From 'obstetric complications' to a maternal–foetal origin hypothesis of mood disorder

VERONICA O'KEANE and JAN SCOTT

The original findings of apparently higher rates of maternal obstetric complications among people with schizophrenia, compared with control populations, suggested that non-genetic intra-uterine events might influence the development of schizophrenia in adulthood. This concept evolved into the neurodevelopmental hypothesis of schizophrenia and led to several new lines of investigation, including developmental epidemiological studies examining childhood risk factors for adult schizophrenia. The obstetric complications literature appears to have expanded conceptually in parallel with the evolving story of the neurodevelopmental hypothesis. A large number of studies examining the importance of antenatal and birth-related insults, with a wide range of designs from retrospective case–control studies to ecological studies, are encompassed in this broad category (Cannon *et al*, 2002). This investigative work has gradually become divorced from the core meaning of the term, i.e. medical complications of pregnancy and labour.

A parallel approach has occurred in the mood disorder literature, where investigations of antenatal risk factors in the aetiology of mood disorders are performed largely using atheoretical models, which may explain why the findings are ostensibly negative. In contrast, there is much evidence from other sources that antenatal events can have profound influences on the subsequent development of mood disorders. This evidence is presented below, together with a hypothesised pathophysiological process.

OBSTETRIC COMPLICATIONS: WHAT ARE WE MEASURING?

Pasaminick *et al* (1956) first introduced the concept of the 'continuum of reproductive casualty' as a possible relevant mechanism in the aetiology of behavioural disorders. Research into mood disorders, as in schizophrenia, has mainly focused on quantifying pregnancy complications (e.g. diabetes, pre-eclampsia or bleeding) or delivery complications (e.g. emergency Caesarean section) in case–control study designs. Although some studies identify an excess of specific events in cases, there is no consistent pattern in their gestational timing or nature. A recent meta-analytic review has found no significant association between 'broadly defined' obstetric complications and later affective disorder (Scott, 2004). The majority of these studies, however, have applied measures of obstetric complications that encompass a wide range of unrelated events and exposures, and have generally viewed such complications as a unitary phenomenon. Clustering of the phenomena into a homogeneous group is difficult to justify intellectually and may also camouflage group differences in more discrete areas. A hypothesis-based approach, based upon a consideration of the physiological processes leading to the obstetric complication, would be more informative.

MATERNAL PSYCHOLOGICAL STRESS AND BIRTH OUTCOME

If one moves from a position of measuring a cluster of obstetric events to one of assessing more global measures of obstetric health and gestational outcome, a different picture emerges. Birth weight is the gold standard measure of pregnancy outcome. Barker's seminal 'Hertfordshire cohort' studies demonstrated a relationship between decreasing birth weight and increasing risk of depression in old age in men (Thompson *et al*, 2001). Furthermore, a study of offspring of parents with bipolar disorder demonstrated that low birth weight was associated with subsequent development of mood disorders, irrespective of genetic loading (Wals *et al*, 2003).

There is an emerging consensus from the obstetric literature that psychosocial stress during pregnancy is associated with low birth weight and preterm delivery (Dole *et al*, 2003). Although depression represents the best-studied model of a chronic stress response, there is no report on the effects of operationally defined depression during pregnancy on baby outcome. However, self-reported depression and probable 'caseness' measured using the Edinburgh Postnatal Depression Scale have been found to predict preterm delivery and small-for-gestational-age babies (Steer *et al*, 1992; Dyan *et al*, 2002).

The association of gestational stress with poor pregnancy outcome is made more pertinent by the relatively new finding that pregnancy-related mood disorder may be both more common and symptomatically more severe than postnatal depression in community populations (Evans *et al*, 2001). A 4-year follow-up of the offspring from the Avon Longitudinal Study of Parents and Children found increased emotional and behavioural problems in the male offspring of women with high anxiety scores during pregnancy (O'Connor *et al*, 2002). This is the first prospective human study linking maternal psychopathology in the antepartum period with that in the offspring. These prospective findings confirm earlier retrospective reports of an association between antenatal maternal stress (e.g. following loss of a spouse, or following exposure to famine or earthquake) and subsequent development of psychopathological disorder in the offspring (see Cannon *et al*, 2002).

