Nephropathy

How can we improve pregnancy outcomes in women with type 1 diabetes and nephropathy?

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The outcome of pregnancy in women with diabetes has improved greatly over the last 40 years, although fetal morbidity (mainly major congenital malformation) and mortality remain stubbornly high, at around 8% and 3%, respectively (Bell et al, 2012; Tennant et al, 2014). For reasons that remain unclear, preconception nephropathy increases the risk of congenital anomaly 2.5-fold (Bell et al, 2012).

In the featured paper (summarised alongside), Klemetti et al report on the outcomes of pregnancy in women with type 1 diabetes and nephropathy from a single centre in Finland over a 24-year period. This is one of the largest such series ever reported. What does it tell us and what can we learn from their experience?

Firstly, the prevalence of nephropathy appears to be declining (14.7% vs. 6.5% in the first and second 12-year periods, respectively). This latter figure is similar to recent data from Denmark (5.8%, including microalbuminuria and macroalbuminuria; Damm et al, 2013) and the north-east of England (4.3%, clinician defined; Tennant et al, 2014).

Secondly, adverse maternal outcomes are common. Nearly all of the babies were delivered by caesarean section and before 37 weeks' gestation. Nearly 50% of the mothers developed pre-eclampsia, and over 90% had a blood pressure (BP) of >130/80 mmHg by the third trimester, despite administration of antihypertensive medication in over 60%. The median creatinine clearance rate remained stable overall, but it declined by the third trimester in some, and one woman required haemodialysis.

Thirdly, the perinatal mortality rate was 3.4% overall, similar to that in the north-east of England (3.0%). Major congenital malformations occurred in 9.5% over the study period (compared with 8.2% in the north-east of England). Babies were seven times more likely to be large for gestational age and four times more likely to be small for gestational age (SGA).

Distinguishing between pre-eclampsia and nephropathy-associated hypertension is very difficult clinically, and true rates may be higher. Either way, hypertension and increasing proteinuria were associated with an earlier delivery. Deteriorating creatinine clearance was, unsurprisingly, associated with a rise in both BP and proteinuria, and the likelihood of an SGA infant. Depressingly, the incidence of most of these outcomes did not change between the first half of the study and the second, and admissions to neonatal intensive care actually increased. Why might this be?

Glycaemic control at booking was similar during both time periods (median HbA_{1c}, 66 mmol/mol [8.2%] vs. 69 mmol/mol [8.5%], with very high upper limits of the range of 113 and 124 mmol/mol [12.5% and 13.5%], respectively). This is similar to the median in the north-east of England but considerably higher than in Denmark (53 mmol/mol [7.0%]). Poor control at conception was associated with SGA infants in the north-east of England. Preconception preparation would help here.

Secondly, BP control was not optimal, with only 60% of women put on antihypertensive therapy despite their BP being above target. In the Danish study, 25 of 26 women were on antihypertensives by the third trimester and 14 required two different classes of agent; only one developed nephrotic-range proteinuria compared to a median protein excretion rate of 4.2 g/day in the current series. Finally, only 7% of women in the current study were on prophylactic aspirin, compared to 27% in the Danish series.

Women with nephropathy who wish to have a family need to be counselled about the increased risks to themselves and their baby. They should be urged to engage with pre-pregnancy care and, once pregnant, have intensive surveillance from the joint diabetes/renal/obstetric team. Early and intensive antihypertensive therapy and regular nephrological assessment, with repeat urine collections to assess creatinine clearance rate and proteinuria, are mandatory, and early delivery should be induced in the case of a deterioration in maternal renal function. ■

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Diabetologia

Birth outcomes in women with T1D and nephropathy

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this study, the records of 108 pregnant women with T1D and nephropathy over a period of 24 years (1988–2011) were retrospectively reviewed to analyse temporal changes in glycaemic control, blood pressure (BP), renal function and birth outcomes.

2 Overall, the prevalence of diabetic nephropathy fell from 14.7% in the first half of the study to 6.5% in the second half.

3 However, maternal outcomes in this population remained poor in the second half of the study, with 93% of deliveries occurring through caesarean section (down from 100%) and 42% of mothers developing pre-eclampsia (down from 52%).

4 The prevalence of hypertension (BP, >130/80 mmHg) was high, at around 60% in the first trimester and 95% in the third, and did not change over the study course, despite a doubling of antihypertensive usage to around 60%.

5 Overall, the perinatal mortality rate was 3.4% and major malformations occurred in 9.5% of the newborns. The rate of delivery before 37 weeks of gestation remained high in the second half of the study (76.7%; up from 70.8%). Increasing proteinuria, first-trimester hypertension and final HbA_{1c} before delivery were associated with preterm birth.

6 The neonatal intensive care unit admission rate increased from 26% to 49% and was associated with first-trimester hypertension and second-trimester proteinuria ≥3 g/day.

