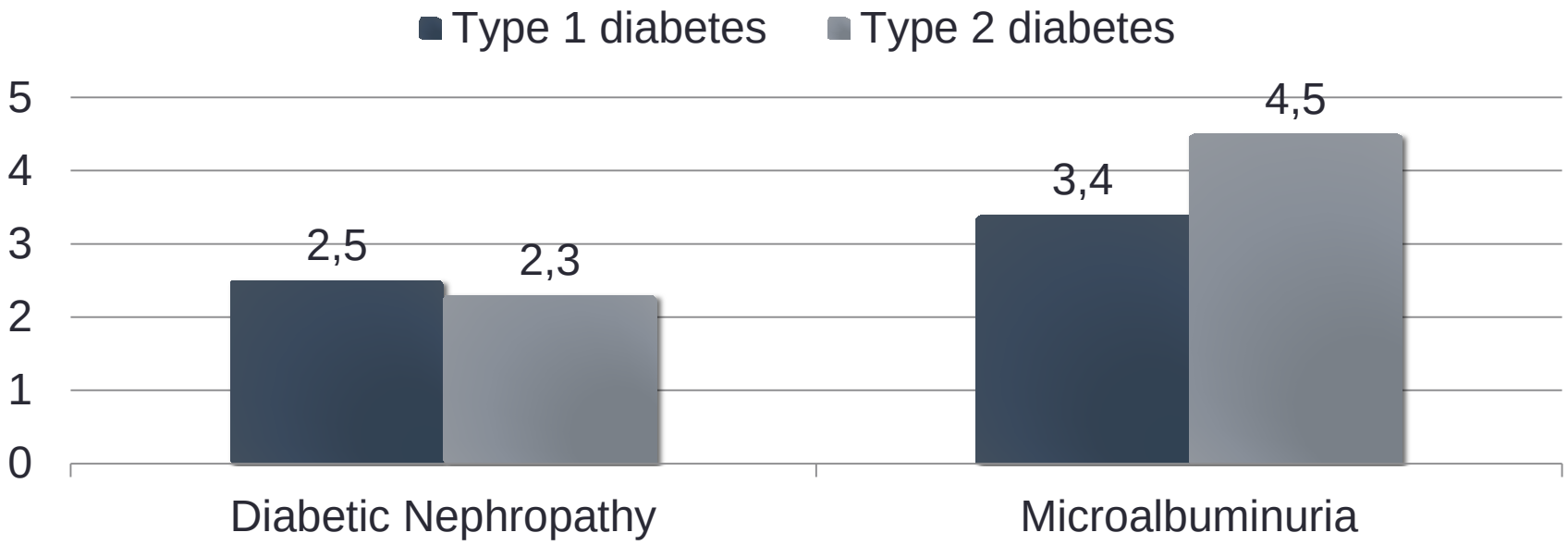
- Age of diabetic women who become pregnant is increasing.
- The prevalence of young T2DM women with renal disease is increasing.

Pregnancy and progression of diabetic nephropathy



Pregnancy has no adverse long-term impact on kidney function and survival in Type 1 diabetic patients with well-preserved kidney function (normal serum creatinine) suffering from diabetic nephropathy.

Prevalence of diabetic nephropathy and microalbuminuria in 220 women with T2 diabetes and 445 women with T1 diabetes giving birth from 2007-2011



Total prevalence of kidney involvement in early pregnancy:
6.8% for type 2 diabetes vs. 5.8% for type 1 diabetes (P = 0.62).

Maternal characteristics among 41 women with type 2 diabetes or type 1 diabetes and kidney affection during pregnancy

