Depression during pregnancy: molecular regulations of mothers’ and children’s behaviour

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Abstract
Depression in pregnancy (also called ‘antenatal depression’) is being increasingly recognized as a clinically relevant condition that affects obstetric outcome, maternal behaviour and children’s future mental health. The present review focuses on the molecular mechanisms operating in utero that underlie the potential effects of antenatal depression on mothers’ and children’s behaviour. In particular, I discuss evidence, coming largely from animal and cellular studies, that activation of the main hormonal stress-response system, the HPA (hypothalamic–pituitary–adrenal) axis, in mothers who are depressed during pregnancy may affect maternal care as well as offspring’s behaviour and future psychopathology. The evidence summarized in the present review supports the notion that preventing or treating depression in pregnancy will alleviate not only the suffering of mothers, but also the suffering of the next generation.

Introduction
Although postnatal depression is well known for its social and clinical impact, depression in pregnancy (also called ‘antenatal depression’) remains a taboo in our society. There is therefore a paucity of information on the potential negative impact of this condition, which ranges from adverse obstetric outcomes to an abnormal psychopathological trajectory in the offspring. The present review focuses on the molecular mechanisms operating in utero underlying the potential effects of antenatal depression on mothers’ and children’s behaviour.

Clinical relevance of antenatal depression
As a note of clarification, I use the term ‘antenatal depression’ to indicate clinically significant depression during pregnancy which reaches depression ‘case-status’ as assessed by psychometric measures, not therefore transient changes in mood which may frequently occur as an adjustment to the new condition of being pregnant. Even according to this strict definition, antenatal depression is common: American estimates of the prevalence of major depression during pregnancy show that between 8.3 and 12.7% of women experience this condition [1]. A systematic review of prevalence and incidence of perinatal depression in developed countries estimated the incidence of a new episode of MDD (major depressive disorder) occurring during pregnancy as 7.5% [1]. The same review found fewer studies of period prevalence, but the best estimate of MDD during pregnancy is 12.7% [1]. Prevalence rates as high as 25% are reported in epidemiological studies in developing countries [2]. As the majority of studies have tended to focus on postnatal depression, it is also important to emphasize that 50% of cases of ‘postnatal depression’ begin in the antenatal period, and approximately one-third of the sufferers of antenatal depression continue to be depressed in the postpartum period [3].

In terms of negative impact, there is clear evidence that antenatal depression affects obstetric outcomes and early maternal behaviour: for example, it increases the risk of premature delivery and of not initiating breastfeeding [4]. Moreover, research conducted by us and others has shown that antenatal depression (and stress) have long-term consequences on the offspring’s behaviour in later childhood and adolescence, including increased vulnerability to subsequent stressors, increased psychopathology and increased reactivity of the biological systems involved in the stress response [5–9]. Therefore antenatal depression is a much more clinically relevant problem than ordinarily perceived by the scientific community and the public at large.

But how does antenatal depression affect mothers’ and children’s behaviour, and create a milieu for making the offspring more vulnerable to future life stressors and psychopathology?

Depression and pregnancy act on the same stress-related biological systems
Both the HPA (hypothalamic–pituitary–adrenal) axis and the inflammatory systems are hyperactive in adults who experience depression [10]. My laboratory, and others, have contributed extensively to the understanding of the mechanism underlying HPA axis hyperactivity in depression, and have proposed an explanatory model centred on the
GR (glucocorticoid receptor), which is one of the most important receptors and transcription factors governing the stress response [10–13]. Glucocorticoid hormones, like cortisol in humans and corticosterone in rodents, are the final output of the HPA axis, and the main hormones involved in the stress response. Through binding to the GR [and to the MR (mineralocorticoid receptor)], cortisol exerts its cellular actions, including the negative-feedback regulation of the HPA axis (by which stress-induced activation of the HPA axis is followed by a rapid return to normal functioning), and the restraint of the inflammatory response (which maintains a physiological control on immune processes). The GR is particularly relevant when the levels of glucocorticoids are high, such as during stress or depression. Interestingly, depression, and risk factors for depression such as childhood maltreatment, induce persistent glucocorticoid resistance, i.e. a reduction in GR function, which leads in turn to both the HPA axis hyperactivity and the increased inflammation, because of the lack of the GR-mediated negative feedback on the HPA axis and the GR-mediated restraint of inflammation respectively [10–13]. We have demonstrated that stress and depression reduce GR gene expression and GR function in a variety of cellular and clinical models and that this is accompanied by both increased HPA axis activity and increased inflammation [14–17].

