

## Male predominance of congenital malformations in infants of women with type 1 diabetes

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*Objective:* To investigate gender related differences in maternal, perinatal and neonatal outcome in type 1 diabetic pregnancies in the Netherlands.

*Research design & methods:* A nationwide prospective cohort based study. Logistic regression analysis was used to identify gender specific risk factors for adverse pregnancy outcome.

*Results:* 323 Type 1 diabetic pregnancies were included; 314 were ongoing after 24 weeks of gestation. There were 8 twin pregnancies and 1 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[95%CI]: (3.5[1.3-10.0];p=0.02).

*Conclusion:* The higher incidence of congenital malformations in infants of women with type 1 diabetes mellitus appears to be restricted to male infants only.

Since the publication by Miller et al., 27 years ago, it is well established, that congenital malformations are increased in infants of women with type 1 diabetes mellitus and that this incidence is related to glucose control during the periconceptual period(1). However, an increased incidence of congenital malformations also persists with almost adequate glucose values, as assessed by an HbA1c within 2 to 4 times the SD (2). Prompted by a publication on gender related differences in maternal and perinatal outcome (3), we studied gender related differences in maternal, perinatal and neonatal outcome in a non-selected prospective nationwide cohort of pregnant type 1 diabetic women in the Netherlands.

## RESEARCH DESIGN & METHODS

Main outcome measures of this cohort have been published before (2). Logistic regression analysis was used to identify gender specific risk factors for adverse pregnancy outcome.

## RESULTS

The 323 pregnancies in women with type 1 diabetes included 4 therapeutic abortions, 2 due to major congenital malformations (spina bifida, 18 weeks' gestation, male fetus; anencephaly, 12 weeks' gestation, gender unknown) and 2 due to chromosomal abnormalities (both Klinefelter syndrome). One maternal death occurred at 17 weeks' gestation, and 4 other pregnancies ended before 24 weeks of gestation, leaving 314 ongoing pregnancies. Of these, 8 were twin pregnancies and 1 was a triplet pregnancy, resulting in 324 infants born after 24 weeks of gestation. The sex ratio

of male 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%; $p=0.047$ ) as compared to pregnancies with a female newborn. Multiple logistic regression analysis showed that the occurrence of congenital malformations was independently associated with male newborns (OR[95%CI]: 3.5[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%) (4). Glycemic control (i.e. HbA1c-levels) early in pregnancy and overall during gestation was not different in pregnancies with a male or female newborn ( $6.6\pm 1.1$  vs.  $6.4\pm 1.0$ ; $p=0.18$  and  $6.3\pm 0.9$  vs.  $6.3\pm 0.9$ ; $p=0.36$ ).

## CONCLUSION

We have reviewed extensively the large existing literature on congenital malformations in infants of women with type 1 diabetes mellitus, but to the best of our knowledge never a distinction has been made between males 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 the human 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.

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