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Editorial

Diabetes-Induced Congenital Anomalies of the Kidney and Urinary Tract (CAKUT): Nurture and Nature at Work?

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The cause of congenital anomalies of the kidney and urinary tract (CAKUT) is complex, involving environmental and genetic factors. In this issue of *AJKD*, Dart et al[1] evaluate maternal diabetes mellitus as a risk factor for CAKUT in the fetus, with a potential difference between pregestational diabetes and gestational diabetes. In a large case-control study, Dart et al[1] show that pregestational diabetes significantly associates with CAKUT (odds ratio, 1.67; 95% confidence interval, 1.14-2.46), which implies a 67% increased chance of CAKUT in the offspring of mothers with pregestational diabetes compared to the general population (8.3 vs 5.0 per 1,000 births, respectively). Studying the independent role of early versus late exposure to diabetes in pregnancy in relation to kidney and urinary tract abnormalities emphasizes how crucial the timing of exposure is and the importance of thorough monitoring and counseling of diabetic women before and during the first trimester of pregnancy.

Although preconception and antenatal care in developed countries is focused mainly on effective self-management, recommendations for women with diabetes are fragmented and inconsistent among countries and need further evidence-based standardized guidelines.[2,3] Current recommendations involve tight glycemic control in addition to the general advice given to all women hoping to conceive (ie, lifestyle suggestions and information on teratogenic medications and substances).[4,5] Despite these recommendations, the rate of birth defects in diabetic pregnancies remains higher than that in the general population. Unfortunately, the pathobiological mechanisms underlying diabetic embryopathy are not well understood; thus, more insight into the molecular mechanisms involved is needed to develop efficient interventions that protect against the early teratogenic effects of hyperglycemia.[6]

We know that kidney development is a tightly regulated interplay of cellular processes such as proliferation, apoptosis, migration, and differentiation. These processes involve many key molecular players that show tissue and time-specific expression patterns.[7] Importantly, tissue-specific gene expression is known to be under epigenetic control, comprising transcription factors, DNA methylation, noncoding RNA, and histone modifications. Previously, it has been demonstrated that exposure to maternal diabetes during pregnancy changes gene expression levels in the mouse embryo, thereby disrupting essential cellular activities.[8] In the developing kidney, this could lead to disruption of crucial epithelial and mesenchymal cell interactions, leading to kidney and urinary tract malformation.[9] The exact underlying mechanisms are still unknown. Besides the proposed effects of oxidative stress, discussed by Dart et al,[1] hypotheses have been postulated on how environmental factors could influence gene expression in the embryo by epigenetic changes.[10] Salbaum and Kappen[11] suggested that a hyperglycemic state might lead to a lack of precision in the developmental regulatory program, which is essential for organogenesis. Thus, hyperglycemia during pregnancy could have a teratogenic effect by altering the embryonic epigenome, leading to defects like CAKUT in the fetus.[12,13]

What are the implications of findings that link epigenetic changes to diabetic embryopathy? Other than CAKUT, neural tube defects in the fetus are associated with maternal diabetes, and recent studies have shown that the underlying mechanisms probably involve tissue-specific epigenetic changes and concomitant altered gene expression in neural stem cells.[14] Similar mechanisms could be involved in CAKUT.[15] Furthermore, epigenetic changes might be therapeutic targets to prevent birth defects. Interestingly, folic acid supplementation has been shown to be essential for normal organogenesis and to be protective against congenital defects.[16,17] Folic acid is required for cell division and cell maintenance and is an important factor in DNA methylation, which is essential for epigenetic regulation of gene expression. The potential effect of extra folic acid supplementation in diabetic mothers needs additional evidence, especially in relation to CAKUT incidence. In many countries, including Canada and the United States, folic acid fortification of all cereal grain products was introduced in 1998, leading to a significant reduction in the prevalence of neural tube and cardiac defects.[16] The Canadian birth and diabetes registries give great opportunities for defining the possible protective effect of folate supplementation. Future investigations of hyperglycemia-induced epigenetic changes—and interventions such as folic acid supplementation

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that may target these changes—require accurate cell type–specific epigenomic profiling at different time points, comparing normal and disrupted kidney development.

Genetic profiling is becoming more important in prenatal risk assessment, diagnostics, and prognostics. DNA testing for human CAKUT is aimed at *HNF1B* and *PAX2* screening because mutations in these genes are causal for syndromes involving CAKUT, as well as isolated forms of CAKUT.[18,19] Dart et al did not investigate genetic predisposition to diabetes and CAKUT,[1] yet *HNF1B* mutations could explain part of the association found between maternal diabetes and CAKUT.[20] The lack of genetic data is an important limitation of the study. Furthermore, this study did not evaluate the multigenerational medical histories of the families, which also could have pointed toward genetic predisposition in some of the cases included in the study.