In this context, it is important to highlight that antenatal depression is also associated with glucocorticoid resistance and hyperactivity of the HPA axis and the inflammatory system. Indeed, there is evidence that normal pregnancy is associated with glucocorticoid resistance, as indicated by studies showing impaired GR-mediated negative-feedback regulation of the HPA axis [18], and reduced GR function [19]. Consistent with this, both the HPA axis and the inflammatory system are hyperactive during normal pregnancy. More importantly, there is also specific evidence that GR resistance is more marked in women who experience depressive symptoms or stress during pregnancy, as shown by both a further reduction of GR function [19] and an even higher activity of the HPA axis and the inflammatory system [20,21]. We propose that these biological changes affect both mothers’ and children’s behaviour.

**Molecular mechanisms by which antenatal depression may affect maternal care**

Depression-induced HPA axis hyperactivity in pregnancy may compromises maternal care via OXTR (oxytocin receptor) and ER (oestrogen receptor) gene-expression changes. Animal models have been used to understand how stress during gestation alters maternal care behaviour; in the best-characterized model, the rats ‘licking and grooming’ behaviour, dams receiving restraint stress in pregnancy show increased HPA axis activity, reduced maternal care behaviour and reduced brain gene expression of OXTR. Oxytocin is a neurotransmitter that regulates maternal care by increasing the reward-associated activation of dopaminergic neurotransmission [22]. The HPA axis hyperactivity and the reduced OXTR expression are likely to be related, since administration of the synthetic HPA axis hormone, dexamethasone, has also been shown to decrease oxytocin secretion, brain OXTR and maternal care behaviour [23].

Of note, there is evidence in humans that higher maternal oxytocin levels in pregnancy improve maternal bonding behaviour [24] and protect against the occurrence of postnatal depression [25]. Moreover, reduced OXTR gene expression and DNA hypermethylation have been demonstrated in patients with autism [26], another condition associated with maternal stress in pregnancy; and acute OXTR hypermethylation following psychosocial stress has also been shown [27].

This evidence would suggest a role for cortisol-induced hypermethylation of the OXTR as a molecular mechanism underlying this effect. Of note, however, in pilot bioinformatic work conducted for the present review, using both the most commonly reported GR sequence [28] and a more recently identified GR sequence [29], only limited evidence that the OXTR promoter contains GR-binding sites was found (see Box 1). Therefore indirect mechanisms may also be involved: for example, decreased expression of ERα gene expression has been shown in rats exposed to low maternal care, together with hypermethylation of its promoter, and this may be an upstream inducer of the reduced OXTR expression [22].

Taken together, this evidence indicates a possible molecular pathway by which maternal HPA axis hyperactivity during pregnancy (because of the depression) affects maternal care by changing the expression of cortisol-, oxytocin- and oestrogen-target genes.

**Molecular mechanisms by which antenatal depression may affect child development, behaviour and reactivity to stress**

Clinical studies have shown that depression and anxiety in pregnancy predict emotional and behavioural problems in the offspring, such as attention-deficit hyperactivity disorder and disruptive behaviour disorder [7,30]. This is relevant in the context of the evidence showing that antenatal depression...
Two gene-expression pathways are regulated by both prenatal stress (rat hippocampus) and cortisol in vitro (human hippocampal neuronal precursors) [15].

<table>
<thead>
<tr>
<th>Pathway name</th>
<th>Change</th>
<th>$P$ value (rat hippocampus)</th>
<th>$P$ value (human cells)</th>
<th>Relationship to maternal care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedgehog</td>
<td>↓</td>
<td>0.047</td>
<td>0.0002</td>
<td>Decreased ERα activity may inhibit the Hedgehog pathway [44]</td>
</tr>
<tr>
<td>TGFβ receptor/Smad2/3</td>
<td>↓</td>
<td>0.026</td>
<td>0.001</td>
<td>Decreased TGFβ signalling may reduce OXTR expression [45]</td>
</tr>
</tbody>
</table>