Klemetti MM, Laivuori H, Tikkanen M et al (2015) Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988–2011. *Diabetologia* **58**: 678–86

Diabetes Care

Impact of long-term HbA_{1c} on development of retinopathy and nephropathy in T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The optimal glycaemic targets to balance the risk of microvascular complications with the risk of hypoglycaemia and effects on quality of life remain a matter of debate in the management of T1D.

2 Therefore, these authors evaluated the risk of retinopathy and nephropathy according to achieved HbA_{1c} over a follow-up of 20–24 years among 451 people diagnosed with the condition between 1983 and 1987.

3 The long-term mean HbA_{1c} was calculated from two to four measurements per year and weighted to account for the time between measurements.

4 The cumulative incidence of both retinopathy and nephropathy increased sharply as long-term mean HbA_{1c} increased.

5 While clinically insignificant retinopathy and nephropathy occurred at almost all mean HbA_{1c} levels, only one participant with an HbA_{1c} under 61 mmol/mol (7.7%) developed proliferative retinopathy, compared with half of those with an HbA_{1c} over 80 mmol/mol (9.5%).

6 Similarly, while microalbuminuria occurred at all HbA_{1c} levels in 15% of the total cohort, macroalbuminuria occurred only in those with an HbA_{1c} of ≥69 mmol/mol (8.4%).

7 The authors thus conclude that an HbA_{1c} target of <60 mmol/mol (7.6%) can prevent retinopathy and nephropathy for up to 20 years.

Nordwall M, Abrahamsson M, Dhir M et al (2015) Impact of HbA_{1c}, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy: the VISS Study (Vascular Diabetic Complications in Southeast Sweden). *Diabetes Care* **38**: 308–15

Diabetes Care

Safety of saxagliptin in people with T2D and renal impairment

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Saxagliptin is a dipeptidyl peptidase-4 inhibitor that is primarily eliminated via the kidneys.

2 In this international study, the cardiovascular (CV) safety of saxagliptin was evaluated in 16 492 people with T2D and varying degrees of renal impairment at baseline.

3 Over a median of 2 years' treatment, compared with placebo, saxagliptin neither increased nor decreased the risk of the composite endpoint of CV death, myocardial infarction or ischaemic stroke.

4 The agent also reduced the progression of albuminuria and HbA_{1c} independently of baseline renal function.

5 However, there was an approximate 20% increased risk of heart failure in the saxagliptin group; this risk was independent of baseline renal function.

Udell JA, Bhatt DL, Braunwald E et al (2015) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care* **38**: 696–705

Diabetes Care

Relationship between cardiac autonomic dysfunction and renal risk in T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 In this study of 445 adolescents with T1D, the association between nephropathy risk and measures of cardiac autonomic dysfunction was evaluated.

2 Participants who were in the upper tertile of albumin:creatinine ratio (ACR; indicating the greatest renal risk) were found to have a significantly higher heart rate and less heart rate variability, independently of age and HbA_{1c}.

3 The authors conclude that these signs of autonomic dysfunction are markers of future nephropathy risk that can be detected before the onset of albuminuria. Long-term evaluation of this cohort is planned in order to determine the predictive value of these variables on renal and cardiac outcomes.

Cho YH, Craig ME, Davis EA et al (2015) Cardiac autonomic dysfunction is associated with high-risk albumin-to-creatinine ratio in young adolescents with type 1 diabetes in AdDIT (Adolescent Type 1 Diabetes Cardio-Renal Interventional Trial). *Diabetes Care* **38**: 676–81

Clin J Am Soc Nephrol

FGF23 levels and the risk of incident CKD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 Fibroblast growth factor 23 (FGF23) levels have been shown to rise early in the course of chronic kidney disease (CKD), often before disease progression can be detected clinically.

2 In this subanalysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, these authors sought to determine whether FGF23 levels were predictive of CKD development in 644 people with T2D who were initially free of the disease.

3 While FGF23 levels were higher in these participants than in those who did not develop CKD, adjustment for baseline glomerular filtration rate rendered these findings non-significant.

4 The authors conclude that, while FGF23 elevations may promote the progression of established CKD, they do not induce or predict *de novo* kidney injury.

Isakova T, Craven TE, Lee J et al (2015) Fibroblast growth factor 23 and incident CKD in type 2 diabetes. *Clin J Am Soc Nephrol* **10**: 29–38

"The authors thus conclude that an HbA_{1c} target of <60 mmol/mol (7.6%) can prevent retinopathy and nephropathy for up to 20 years."

References from commentary

Bell R, Glinianaia SV, Tennant PW et al (2012) Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. *Diabetologia* **55**: 936–47

Damm JA, Asbjörnsdóttir B, Callesen NF et al (2013) Diabetic nephropathy and microalbuminuria in pregnant women with type 1 and type 2 diabetes: prevalence, antihypertensive strategy, and pregnancy outcome. *Diabetes Care* **36**: 3489–94

Tennant PW, Glinianaia SV, Bilous RW et al (2014) Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. *Diabetologia* **57**: 285–94