The genetic background for CAKUT is unknown in most cases and is believed to range from monogenic to complex. Thus, in severe, syndromic, or familial cases, only a single gene defect (eg, in *HNF1B*) can cause CAKUT, whereas in sporadic cases, multiple genetic factors in combination with environmental risk factors might be underlying the disease.[21] The occurrence of incomplete penetrance in families, as well as the diverse phenotypic outcome in patients with similar gene mutations, indicates more complex disease mechanisms for CAKUT. Many key players are known to be involved in nephrogenesis and animal studies have proposed numerous candidate genes for human CAKUT, showing the heterogeneous nature of these malformations.[7,22] The ideal genetic test for patients with CAKUT would include all the genes proved to be involved in the cause of human CAKUT. Current efforts are aimed at identifying and characterizing causal gene mutations in order to identify and understand the genetic background of CAKUT and optimize the diagnostics toolbox for CAKUT.[23]

Altogether, birth defects occur in 6% to 10% of babies born to mothers with pregestational diabetes, representing a significant health problem. Because 3 million women of reproductive age (19-44 years) have diabetes in the United States, a number that is expected to double by 2030, we need to take this field to the next level by means of implementing novel intervention strategies. This starts with acquiring more knowledge on the exact mechanisms underlying diabetes-mediated alterations in the embryo. Studies of DNA modifications and gene-environment interactions will help determine the exact role of epigenetics in diabetes-induced CAKUT. Moreover, the additive teratogenic effect of maternal obesity and the protective effect of high folic acid supplementation in relation to diabetic embryopathy need further investigation. We see great opportunities for large collaborative biobank efforts (like the Canadian registry initiatives presented by Dart et al) to reach the critical mass for achieving significant results.

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REFERENCES

1. Dart AB, Ruth CA, Sellers EA, Au W, Dean HJ. Maternal diabetes mellitus and congenital anomalies of the kidney and urinary tract (CAKUT) in the child. *Am J Kidney Dis*. 2015;65(5):684-691.

2. Shawe J, Delbaere I, Ekstrand M, et al. Preconception care policy, guidelines, recommendations and services across six European countries: Belgium (Flanders), Denmark, Italy, the Netherlands, Sweden and the United Kingdom. *Eur J Contracept Reprod Health Care*. 2015;20:77-87.

3. Jack BW, Atrash H, Coonrod DV, Moos MK, O'Donnell J, Johnson K. The clinical content of preconception care: an overview and preparation of this supplement. *Am J Obstet Gynecol*. 2008;199(6)(suppl 2):S266-S279.

4. Allen VM, Armson BA, Wilson RD, et al. Teratogenicity associated with pre-existing and gestational diabetes. *J Obstet Gynaecol Can*. 2007;29(11):927-944.

5. Wilmot EG, Mansell P. Diabetes and pregnancy. *Clin Med*. 2014;14(6):677-680.

6. Zhao Z, Reece EA. New concepts in diabetic embryopathy. *Clin Lab Med*. 2013;33(2):207-233.

7. Schedl A. Renal abnormalities and their developmental origin. *Nat Rev Genet*. 2007;8(10):791-802.

8. Pavlinkova G, Salbaum JM, Kappen C. Maternal diabetes alters transcriptional programs in the developing embryo. *BMC Genomics*. 2009;10:274.

9. Kanwar YS, Nayak B, Lin S, et al. Hyperglycemia: its imminent effects on mammalian nephrogenesis. *Pediatr Nephrol*. 2005;20(7):858-866.

10. Bollati V, Baccarelli A. Environmental epigenetics. *Heredity (Edinb)*. 2010;105(1):105-112.

11. Salbaum JM, Kappen C. Diabetic embryopathy: a role for the epigenome? *Birth Defects Res A Clin Mol Teratol*. 2011;91(8):770-780.

12. Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. *Nat Rev Genet*. 2011;13(2):97-109.

13. Vrachnis N, Antonakopoulos N, Iliodromiti Z, et al. Impact of maternal diabetes on epigenetic modifications leading to diseases in the offspring. *Exp Diabetes Res*. 2012;2012:538474.

14. Shyamasundar S, Jadhav SP, Bay BH, et al. Analysis of epigenetic factors in mouse embryonic neural stem cells exposed to hyperglycemia. *PLoS One*. 2013;8(6):e65945.

15. Jin M, Zhu S, Hu P, et al. Genomic and epigenomic analyses of monozygotic twins discordant for congenital renal agenesis. *Am J Kidney Dis*. 2014;64(1):119-122.

16. Linask KK, Huhta J. Folate protection from congenital heart defects linked with canonical Wnt signaling and epigenetics. *Curr Opin Pediatr*. 2010;22(5):561-566.

17. Czeizel AE, Dudas I, Vereczkey A, Banhidy F. Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. *Nutrients*. 2013;5(11):4760-4775.

18. Heidet L, Decramer S, Pawtowski A, et al. Spectrum of HNF1B mutations in a large cohort of patients who harbor renal diseases. *Clin J Am Soc Nephrol*. 2010;5(6):1079-1090.

19. Madariaga L, Moriniere V, Jeanpierre C, et al. Severe prenatal renal anomalies associated with mutations in HNF1B or PAX2 genes. *Clin J Am Soc Nephrol*. 2013;8(7):1179-1187.

20. Schreuder MF, Renkema KY. Association between maternal diabetes and renal malformations in the offspring: more than environmental factors. *Birth Defects Res A Clin Mol Teratol*. 2011;91(2):125.

21. Vivante A, Kohl S, Hwang DY, Dworschak GC, Hildebrandt F. Single-gene causes of congenital anomalies of the kidney and urinary tract (CAKUT) in humans. *Pediatr Nephrol*. 2014;29(4):695-704.

22. Blake J, Rosenblum ND. Renal branching morphogenesis: morphogenetic and signaling mechanisms. *Semin Cell Dev Biol*. 2014;36C:2-12.

23. Renkema KY, Stokman MF, Giles RH, Knoers NV. Next-generation sequencing for research and diagnostics in kidney disease. *Nat Rev Nephrol*. 2014;10(8):433-444.