	Diabetic nephropathy		Microalbuminuria	
	Type 2 diabetes	Type 1 diabetes	Type 2 diabetes	Type 1 diabetes
n	5	11	10	15
Maternal age (years)	31 (21–39)	32 (28–40)	31 (23–37)	31 (22–37)
Diabetes duration (years)	2 (0.5–13)	19 (10–34)**	2 (0.5–8)	22 (10–31)**
Nullipara	2 (50)	5 (45)	3 (30)	10 (67)
Maternal smoking	0	3 (27)	3 (30)	4 (27)
Folic acid at first visit	2 (50)	10 (91)	6 (60)	12 (92)
Gestational age at first visit (days)	66 (44–69)	68 (49–95)	84 (47–122)	55 (42–147)*
BMI before pregnancy (kg/m^2)	28.2 (24.7–39.3)	23.7 (18.9–34.7)	31.4 (22.5–43.3)	25.8 (21.2–37.5)
HbA_{1c} at first visit (%)	6.8 (5.5–13.2)	7.0 (6.0–9.4)	6.8 (5.8–8.8)	7.1 (6.0–8.3)
HbA_{1c} at first visit (mmol/mol)	51 (37–121)	53 (42–79)	51 (40–73)	54 (42–67)
HbA_{1c} at last visit (%)	5.5 (5.2–5.9)	6.1 (5.5–6.7)	6.2 (5.6–8.2)	6.3 (5.3–6.6)
HbA_{1c} at last visit (mmol/mol)	37 (33–41)	43 (37–50)	44 (38–66)	45 (34–49)

Maternal characteristics among 41 women with type 2 diabetes or type 1 diabetes and kidney affection during pregnancy

	Diabetic nephropathy		Microalbuminuria	
	Type 2 diabetes	Type 1 diabetes	Type 2 diabetes	Type 1 diabetes
n	5	11	10	15
Diabetic retinopathy at first visit	3 (75)	5 (56)	2 (20)	11 (85)**
Serum creatinine at first visit (μmol/L)	52 (40–73)	61 (34–168)	40 (31–63)[a]	51 (35–87)*
Albumin-creatinine ratio at first visit (mg/g)	474 (350–2,950)	712 (350–3,000)	110.5 (51–206)	84.5 (33–222)
Two urine samples collected before 20 weeks	5 (100)	11 (100)	7 (70)	12 (80)
Antihypertensive therapy at first visit	0	7 (64)	0	9 (60)**
Systolic blood pressure at first visit (mmHg)	132 (100–164)	140 (97–176)	128 (108–149)	132 (107–155)
Diastolic blood pressure at first visit (mmHg)	88 (73–91)	80 (63–100)	78 (68–88)	80 (68–87)
Weight gain during pregnancy (kg)	16.7 (2.5–28)	9.25 (1.3–16.2)	8.25 (−2.2 to 15.1)	11.7 (−1.5 to 24.9)
Insulin dose at first visit (IU/kg)	0.40 (0–0.62)	0.68 (0.37–1.17)	0.35 (0–1.23)	0.72 (0.46–1.51)