MATERNAL–FOETAL ORIGINS HYPOTHESIS

An association between low birth weight and the development of adult medical and metabolic diseases has been repeatedly demonstrated. The foetal origins hypothesis, derived from this association, suggests that exposure of the foetus to an adverse environment *in utero* leads to permanent programming of tissue function and subsequent increased risk of developing adult cardiovascular and metabolic diseases (Barker, 1998). One system implicated in the putative altered programming *in utero* is the hypothalamic–pituitary–adrenal (HPA) axis.

A neurobiological model of prenatal stress is now emerging which proposes that

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maternal stress exerts a negative influence on foetal developmental outcome that is mediated by the HPA system (Wadhwa *et al*, 2002). Central to an understanding of how overdrive of the maternal HPA axis may alter foetal development is the knowledge that maternal–foetal communication during gestation is endocrine rather than neural, and cortisol levels in the foetus correlate with those in the maternal circulation. This has important implications, since high levels of cortisol inhibit intra-uterine growth, may accelerate the onset of parturition indirectly and may alter the regulation of glucocorticoid receptors in the brain of the developing foetus. Hypercortisolaemia has been consistently found in association with major depressive disorder, and is widely attributed to oversecretion of the hypothalamic peptide corticotrophin-releasing hormone (CRH), which in turn has been attributed to reduced negative feedback by glucocorticoids on CRH secretion in the brain (Pariante & Miller, 2001). Intrauterine exposure to high levels of cortisol could permanently increase the 'set point' for HPA axis deactivation in relevant brain areas, resulting in stress responses and behavioural alterations consistent with depressive illness (Thompson *et al*, 2001).

Support for the prenatal stress hypothesis is derived from animal models. The offspring of pregnant rhesus monkeys, exposed to either large amounts of synthetic glucocorticoids or psychological stress, have increased HPA axis stress responses, reduced suppressibility of the HPA axis, increased levels of emotional reactivity, altered immune responses, and reduced hippocampal volume and neurogenesis in the dentate gyrus (Coe *et al*, 2003). These findings are all consistent with those in depression in humans.

There is no empirical evidence at present that the foetal HPA axis is modified by maternal stress, resulting in long-term alterations to the stress response of the offspring. However, some indirect evidence exists that gestational stress results in maternal HPA activation and is associated with poorer baby outcome. Measures of psychosocial stress during pregnancy are correlated with adrenocorticotrophic hormone and cortisol levels (Wadhwa *et al*, 1998), and high CRH levels have been found to predict shorter gestational length (Moawad *et al*, 2002).

In summary, it is increasingly evident that the health status of an infant at birth is both determined by multiple medical, obstetric and psychological events during pregnancy, and is prospectively a determinant of long-term health and quality of life. The literature on obstetric complications in psychiatry has traditionally examined the impact of adverse events during the antepartum period and birth on the subsequent development of schizophrenia. Transposing this methodology in an unmodified way to mood disorders results in largely negative findings, i.e. a lack of a causal association between obstetric complications and adult mood disorders (Scott, 2004). From the perspective of prenatal stress, however, there is a wealth of evidence to support such an aetiological link. Psychological stress in pregnancy is associated with poor birth outcome; population follow-up studies demonstrate that poor birth outcome is associated with mood disorders in adulthood; and there is compelling animal evidence that gestational stress leads to animal analogues of depression in the offspring. The growing evidence that psychological trauma during childhood permanently alters HPA axis responses (Wadhwa *et al*, 1998, 2002) demonstrates the prolonged plasticity and vulnerability of these stress systems in humans and underlies the potential impact that maternal stress may have on foetal brain development. Psychiatry must revisit the notion of obstetric complications and the genesis of mood disorders in the light of these findings. An obvious starting point is maternal mental health during pregnancy – an issue that has been overlooked by clinicians and researchers for too long.

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DECLARATION OF INTEREST

None.

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