Prenatal stress modifies RNA expression of HSD11β-2 and the hypothalamic-pituitary-adrenocortical axis in fetal growth restriction

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Objective

Placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) operates as a functional barrier to protect the fetus from excessive exposure to maternal cortisol. Previous studies have stated that prenatal stress can influence the expression of glucocorticoids related genes in animal models. However, no studies have showing a complete picture of the maternal and fetal compartments, as well as the influence in the expression of the enzyme in the human placenta. The objective was to determine the role of maternal stress in sub-optimal fetal growth and its relation with RNA expression and DNA methylation of the placental 11β-HSD2.

Methods

Nested case-control study in full-term singleton gestations. The Perceived Stress Scale (PSS) and the state-trait anxiety inventory were assessed in mothers of pregnancies with antenatal suspicion of sub-optimal fetal growth that subsequently delivered a small for gestational age (SGA) neonate [birthweight (BW)<10th centile; n=205] and in a control group who delivered normally grown neonates (n=247). In addition, in a subset of patients (n=35 cases and 26 controls), RNA expression levels of placental 11β-HSD2 were analyzed, as well as the extent of DNA methylation (four CpG sites) of the locus.

Results

Maternal perceived stress scale was significantly higher in cases than in controls [Mean: 22 (SD ± 8. 7) vs. 20. 2 (SD ± 8. 5); p=0. 03]. Similarly, maternal state anxiety was significantly higher in mothers that subsequently delivered a SGA neonate compared to controls [1. 8 (1. 5 – 2. 2) vs. 1. 95 (1. 7 – 2. 35); p=0. 0004]. Furthermore, placental 11β-HSD2 RNA expression (α)(Ln) was significantly lower in cases than in controls [0. 41 (0. 29 – 0. 87) vs. 1. 1 (0. 62 – 1. 75); p=0. 003]. No differences were found in the average or mean percentage of placental 11β-HSD2 methylation between cases and controls. However, when groups were subdivided according to the presence of maternal stress, SGA cases with maternal stress (n=12) had a significantly different median level of methylation compared to controls [8. 3 % (7. 6 - 10. 3) vs. 11. 4 % (10. 2 - 13. 1); p=0. 02].

Conclusion

Our findings suggest a significant association between pregnant women´s stress and suboptimal fetal growth, affecting RNA expression and DNA methylation of glucocorticoids-related placental genes.