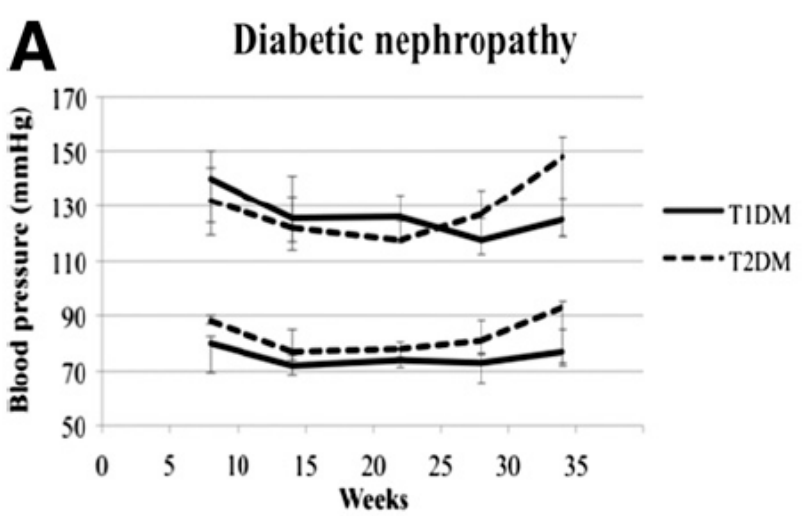
Clinical management

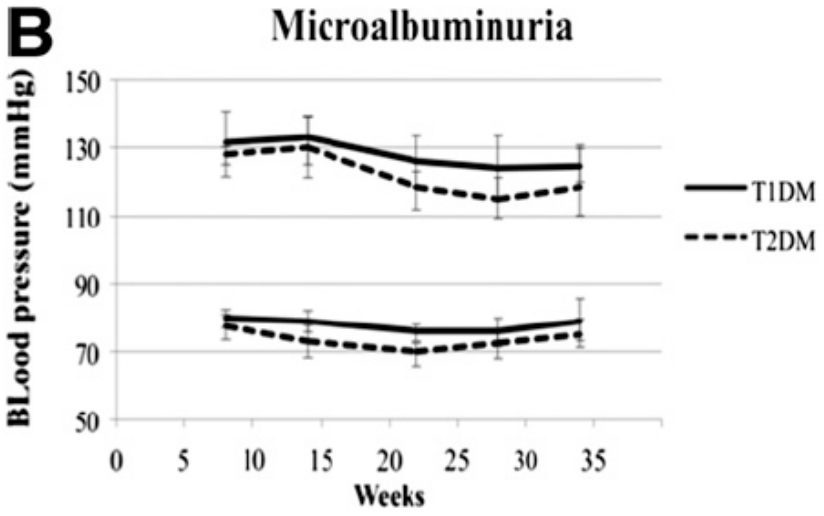
- If urinary albumin-creatinine ratio was ≥ 300 mg/g or blood pressure ≥ 135/85 mmHg, antihypertensive therapy was initiated or intensified.
- If ACE inhibitors were withdrawn during prepregnancy planning, another antihypertensive therapy was initiated unless the albumin-creatinine ratio was close to normal.
- Methyldopa was the first choice therapy in most cases, and, when indicated, labetalol and/or nifedipine were added.
- If given before pregnancy, furosemide or thiazide was continued during pregnancy to reduce the risk of rebound fluid retention with increased blood pressure and urinary albumin excretion when discontinuing the drug.