is also associated with an increased risk of the offspring being exposed to subsequent stressors in childhood and adolescence [5,6,31], because children’s difficult behaviour may elicit harsh responses and maltreatment from others [32]. Moreover, studies examining adolescent offspring outcomes have found an association between exposure to antenatal depression or anxiety, and depression and antisocial behaviour in the offspring [8,9,33]. These studies have also demonstrated that the association between exposure to maternal depression/anxiety in utero and offspring psychopathology is independent of the effects of the postnatal environment, thus suggesting that the biological environment in utero induces persistent fetal brain changes [8,9,33]. Interestingly, studies in both humans and other animals have found that stress during pregnancy leads to increased stress response in the offspring, as shown by an increase in both basal and stress-induced HPA axis activity [30,34].

In terms of molecular mechanisms that may be involved in this behavioural changes, in the aforementioned animal model of ‘licking and grooming’, pups of mothers expressing low maternal care also exhibit decreased GR expression, as well as increased DNA methylation of the GR in the promoter region 1F; this is due to the lack of the demethylation that is actively stimulated by appropriate maternal care, and is mediated by increased serotonergic transmission [35,36]. Interestingly, evidence in humans of GR epigenetic regulation by intergenerational stress is now emerging. For example, exposure to childhood maltreatment correlates with increased methylation of the GR in post-mortem brains of suicide victims at the 1F promoter region [37], the region equivalent to 1γ in rodents. Even more relevant, mothers who have suffered from stress or depression in pregnancy have offspring with increased GR1F methylation at birth [38] or during adolescence [39].

My laboratory has recently examined the hippocampal gene expression in adult rats born to dams exposed to stress in pregnancy [15]. These animals show HPA axis hyperactivity together with a molecular signature that includes a number of cortisol-target pathways; indeed, changes in two pathways identified in the rat hippocampus can be mimicked in vitro by incubating a human hippocampal neuronal cell line with stress-relevant concentrations of the HPA axis hormone cortisol [15]. This latter experimental model is a unique clinically relevant model of the human brain in utero, the conditionally immortalized, multipotent, fetal hippocampal neuronal precursor progenitor cell line HPC03A/07.

Differentiated HPC03A/07 neurons co-express the synaptic markers synaptophysin and Homer1, as well as the hippocampal granule cell marker Prox1, and we have recently validated the use of this cell line as a novel in vitro model for investigating molecular mechanisms underlying psychiatric disorders [40–43]. In this specific study [15], we have identified consistent molecular changes following exposure to cortisol in our cellular model and following exposure to stress in utero in rodents, especially in the Hedgehog pathway and in the TGFβ (transforming growth factor β) receptor/Smad2/3 pathways (Table 1). Of note, both these pathways are relevant to maternal care [44,45], thus potentially conferring an intergenerational risk for abnormal maternal behaviour and psychopathology also in the subsequent generations, as indeed we have demonstrated clinically [6].

Conclusions

The evidence summarized in the present review, coming from both clinical and experimental studies, and spanning human, animal and cellular models, indicates an important molecular basis to the clinical and social phenomenon of antenatal depression and of its associated impact on maternal care and psychopathology in the offspring. The evidence supports the notion that preventing or treating depression in pregnancy will alleviate not only the suffering of the mothers, but also the suffering of the next generation. This evidence should therefore inform and inspire new research, with the ultimate aim to deliver biomarkers of risk that will allow us to identify vulnerable mother–offspring dyads, as well as novel therapeutic pathways that will break the intergenerational transmission of psychopathology.

Funding

My work is supported by the Medical Research Council (MRC) and other U.K. governmental agencies (45%), including an MRC grant [grant number MR/J002739/1] on the relationship between inflammation and fatigue, and a Marie Curie Fellowship (to Martin Egeland) modelling early trauma in animals, the National Institute of Health Research and other National Health Service-related funding (35%), including funding from the Biomedical Research Centre in Mental Health at South London and Maudsley NHS Foundation Trust and King’s College London, to investigate correlates of treatment-resistant depression; the Wellcome Trust and other
charities (15%), including a grant from the National Alliance for Research on Schizophrenia and Depression (NARSAD) (to Sarah Osborne) on the relationship between stress and pregnancy (15%); and pharmaceutical companies, including companies interested in developing novel antidepressant strategies (5%).

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Received 15 October 2013
doi:10.1042/BST20130246