Folic acid, body mass index and cardiovascular malformations

Dear Editor,

We have read the study titled "Predictors of postnatal complications and congenital heart diseases in babies of mothers who have prenatal diabetes and who develop diabetes during pregnancy" conducted by Demirpençe et al. (1) and published in the edition of 2014 December of the Turkish Archives of Pediatrics with interest. In this research study, a significant subject was emphasized by trying to evaluate postnatal complications, congenital malformations and the variables which might affect presence of cardiovascular anomalies in babies of mothers who had prenatal diabetes and developed diabetes during pregnancy.

However, we thought that there were some important methodological problems, when we examined the study in detail. We found that the authors did not consider some important variables which had previously been shown to be related with cardiovascular malformations in different studies (including folic acid and body mass index) and they did not state this as a limitation of their study.

The effect of use of folic acid in pregnancy in preventing neural tube defects is well known. Current studies have shown that use of folic acid in pregnancy is also effective in preventing cardiovascular anomalies (2). In the study of Demirpençe et al. (1), there is no information about the usage of folic acid in the pregnant subjects included in the study. The fact that use of folic acid was not considered in such a study which evaluated pregnancy outcomes and especially malformations is a significant defect in terms of the method of the study.

In a meta-analysis performed by Stothard et al. (3), it was shown that obesity in the mother significantly increased the risk of occurrence of cardiovascular anomaly in addition to increasing the risk of many congenital anomalies (OR, 1,30; 95% CI, 1,12-1,51). In our country, 30,4% of the women aged 15 years and older are

overweight and 20,9% are obese (4). The study group of Demirpençe et al. (1) consisted of diabetic mothers and the relation between obesity and diabetes is well-known (5). Considering these two points, the fact that the pregnant women were not evaluated in terms of obesity and that this was not included in logistic regression analysis is again a significant defect.

We think that the results of this study may be misleading, because the two variables mentioned above and other variables (for example, smoking) which should have definitely been considered in terms of cardiovascular malformations were not included in the statistical analysis. For example, the result that "use of insulin increased the possibility of congenital heart disease 1.4-5.5-fold" which was obtained by the investigators and which was not discussed sufficiently is in fact a result which predicts that insulin is teratogenic. However, this may be related with underlying diabetes and other factors which were not considered by the investigators and some of which have been mentioned above. Insulin does not cross the placenta and is the first-line treatment during treatment in a candidate mother with diabetes.

In conclusion, confounding factors should be known very well and should be definitely evaluated in such studies in which pregnancy outcomes and especially congenital anomalies are studied. The results which have not been evaluated because of different factors should be stated as study limitations. Keeping the accuracy and preciseness of studies conducted at the highest level possible is very important in terms of developing and pursuing beneficial clinical practices for patients.

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Answer

Dear Editor,

In our study, the records of 337 newborns who were being followed up with a diagnosis of infant of diabetic mother between January 2010 and January 2012 in our Neonatology Unit were examined retrospectively and the demographic data related with the diabetic mother and her baby, the problems of infant of diabetic mother in the postnatal period and the congenital heart diseases found on transthoracic echocardiogram were studied. The variables belonging to the mother including age, mode of delivery (cesarean section, normal spontaneous vaginal delivery), status of single-multiple pregnancy, parity, type of diabetes, duration of diabetes, social security, systemic diseases, adjustment with insulin or diet, if oral antidiabetic was used, history of congenital heart disease in the mother or father, history of amniocentesis, presence of polyhydramnios or oligohydramnios, presence of hypertension during pregnancy, consumption of tobacco, alcohol, substance or any medication were investigated. However, the values belonging to all these data were not shown in Table 1, because significant "p" values were obtained only for maternal age and duration of diabetes among these variables in the Oneway ANOVA and chi-square tests and only the significant ones were included.

In respect of the interpretation of "the conclusion that use of insulin increases the possibility of congenital he-

art disease by 1,4-5,5-fold is in fact a conclusion which predicts that insulin is teratogenic", the association mentioned here is not if insulin crosses the placenta or not in infants of diabetic mothers who receive insulin treatment for regulation of blood glucose. Since the mothers of the infants of diabetic mothers were followed up in different centers in our study, we lacked the data related with HbA1c levels just before pregnancy and in the first three months of pregnancy and we could not make any evaluation in this respect. This was mentioned in the part of "the limitations of our study". It was reported that the risk of congenital heart disease as a risk factor which was not independent was increased in infants of diabetic mothers who were receiving insulin.

In respect to folic acid and body mass indexes of the mothers; a method was tried to be established in the light of the present information, because our study was conducted by retrospectively screening the files of the infants hospitalized in the neonatal intensive care unit and the variables found in the files were noted in detail. It is very natural to find some defects in the establishment of the method in studies in which retrospective file screening is performed. In the part of "limitations" it should be stated that these data are not included in the evaluation because of absence in the file. We thank the relevant authors for their attention and sensitivity in this issue.

Best regards.

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