Clinical management of Hypertension

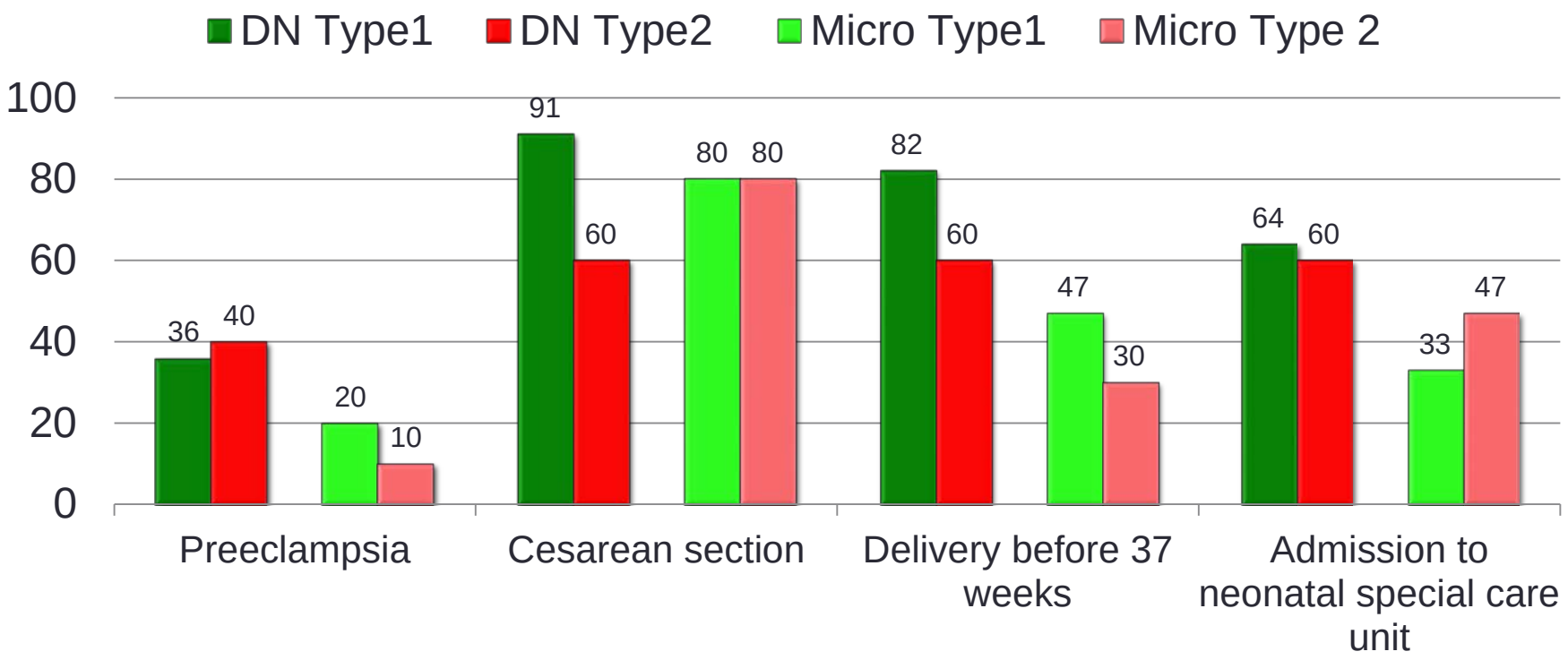
- Antihypertensive therapy in women with **type 2 diabetes**:
  - in four (80%) women with diabetic nephropathy and in two (20%) women with microalbuminuria.
  - In two (40%) women with diabetic nephropathy, at least three classes of antihypertensive drugs were indicated.
- Antihypertensive therapy in women with **type 1 diabetes**:
  - nine were treated with ACE inhibitors before pregnancy, and eight continued this treatment during the organogenesis.
  - Antihypertensive therapy was initiated or continued during pregnancy in 25 of 26 women, and 14 (54%) women received at least two classes of drugs. In women with diabetic nephropathy, six (55%) received at least three classes of drugs.

