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Letters to the Editor

Association between paternal schizophrenia and low birthweight: ADAM12 may matter

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Dear Editor,

I am Dr Hans-Gert Bernstein from the Department of Psychiatry, University of Magdeburg, Germany. Although it is now a well-established fact that mothers with schizophrenia are at higher risk for obstetric complications (preterm births, preeclampsia, low birthweight [LBW] and small-for-gestational-age babies), a putative paternal impact was largely ignored until recently. Now a comprehensive, population-based study in Taiwan, China has revealed that infants whose fathers had schizophrenia were much more likely to have LBW than those whose fathers did not (12.6% *vs.* 8.0%) [1]. Unlike the situation with schizophrenic mothers, in whom inadequate prenatal care was identified as one major cause for obstetric complications [2], it remains to be established how the mental illness of the father may influence the outcome of a pregnancy. Although social factors cannot be ruled out, mainly biological factors are supposed to contribute to the increased risk of LBW of children sired by schizophrenic fathers [1]. The expression of paternal genes might significantly influence placental and fetal growth development [3]. The identity of such paternal factors remained largely unknown, as yet. However, from several points of view, A disintegrin and metalloprotease (ADAM)12, which in many ways may influence the outcome of a pregnancy, emerges as an interesting candidate. ADAM12, which is highly expressed in the placenta, has been proposed to be a regulator of trophoblast fusion, which is a crucial event of major importance for the preservation of a healthy pregnancy. This process takes place throughout pregnancy and is crucial for the maintenance of the syncytiotrophoblast layer, the direct border between maternal blood and fetal tissues [4]. Recent evidence also suggests a prominent involvement of ADAM12 in promoting the uterine decidualization, which is characterized by the proliferation of stromal cells and their differentiation into specialized decidual cells, surrounding the implanting blastocyst [5]. Proper decidualization is another prerequisite for a healthy pregnancy. Further, a truncated form of ADAM12 is released from the trophoblast into maternal blood and regulates by degradation the levels of insulin-like growth factors, which are prominently involved in the control of fetal growth and development [6]. Lastly, ADAM12 is an established sheddase of placental leucine aminopeptidase (oxytocinase) [7], an enzyme critically involved in the induction of labour and hence probably having an important role in preterm births [8]. Support of pathophysiological functions of ADAM12 in obstetric complications comes from observations of reduced maternal blood levels of ADAM12 in cases of small-for-gestational-age fetuses [6] and preeclampsia [9]. Although there is yet no evidence for a paternal imprinting of ADAM12, a considerable paternal influence on the placental expression of this enzyme

must be assumed. The possible link between ADAM12 expression/activity and genetic aspects of paternal schizophrenia is given by the location of the ADAM12 gene on human chromosome 10q26.3. This gene locus has repeatedly been linked to schizophrenia, and there is recent evidence showing that at least one SNP within the human ADAM12 gene is significantly associated with this disease (reviewed in Farkas *et al.* [10]). Moreover, we recently could show that in postmortem brains of male and female patients with schizophrenia the cellular expression of ADAM12 is indeed significantly reduced [10].

Thus, a possible link between paternal schizophrenia and LWB might be existing through reduced ADAM12 expression levels. However, unlike for other obstetric complications, a decreased ADAM12 expression during pregnancy that contributes to LWB has not been shown yet, and is thus a hypothesis worth to be tested in andrological/gynecological practice.

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