The effect of hypertensive disorders of pregnancy on the risk of attention-deficit/hyperactivity disorder in the offspring - Long term consequences for mother and child

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Introduction
Attention-deficit/hyperactivity disorder (ADHD) is a frequent neurodevelopmental disorder. Inadequate placentation as a result of hypertensive disorders of pregnancy has been proposed to be a central mechanism of fetal neurodevelopmental comprise. Recently it has been shown that pre-eclampsia increases the risk of ADHD [Mann and McDermott, 2011].

Objectives
We examined the association between hypertensive disorders of pregnancy and ADHD and behavioural difficulties among 7-year old children. We also examined whether circulating factors in serum from women with a HDP alter early patterns of fetal neural growth.

Methods
The study cohort consisted of 13,192 children (weighted = 13,500) who participated in the 7-year old wave of the Millennium Cohort Study (MCS); a representative cohort of British children born in 2000–2001. Hypertensive disorders of pregnancy (raised blood pressure, pre-eclampsia, eclampsia and toxemia) were reported by mothers nine months post-delivery. ADHD was based on a doctor or health care professional diagnosis at age seven. Weighted logistic regression was performed, adjusting for several variables (e.g. depression, age, and poverty status). Sensitivity analyses were performed according to infant sex, parity and pre-pregnancy hypertension. To examine fetal neuronal growth, gestational day (GD) 14 rat cortical neurons were treated with 3% serum from either 5 severe cases of preeclampsia or 5 matched controls for 24h. The complexity of 75 individual neurons (15 neurons × 5 serum samples per group) was analysed using a modified line intercept approach to measure neurite number, total neurite length and branching.

Results
1069 (7.9%) women reported hypertensive disorders of pregnancy and 166 (1.2%) children had an ADHD diagnosis. There was a significant association between HDP and ADHD (adjusted OR = 1.78; [95% CI: 1.03, 3.07]). This association was slightly reduced when women with pre-pregnancy hypertension were excluded (OR = 1.68; [95% CI: 0.96, 2.94]), but not when we excluded women with depression (OR = 2.15; [95% CI: 1.05, 4.43]). Stratifying the analyses by parity and infant sex did not influence these findings. In addition, exposure of GD 14 rat cortical neurons to serum from women with established pre-eclampsia lead to a significant increase in neuronal growth and branching (P < 0.001: n = 75), when compared to those treated with serum from healthy controls.

Conclusions
These findings suggest that hypertensive disorders of pregnancy is associated with an increased risk of ADHD. It is important to confirm this in larger cohorts, and to understand the biological basis of this association and the contribution of in utero adversity to the aetiology of ADHD. We also show that exposure to serum from women with a hypertensive disorder of pregnancy, can alter early patterns of fetal neuronal growth, which in turn may affect early patterns of brain wiring, which has been implicated in ADHD.