Blood pressure during pregnancy among 41 women with type 2 (T2DM) or type 1 diabetes (T1DM)

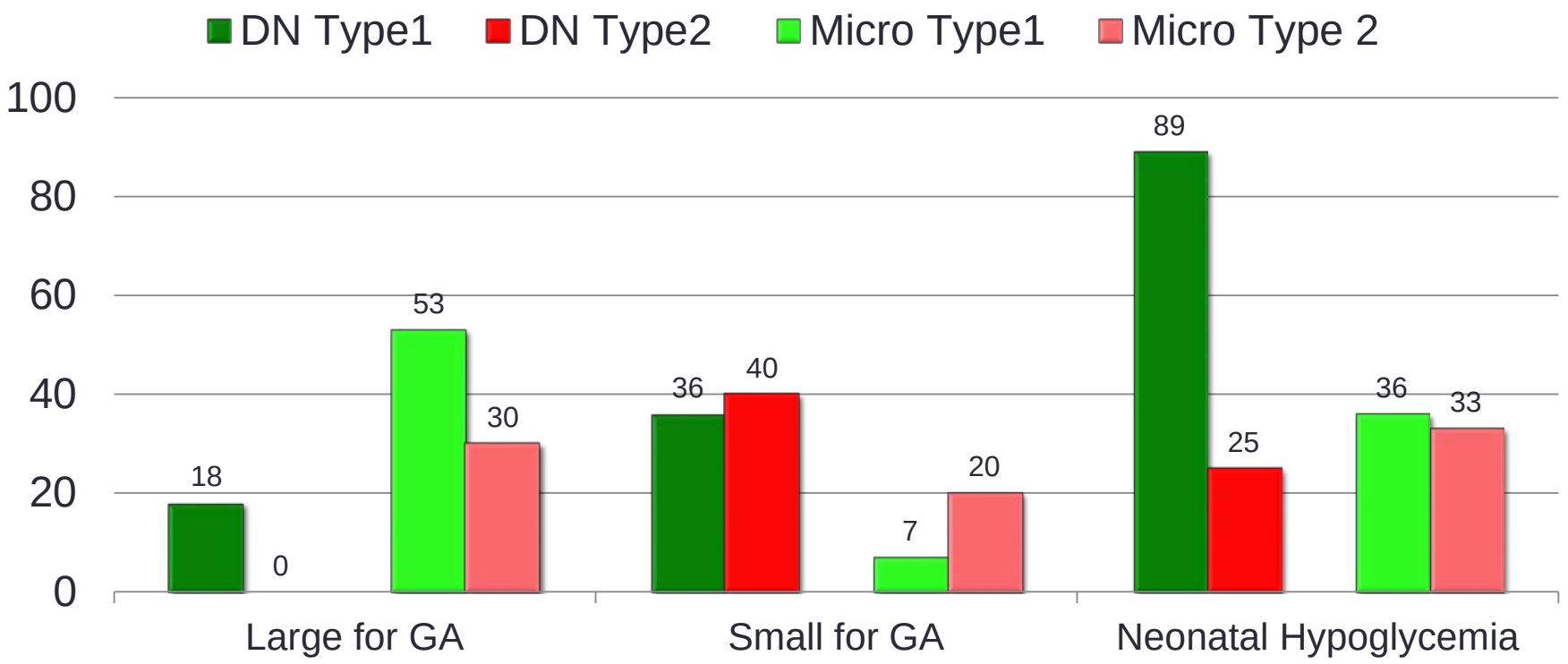




Pregnancy outcome among 41 pregnancies in women with type 2 or type 1 diabetes and kidney affection during pregnancy



Pregnancy outcome among 41 pregnancies in women with type 2 or type 1 diabetes and kidney affection during pregnancy



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ARTICLE

Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988–2011

Miira M. Klemetti · Hannele Laivuori · Minna Tikkanen · Mika Nuutila · Vilho Hiilesmaa · Kari Teramo

Comparison of maternal characteristics of 108 diabetic nephropathy patients with a singleton delivery at HUCH during 1988–1999 and 2000–2011

Maternal characteristic	1988–1999 (n=65)	2000–2011 (n=43)	p value
Age (years)	29 (4.7)	31 (5.1)	0.02
Age at diabetes diagnosis (years)	8 (1–21)	8 (1–17)	0.69
Duration of diabetes (years)	19 (10–34)	24 (12–33)	0.01
Nulliparous	30 (46.2)	26 (60.5)	0.15
Prepregnancy BMI (kg/m^2)	23.6 (18.8–32.0) [58]	23.4 (18.4–38.4)	0.61
Overweight (BMI 25.0–29.9 kg/m^2)	20 (34.5) [58]	14 (32.6)	0.84
Obese (BMI ≥30.0 kg/m^2)	2 (3.4) [58]	1 (2.3)	1.00
Smokers	17 (26.2)	12 (28.6)	0.78
Proliferative retinopathy	33 (50.8)	28 (65.1)	0.14
Prepregnancy HbA_{1c} (%)	8.2 (5.7–12.5) [36]	8.5 (6.1–13.5) [34]	0.16
Prepregnancy HbA_{1c} (mmol/mol)	66 (39–113)	69 (43–124)	
First HbA_{1c} in first trimester (%)	8.3 (5.7–11.8) [55]	8.4 (5.6–13.7) [41]	0.67
First HbA_{1c} in first trimester (mmol/mol)	67 (39–106)	68 (38–126)	
Mid-trimester HbA_{1c} (%)	6.7 (4.7–9.3) [50]	6.9 (5.1–9.0) [38]	0.11
Mid-trimester HbA_{1c} (mmol/mol)	50 (28–78)	52 (32–75)	
Last HbA_{1c} before delivery (%)	6.7 (4.6–10.0)	6.8 (5.3–9.3)	0.67
Last HbA_{1c} before delivery (mmol/mol)	50 (27–86)	51 (34–78)	
Vaginal delivery[a]	0 (0)	3 (7.1) [42]	0.06
Elective CS[a]	46 (70.8)	19 (45.2) [42]	0.01
Emergency CS[a]	19 (29.2)	20 (47.6) [42]	0.05
CS (total)[a]	65 (100.0)	39 (92.9) [42]	0.06

Comparison of antihypertensive medication usage, hypertension frequencies and markers of renal function among 108 diabetic nephropathy patients with a singleton delivery at HUCH during 1988–1999 and 2000–2011

