Diabetic Nephropathy and Pregnancy

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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.

Keywords: Diabetes, nephropathy, preeclampsia, pregnancy

Earlier this century, fetal mortality rates for women with diabetic nephropathy were reported to be between 30%-60%.[1] Although maternal and neonatal mortality have decreased over recent decades, women with both type 1 and type 2 diabetes with and without preexisting nephropathy continue to have high rates of adverse pregnancy outcomes compared with nondiabetic women.[2] Fertility does not appear to be affected by type 1 diabetes, but there are reports of increased menstrual irregularities, delayed menarche, and premature menopause.[3] Ovulation also might be impaired in women with type 2 diabetes and co-existing polycystic ovarian syndrome.

Studies from the UK have estimated that approximately 1 in 250 pregnancies are complicated by type 1 and type 2 diabetes, and the proportion of those with type 2 diabetes has substantially increased in the past 10 years from 27% to 41%.[2,4] Reassuringly, a recent Finnish retrospective study reported that the percentage of pregnant women with diabetes complicated by nephropathy has more than halved (14.7% in 1988-1999 to 6.5% 2000-2011),[5] likely related to the early use of angiotensin-converting enzyme (ACE) inhibitors, hypertension management, and aggressive glycemic control.

PREPREGNANCY OPTIMIZATION

Frequently pregnancy is unplanned in women with diabetes,[2] despite international recommendations for optimization of disease before pregnancy.[6,7] All women with diabetic nephropathy should be offered prepregnancy counseling to inform them of potential adverse outcomes, enable them the opportunity to optimize glycemic and hypertension control, and to improve pregnancy outcomes.

Glycemic control is the primary aim that needs to be addressed before pregnancy to reduce the risk for all adverse maternal and fetal outcomes and, importantly, to minimize the likelihood of congenital abnormalities. Up to 25% of the fetuses from women that have hemoglobin (Hb) A_1c levels >10% before pregnancy have malformations,[2] and a linear relationship between the risk for fetal abnormalities and HbA_1c, even after adjustment for additional risk factors (eg, maternal age), has been described (30% increase in risk for each 1% increase in HbA_1c).[8] A meta-analysis on pregnancy outcomes in women with diabetes reported that the association between glycemic control and congenital abnormalities appeared to be comparable between those with type 1 and type 2 diabetes.[9]

Cardiac and neural tube defects are common and sacral agenesis is rare in pregnancies not complicated by diabetes. Recently, the presence of nephropathy has been reported to confer an additional risk for congenital malformations in women with type 1 diabetes,[8] but the underlying mechanisms remain unclear. Thus, women with diabetic nephropathy are recommended to take folic acid (5 mg) before pregnancy to reduce the risk for fetal abnormalities. Furthermore, a UK population study has recently reported that lack of folic acid supplementation before conception is independently associated with a higher incidence of fetal and infant death.[10]

The second aim of prepregnancy optimization is to reduce proteinuria with renin-angiotensin-aldosterone system (RAAS) blockade, although current guidelines are conflicting. The American Diabetes Association recommends that ACE inhibitors and angiotensin receptor blockers (ARB) should be stopped in any

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sexually active woman of child-bearing potential because of the risk for congenital abnormalities.[7] However, a recent population study provided convincing evidence that exposure to ACE in the first trimester does not appear to be associated with any additional risk for cardiac abnormalities, other than that posed by the presence of hypertension alone.[11] Nonetheless, second and third trimester exposure is undoubtedly associated with the increased risk for renal-related injury, oligohydramnios, neonatal hyperkalemia, and renal impairment.[12]

The National Institute of Clinical Excellence guidelines for the management of diabetes in pregnancy recommend continuation of RAAS blockade until conception to minimize the length of time that women with diabetic nephropathy are suboptimally treated while trying to conceive.[6] Evidence to support RAAS blockade use before pregnancy is limited, but data from small studies (involving 8-24 persons) suggest that intensive RAAS use (capable of decreasing proteinuria to levels <300 mg/day) together with optimization of glycemic control, reduces the incidence of heavy proteinuria during pregnancy,[13,14] although pregnancy outcomes are variable with rates of preterm delivery ranging from 12% to 17%.[13–15] Regular testing for pregnancy in women taking RAAS blockade is recommended for those attempting to conceive, particularly for those with irregular menstrual cycles.

Blood pressure control before pregnancy in women with diabetic nephropathy has not been formally studied; however, in a retrospective study, the suboptimal control of first trimester blood pressure in a cohort of 108 women was an independent predictor of preterm delivery.[5] Aggressive treatment of hypertension with RAAS blockade before pregnancy in women with diabetic nephropathy to improve pregnancy outcomes warrants further study.

Women who are not preparing for pregnancy are advise to take contraception. Estrogen-containing preparations usually are contraindicated in women with diabetic nephropathy because of an increased risk for thrombosis, cardiovascular disease, and the progression of albuminuria. Progesterone-only preparations, including oral contraceptives and implantable and intrauterine devices are preferred. Prepregnancy optimization is summarised in Table 1.

MANAGEMENT DURING PREGNANCY

Antenatal care for women with diabetic nephropathy should be provided by a multidisciplinary team with experience in high-risk pregnancies who continually focus on maintaining tight glycemic and hypertension control in the mother and frequently monitor the fetus.

Glycemic Control

Glycemic control during pregnancy is challenging, even for those with good management outside of pregnancy, because of the production of placental hormones, which contribute to insulin resistance. In general, insulin requirements increase with gestation, but in an unpredictable manner, with reduced fasting blood glucose and higher postprandial measurements in comparison with the individual's prepregnancy readings.[16] Although there is significant individual variation, women should anticipate an approximate 5% increase in insulin dose per week of pregnancy,[17] thus frequent monitoring before and after meals and careful titration of insulin is recommended.[6,7] There is, however, a rapid reduction in insulin requirements with breastfeeding, and thus, vigilance should be maintained in the postpartum period.

Safety profiles of insulins are being revised because new insulins are appearing to be effective during pregnancy with no signs of fetal risk,[18,19] although neutral protamine Hagedorn (Humulin) remains the first-line treatment recommended by current guidelines. Many women now continue with prepregnancy insulins, but to date there are no randomized controlled trials demonstrating superiority for any individual agent or pump. However, four times daily administration has been shown to be associated with better pregnancy outcomes than twice daily.[20]

Metformin and sulfonylureas are considered safe in pregnancy, but oral hypoglycemic agents have been shown to be inferior to insulin for achieving adequate glycemic control.[21] Thus, women with type 2 diabetes are recommended to switch to insulin after conception. More data are needed to confirm safety of newer drugs, eg, thiazolidinediones.

HbA_1c loses accuracy for glycemic control during pregnancy because of the increased red blood cell turnover and other metabolic changes, with an overall reduction in HbA_1c values from 6.3% to 5.6% in normal pregnancy. For this reason, most specialists do not use HbA_1c for monitoring glycemic control; however, $HbA_1c > 6.5\%$ recently has been demonstrated in a prospective study of women with type 1 diabetes to be a predictor of adverse pregnancy outcomes, including preeclampsia, preterm delivery, and large-for-gestational-age infants.[22] Glycosuria is also inaccurate at monitoring diabetes during pregnancy because it is frequently present in women without diabetes due to saturation of renal tubular uptake.

Hypoglycemia occurs more frequently in pregnancy, particularly in those with recurrent episodes before pregnancy[23] and women with type 1 diabetes.[2] For this group of women, continuous monitoring might help with glycemic control.[2] Low blood glucose is particularly common at 16-20 weeks'