Nadine Zwink
Dr. sc. hum.

Risk factors for congenital anorectal malformations

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Hermann Brenner

Anorectal malformations (ARM) are rare birth defects concerning anus and rectum with largely unknown causes. Despite improvements in surgical correction of ARM, many patients suffer their whole life from incontinence or constipation. Many of them wear diapers or pads lifelong. A serious limitation of the quality of life of patients with ARM is therefore not uncommon.

The aim of this dissertation was to investigate prenatal exposures of the parents as potential environmental risk factors of ARM.

First, a systematic literature review using EMBASE, ISI Web of Knowledge and the Cochrane Library databases and subsequent meta-analyses were performed to summarize the current state of research with respect to environmental risk factors and parents of ARM infants. In total, 22 articles met the inclusion criteria. However, only few of these studies reported on the same risk factors. Studies were heterogeneous with respect to case numbers, control types and adjustment for covariates. Consistently increased risks were observed for paternal smoking and maternal overweight, obesity and diabetes, but not for maternal smoking and alcohol consumption.

Second, assisted reproductive techniques (ART) as potential risk factor for ARM were investigated in the context of the CURE-Net study. CURE-Net is an ongoing, multicenter study to investigate environmental and genetic risk factors, clinical implications and psychosocial outcome for congenital uro-rectal malformations which was initiated in 2009. Data of affected patients born between 1997 and 2011 were compared with nationwide data of the German IVF register and the Federal Statistical Office (DESTATIS). Results showed a strongly increased risk for ARM among children born after ART. However, the risk of ARM was even higher after IVF than after ICSI. Further, separate analyses of patients with isolated ARM and those with associated anomalies showed strongly increased risks in both groups. A strongly increased risk of ARM was also seen among both singletons and multiple births.

Third, a case-control study was conducted to assess prenatal exposures of the parents to parental smoking, maternal birth weight, maternal intake of multivitamins and folic acid, maternal chronic diseases and parental occupational hazards. Data of affected ARM patients born between 1993 and 2010 were compared with data of healthy children born over the same period, identified and recruited through the Malformation Monitoring Center Saxony-Anhalt. However, analyses indicated a selection bias due to the regional control group. As another suitable nationwide control group was not available, a new control group was recruited with healthy infants all over Germany. In a multicenter case-control study, these prospectively collected data were used for the comparison with data of prospectively collected ARM infants born between January 2009 and January 2012. With more than 150 ARM cases, this study represents the largest multicenter epidemiological study from Germany investigating parental risk factors for ARM. In addition, the extensive data acquisition of more than 600 healthy control infants is unique and offers the opportunity for cooperation projects in the future in which risk factors can be also assessed for other congenital malformations like oesophageal atresia.

Summarizing the results of the multicenter case-control study, strongly increased risks were observed between ARM and maternal chronic respiratory diseases, maternal extreme emotional stress and infections during the first trimenon of pregnancy, maternal periconceptional contact with house colours, maternal periconceptional contact with hair sprays or polishes, maternal and paternal periconceptional increased animal contact and the existence of a single umbilical artery. A weak association was found for maternal periconceptional multivitamin intake and paternal smoking. In addition, an inverse association of ARM was observed with maternal nausea and vomiting during the first trimenon of pregnancy.

The results on ART, maternal periconceptional hair sprays or polishes and house colours suggest an association between ARM and parental hormonal disorders and fertility problems. In addition, the strong association with a single umbilical artery suggests that an under-supply of the child during pregnancy also increases the risk for these rare birth defects. It can be therefore hypothesized that a common background with these factors plays a key role in the development of ARM. Further research should be conducted to elucidate these underlying mechanisms and to identify possible preventive actions for ARM in this context.