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
Any antihypertensive medication			
Prepregnancy	21 (34.4) [61]	28 (65.1)	0.002
1st trimester	13 (21.3) [61]	14 (32.6)	0.20
2nd trimester	15 (24.6) [61]	20 (46.5)	0.02
3rd trimester	22 (36.1) [61]	26 (60.5)	0.01
SBP ≥140 mmHg and/or DBP ≥90 mmHg			
1st trimester	22 (37.9) [58]	20 (46.5)	0.39
2nd trimester	28 (45.2) [62]	26 (60.5)	0.12
3rd trimester	55 (87.3) [63]	35 (81.4)	0.40
SBP >130 mmHg and/or DBP >80 mmHg			
1st trimester	36 (62.1) [58]	26 (60.5)	0.87
2nd trimester	37 (59.7) [62]	33 (76.7)	0.07
3rd trimester	60 (95.2) [63]	40 (93.0)	0.69
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
Serum/plasma creatinine (μmol/l)			
Prepregnancy	82 (60–122) [21]	68 (38–485) [24]	0.08
1st trimester	70 (57–144) [39]	67 (44–430) [31]	0.10
2nd trimester	75 (52–157) [28]	73 (44–338) [27]	0.61
3rd trimester	77 (59–291) [52]	81 (43–240) [28]	0.81
Creatinine clearance (ml s^{-1} [1.73 m]$^{-3}$)			
Prepregnancy	1.12 (0.72–2.23) [10]	1.74 (0.21–3.69) [8]	0.27
1st trimester	1.42 (0.54–2.18) [20]	1.69 (0.88–3.26) [12]	0.50
2nd trimester	1.38 (0.48–2.61) [23]	1.48 (0.67–2.83) [20]	0.23
3rd trimester	1.31 (0.25–2.20) [36]	1.67 (0.41–2.56) [21]	0.45

Comparison of perinatal outcomes of 108 diabetic nephropathy patients with a singleton delivery at HUCH during 1988–1999 and 2000–2011

Perinatal outcome	1988–1999 (n=65)	2000–2011 (n=43)	p value
Perinatal death	3 (4.6)	2 (4.7)	1.00
Gestational age (days)	254 (186–275)	246 (192–273)	0.17
Delivery <32 weeks of gestation	9 (13.8)	9 (20.9)	0.33
Delivery <37 weeks of gestation	46 (70.8)	33 (76.7)	0.49
Birthweight (g)	2978 (971)	2694 (1029)	0.15
Relative birthweight (SD units)	0.5 (1.8)	0.3 (1.8)	0.55
Birthweight >2.0 SD units (>97.7th percentile)	14 (21.5)	7 (16.3)	0.50
Birthweight <–2.0 SD units (<2.3th percentile)	5 (7.7)	4 (9.3)	1.00
Birthweight >90th percentile (>1.28 SD units)	23 (35.4)	12 (27.9)	0.42
Birthweight <10th percentile (<–1.28 SD units)	10 (15.4)	10 (23.3)	0.30
Apgar score at 1 min <7	10 (15.4)	9 (22.0)	0.39
Umbilical artery pH <7.05[a]	0 (0) [64]	1 (2.6) [38]	0.37
Umbilical artery pH <7.15[a]	3 (4.7) [64]	5 (10.5) [38]	0.42
NICU admission[a]	17 (26.2)	20 (48.8) [41]	0.02
Neonatal hypoglycaemia[a]	39 (60.0)	22 (53.7) [41]	0.52

Maternal factors predicting adverse perinatal outcomes in 108 diabetic nephropathy patients with a singleton delivery at HUCH during 1988–2011

Perinatal outcome	Maternal variable	Non-adjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Delivery before 37 weeks	First trimester BP >130/80 mmHg[b]	3.23 (1.30, 8.03)	3.62 (1.24, 10.56)
	Last HbA_{1c} before delivery (%)[b,c]	2.32 (1.41, 3.82)	2.26 (1.28, 3.98)
Apgar score at 1 min <7	Second trimester proteinuria ≥3 g/24 h	5.28 (1.46,19.14)	4.93 (1.35, 18.01)
Umbilical artery pH <7.15[d]	Last HbA_{1c} before delivery (%)[c]	2.62 (1.17, 5.83)	2.39 (1.05, 5.42)
Macrosomia (>2.0 SD units)	BMI (kg/m^2)	1.22 (1.04, 1.42)	1.24 (1.05, 1.45)
Small-for-date (<−2.0 SD units)	Second trimester proteinuria ≥3 g/24 h	14.00 (1.62, 121.37)	19.52 (1.91, 199.65)
	Maternal age (year)[c]	0.80 (0.67, 0.96)	0.76 (0.60, 0.96)
NICU admission[d]	Second trimester proteinuria ≥3 g/24 h[e]	6.40 (2.20, 18.65)	6.10 (2.07, 17.96)
	First trimester BP >130/80 mmHg[e]	3.76 (1.44, 9.84)	3.18 (1.19, 8.53)

