Male Predominance of Congenital Malformations in Infants of Women With Type 1 Diabetes

INGE M. EVERS, MD, PHD[1,2]
HAROLD W. DE VALK, MD, PHD[3]
GERARD H.A. VISSER, MD, PHD[2]

OBJECTIVE — To investigate sex-related differences in maternal, perinatal, and neonatal outcome in type 1 diabetic pregnancies in the Netherlands.

RESEARCH DESIGN AND METHODS — This was a nationwide prospective cohort-based study. Logistic regression analysis was used to identify sex-specific risk factors for adverse pregnancy outcome.

RESULTS — A total of 323 type 1 diabetic pregnancies were included; 314 were ongoing after 24 weeks of gestation. There were eight twin pregnancies and one triplet, resulting in 324 infants born after 24 weeks of gestation. Multiple logistic regression analysis showed that the occurrence of congenital malformations was independently associated with male newborns (OR 3.5 [95% CI 1.3–10.0]; $P = 0.02$).

CONCLUSIONS — The higher incidence of congenital malformations in infants of women with type 1 diabetes appears to be restricted to male infants only.

Diabetes Care **32:1194–1195, 2009**

Since the publication by Miller et al. (1) 27 years ago, it was well established that congenital malformations are increased in infants of women with type 1 diabetes and that this incidence is related to glucose control during the periconceptional period. However, an increased incidence of congenital malformations also persists with almost adequate glucose values, as assessed by an A1C within two to four times the SD (2). Prompted by a publication on sex-related differences in maternal and perinatal outcome (3), we studied sex-related differences in maternal, perinatal, and neonatal outcome in a nonselected prospective nationwide cohort of pregnant type 1 diabetic women in the Netherlands.

RESEARCH DESIGN AND METHODS

— The main outcome measures of this cohort were published before (2). Logistic regression analysis was used to identify sex-specific risk factors for adverse pregnancy outcome.

RESULTS

— The 323 pregnancies in women with type 1 diabetes included four therapeutic abortions: two due to major congenital malformations (spina bifida, 18 weeks' gestation, male fetus; anencephaly, 12 weeks' gestation, sex unknown) and two due to chromosomal abnormalities (both Klinefelter syndrome). One maternal death occurred at 17 weeks' gestation, and four other pregnancies ended before 24 weeks of gestation, leaving 314 ongoing pregnancies. Of these, eight were twin pregnancies and one was a triplet pregnancy, resulting in 324 infants born after 24 weeks of gestation. The sex ratio of males to females at birth was 0.94:1 (157 male [48.5%] vs. 167 female [51.5%]). Pregnancies with a male newborn were associated with a higher incidence of congenital malformations (12.7 vs. 3.0%; $P = 0.001$), preterm birth (39.5 vs. 28.7%; $P = 0.04$), and respiratory disorders (18.5 vs. 10.6%; $P = 0.047$) compared with pregnancies with a female newborn. Multiple logistic regression analysis showed that the occurrence of congenital malformations was independently associated with male newborns (OR 3.5 [95% CI 1.3–10.0]; $P = 0.02$). Of the 157 male newborns, there were 20 with a congenital malformation: 10 major (5 cardiovascular anomalies, 4 urogenital anomalies, and 1 caudal regression syndrome) and 10 minor. The incidence of 3.0% in female newborns ($n = 5$; 4 major and 1 minor) approaches the incidence of congenital malformations in the national population (2.6%) (2,4). Glycemic control (i.e., A1C levels) early in pregnancy and overall during gestation was not different in pregnancies with a male or female newborn (6.6 ± 1.1 vs. 6.4 ± 1.0, $P = 0.18$; and 6.3 ± 0.9 vs. 6.3 ± 0.9, $P = 0.36$).

CONCLUSIONS

— We have reviewed extensively the large existing literature on congenital malformations in infants of women with type 1 diabetes, but to the best of our knowledge, a distinction has never been made between male and female infants. We hope that our novel observation, i.e., that the increase in incidence of congenital malformations appears to be restricted to male infants only, will prompt authors of earlier publications to reassess their data. In studies on experimental diabetes in pregnant rats, it has been found that oxidative stress may induce the excess of congenital malformations (5). In humans, it has been found that male infants are more vulnerable to oxidative stress (6). Thus, increased vulnerability in male embryos to oxidative stress might be one of the pathways for our findings.

Acknowledgments — No potential conflicts of interest relevant to this article were reported.

From the [1]Division of Perinatology, Academic Medical Center, Amsterdam, the Netherlands; the [2]Division Woman & Baby, University Medical Center Utrecht, Utrecht, the Netherlands; and the [3]Division Internal Medicine and Endocrinology, University Medical Center Utrecht, Utrecht, the Netherlands.
Corresponding author: Inge M. Evers, i.m.evers@amc.uva.nl.
Received 24 February 2009 and accepted 5 April 2009.
Published ahead of print at http://care.diabetesjournals.org on 14 April 2009. DOI: 10.2337/dc09-0367.

Parts of this study were presented in abstract form at the 5th International Symposium on Diabetes and Pregnancy, Sorrento, Italy, 26–28 March 2009.

References

1. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS, Kitzmiller JL. Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med 1981;304:1331–1334
2. Evers IM, de Valk HW, Visser GHA. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004; 328:915–918
3. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med 2007;4:19–30
4. Statistics Netherlands (CBS). Available from http://statline.cbs.nl/statweb. Accessed 27 May 2009
5. Eriksson UJ, Cederberg J, Wentzel P. Congenital malformations in offspring of diabetic mothers: animal and human studies. Rev Endocr Metab Disord 2003;4:79–93
6. Kraemer S. The fragile male. BMJ 2000; 321:1609–1612