Reprint from The Review of DIABETIC STUDIES Vol 10 No 1 2013

The Review of DIABETIC STUDIES

REVIEW

Type 1 Diabetes, Diabetic Nephropathy, and Pregnancy: A Systematic Review and Meta-Study

Giorgina Barbara Piccoli[1], Roberta Clari[1], Sara Ghiotto[1], Natascia Castelluccia[2], Nicoletta Colombi[2], Giuseppe Mauro[2], Elisabetta Tavassoli[3], Carmela Melluzza[3], Gianfranca Cabiddu[4], Giuseppe Gernone[4], Elena Mongilardi[1], Martina Ferraresi[1], Alessandro Rolfo[3], and Tullia Todros[3]

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Preconception counselling of women with preexisting diabetes and nephropathy or microalbuminuria

- Use of safe contraception in the planning phase
- Evaluate the risk of pregnancy induced-maternal kidney failure
- Evaluate the risk of preeclampsia and preterm delivery
- Intensive glycaemic control with HbA1c at least below 53 mmol/mol
- Supplementation with folic acid
- Target for antihypertensive treatment is tight, i.e. blood pressure < 130/80 mmHg and urinary albumin excretion <300 mg/24 h
- Consider change to pregnancy-friendly antihypertensive agents before conception
- Review the medication list for drugs contraindicated in pregnancy, i.e. cholesterol-lowering agents
- Screen for sight-threatening diabetic retinopathy

Treatment of women with preexisting diabetes and nephropathy or microalbuminuria during pregnancy

- Aim for strict glycaemic control with HbA1c below 42 mmol/mol
- Supplementation with folic acid during the first 12 gestational weeks
- Low-dose aspirin from 10–12 weeks until 1 week before delivery
- Targets for antihypertensive treatment is tight, i.e. blood pressure <135/85 mmHg and urinary albumin excretion <300 mg/24 h
- Use pregnancy-friendly antihypertensive agents
- Review the medication list for drugs contraindicated in pregnancy, i.e. cholesterol-lowering agents
- Tight obstetric surveillance
- Screen for sight-threatening diabetic retinopathy
- During breastfeeding several ACE inhibitors are considered safe

Strategy for antihypertensive treatment in pregnant women with type 1 diabetes and microalbuminuria in three cohorts from the same centre.
Improved pregnancy outcomes were seen with early and intensive antihypertensive treatment

	1995–1999	2000–2003	2004–2006
Initiate or intensify antihypertensive treatment during pregnancy if at least one of the following criteria are fulfilled:	Blood pressure >140/90 mmHg	1. Blood pressure >140/90 mmHg 2. Urinary albumin excretion >2000 mg/24 h 3. Shift to pregnancy-friendly antihypertensive agents if antihypertensive treatment was given prior to pregnancy	1. Blood pressure >135/85 mmHg 2. Urinary albumin excretion >300 mg/24 h 3. Shift to pregnancy-friendly antihypertensive agents if antihypertensive treatment was given prior to pregnancy
Number of women	26	20	10
Average week at onset of antihypertensive treatment	29	14	Before pregnancy
Preeclampsia	42 %	20 %	0 %
Preterm delivery before 34 weeks	23 %	0 %	0 %
Preterm delivery before 37 weeks	62 %	40 %	20 %

Adapted from [4]. Copyright 2015 American Diabetes Association. From *Diabetes Care*®, vol. 32, 2009; 38–44. Reprinted by permission of The American Diabetes Association

Diabetic Nephropathy and Pregnancy

Kate Bramham, PhD

Summary: Women with diabetic nephropathy have challenging pregnancies, with pregnancy outcomes far worse than expected for the stage of chronic kidney disease. The underlying mechanisms that cause the adverse events remain poorly understood, but it is a widely held belief that substantial endothelial injury in these women likely contributes. Maternal hypertension, preeclampsia, and cesarean section rates are high, and offspring are often preterm and of low birth weight, with additional neonatal complications associated with glycemic control. This review will present the current evidence for maternal and fetal outcomes of women with diabetic nephropathy and describe prepregnancy, antenatal, and peripartum optimization strategies.
Semin Nephrol 37:362-369
Keywords: Diabetes, nephropathy, preeclampsia, pregnancy

Antenatal Management

Antenatal Care
Regular multidisciplinary team visits (contact every 1-2 weeks throughout gestation) • Continue intensive glycemic control • Target blood pressure systolic 110-130 mmHg; diastolic 70-90 mmHg • At least 4 weekly serum creatinine and ACR checks and at least 2 weekly starting from 32 weeks gestation • Retinopathy assessment in first trimester if not done within 3 months before conception, repeat again at 28 weeks if normal or at 16-20 weeks if retinopathy is present Medication changes • Start aspirin 75-81 mg once daily (continue prepregnancy or at confirmation of conception) • Stop RAAS blockade and other antihypertensives and statin • Start pregnancy safe antihypertensives, eg, nifedipine, methyldopa • Switch to insulin if type 2 diabetes • Treat vitamin D deficiency if present (eg, cholecalciferol 20,000 IU every 2 weeks until replete) • Consider thromboprophylaxis if there is high risk for thrombosis Fetal monitoring • Nuchal scan at 11-13 weeks • Fetal cardiac scan, 4-chamber view and outflow tracts at 18-20 weeks • Uterine artery Doppler at 20-24 weeks • Regular fetal monitoring to detect growth restriction or macrosomia every 4 weeks from 28-36 weeks Offer induction of labor or cesarean section if indicated at 37^{+0}-38^{+6} weeks
Peripartum
Delivery in center with neonatal support Type 1 diabetes, intravenous insulin during labor
Postpartum
Neonatal monitoring for hypoglycemia Restart RAAS blockade as soon as renal function is stable (eg, enalapril, captopril if breastfeeding)

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Antiplatelet agents for preventing pre-eclampsia and its complications (Review)

Duley L, Henderson-Smart DJ, Meher S, King JF

Main results

- Fifty-nine trials (37,560 women).
- **17% reduction in the risk of pre-eclampsia** associated with the use of antiplatelet agents ((46 trials, 32,891 women, relative risk (RR) 0.83, 95% confidence interval (CI) 0.77 to 0.89), number needed to treat (NNT) 72.
- **8% reduction in the relative risk of preterm birth** (29 trials, 31,151 women, RR 0.92, 95% CI 0.88 to 0.97); NNT 72 (52, 119))
- **14% reduction in fetal or neonatal deaths** (40 trials, 33,098 women, RR 0.86, 95% CI 0.76 to 0.98); NNT 243 (131, 1,666)
- **10% reduction in small-for-gestational age babies** (36 trials, 23,638 women, RR 0.90, 95% CI0.83 to 0.98).

Am J Obstet Gynecol. 2017 Feb;216(2):110-120

The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis.

- 45 randomized controlled trials included a total of 20,909 pregnant women randomized to between 50-150 mg of aspirin daily.
- When aspirin was initiated at ≤16 weeks, there was a significant reduction of
  - preeclampsia (relative risk, 0.57),
  - severe preeclampsia (relative risk, 0.47), and
  - fetal growth restriction (relative risk, 0.56)
  - higher dosages of aspirin were associated with greater reduction of the 3 outcomes.

When aspirin was initiated at >16 weeks, there was no significant effect on outcomes.

Conclusions

- In women with diabetic kidney disease, albuminuria typically increases as pregnancy progresses, and regresses to or near prepregnancy levels after delivery.
- Pregnant women with diabetes, microalbuminuria, and normal kidney function appear to be at low risk for loss of kidney function, but may have a transient increase in albuminuria.
- Diabetic kidney disease is associated with an increased risk of pregnancy complications, including fetal growth restrictionand preeclampsia, even in women with good glycemic control. The occurrence of these pregnancy complications may necessitate preterm delivery and increases the chance of cesarean birth.
- In women with diabetic kidney disease, blood pressure should be below 135/85 mmHg. We suggest use of nondihydropyridine calcium channel blockers in the presence of albuminuria, given favorable effects on both blood pressure and proteinuria.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated during all stages of pregnancy because of teratogenic risk.
- In women with chronic primary or secondary hypertension or previous pregnancy-related hypertension, low-dose aspirin from the 12th week of gestation until delivery is suggested, but should be determined on a case-by-case basis.