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Maternal influences on fetal brain development: The role of nutrition, infection and stress, and the potential for intergenerational consequences

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ABSTRACT

An optimal early life environment is crucial for ensuring ideal neurodevelopmental outcomes. Brain development consists of a finely tuned series of spatially and temporally constrained events, which may be affected by exposure to a sub-optimal intra-uterine environment. Evidence suggests brain development may be particularly vulnerable to factors such as maternal nutrition, infection and stress during pregnancy. In this review, we discuss how maternal factors such as these can affect brain development and outcome in offspring, and we also identify evidence which suggests that the outcome can, in many cases, be stratified by socio-economic status (SES), with individuals in lower brackets typically having a worse outcome. We consider the relevant epidemiological evidence and draw parallels to mechanisms suggested by preclinical work where appropriate. We also discuss possible transgenerational effects of these maternal factors and the potential mechanisms involved. We conclude that modifiable factors such as maternal nutrition, infection and stress are important contributors to atypical brain development and that SES also likely has a key role.

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that the antenatal period is a particularly vulnerable period of development in which exposure to adverse environments, such as malnutrition, infection or stress can have long-lasting or permanent impacts on the health trajectory of the offspring – a process that is termed "developmental programming" [1,2]. Much research has focussed on the role of the early life environment in the programming of cardiometabolic disease, including type 2 diabetes and hypertension [3,4]. However, a growing number of studies have shown that exposure to an adverse early life environment is also associated with long-term consequences for offspring neurodevelopment including effects on the hypothalamic-pituitary-adrenal axis [5] and an increased risk of mental health disorders [6]. The developing brain may be particularly vulnerable to adverse environmental exposures in the antenatal period because of the dramatic developmental trajectory which occurs during this time. Optimal brain development relies upon a highly temporally constrained series of transcriptional and epigenetic states [7,8]; indeed this is underscored by the results from large genetic studies showing that the peak expression of common gene variants involved in the aetiology of several neurodevelopmental disorders occurs during pregnancy [9]. Disruption of these expression networks may mediate some of the risk for atypical neurodevelopment.

An adverse intra-uterine environment can affect fetal neurodevelopment either through direct effects and/or maternal signals, or indirectly as a consequence of preterm birth, which is independently associated with poor neurodevelopmental outcome [10]. In this short review we will focus on maternal-fetal communication in the domains of nutrition, infection and stress, all of which can affect fetal neurodevelopment.

1. Nutrition

Both maternal under- and overnutrition may have consequences for fetal neurodevelopment. The detrimental effects of maternal undernutrition have been characterised in studies of individuals who were exposed to severe undernutrition *in utero* during the Dutch Hunger Winter. In early 1944, the western part of The Netherlands was under German occupation and endured severe food shortages. During this time the population, including pregnant women, had an estimated caloric intake of 400–800 per day for a 5–6 month period [11]. The increased incidence of chronic heart disease and type 2 diabetes in the offspring of these pregnancies is well documented [12]. Although in an early follow-up study, general cognition was not found to be affected in individuals at 19 years of age [13], a subsequent study of individuals at the age of 56–59 years showed that those exposed during early gestation performed more poorly on a selective attention task, which

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associates with accelerated age-related cognitive decline [14]. Although this degree of undernutrition is uncommon, at least in developed nations, fetal exposure to an unbalanced maternal diet, which may associate with deficiencies in specific nutrients, has also been associated with effects on the response to stress in young adulthood [15]. Studies in animal models aimed at delineating the long-term consequences of *in utero* undernutrition have demonstrated adverse effects on neurodevelopment. For example in mice, exposure to a low protein diet during gestation affects neural progenitor populations at several points during embryogenesis in both the cortex and the ganglionic eminence, and in adulthood these mice display deficiencies in short term memory [16].

In 2017 62% of women in England were overweight and of these, 30% were obese [17] – these figures include women of childbearing age. Maternal obesity during pregnancy is associated with increased adiposity and cardiometabolic risk factors in adult offspring [18]. Maternal obesity is also associated with impaired neurodevelopment and executive functioning [19,20] and with adverse neuropsychiatric outcomes in children [20], including Attention Deficit Hyperactivity Disorder (ADHD) [21] and Autism Spectrum Disorder (ASD) [22,23]. Studies in mouse models of maternal obesity suggest that there are adverse effects on brain development and behaviour [24,25] and in non-human primates, exposure to a high fat diet during pregnancy is associated with an increase in offspring anxiety-like and repetitive behaviours [26]. Some of these effects may be mediated by epigenetic alterations, for example in mice, exposure to excess dietary ω-6 polyunsaturated fatty acids (used to model a western high fat diet) has been associated with altered DNA methylation and chromatin architecture in the offspring cortex [27].

Population data from England and Wales in 2014 indicated that 5% of pregnant women had diabetes [28], of which 87.5% had gestational diabetes (GDM). GDM is a condition which arises during pregnancy, typically resolves postnatally and is closely associated with BMI [28,29]. Diabetes during pregnancy is associated with a range of fetal effects across various organ systems, including an increased incidence of neural tube defects [30,31]. In mice, hyperglycaemia during pregnancy is associated with disrupted neurogenesis in the embryo [32] and with apoptosis in epithelial cells within the neural tube [33], and additionally affects social behaviours in adulthood [34].

Some of the effects of maternal obesity on the offspring may be mediated by the associated increase in inflammation. Higher levels of maternal inflammation during pregnancy are associated with an increased risk of neurodevelopmental delay during childhood and mediate the effect of prenatal environmental adversity on child neurodevelopmental delay [35]. Exposure to maternal obesity during the antenatal period may result in the fetus being more susceptible to other insults such as infection or inflammation; for example, in mice, high fat diet-induced diabetes during pregnancy can potentiate the transcriptional response to a subsequent inflammatory stimulus in the fetal brain [36]. This is in line with the multi-hit hypothesis which is commonly cited for schizophrenia but may have relevance to other neurological disorders [37].

2. Infection

Pregnant women are more susceptible to infection and display an increased inflammatory response to some pathogens, but the mechanisms behind this are largely unknown [38,39]. Maternal viral infections during pregnancy may increase the risk of psychiatric disease in the offspring, with the time of infection being particularly important. For instance, a large Danish study found a significant association between maternal hospitalisation for influenza during the first trimester and ASD in her offspring [40]. Maternal exposure to measles [41], rubella [42] and polio [43] have all been associated with an increased risk of schizophrenia in offspring. Other maternal infections (for example untreated genital herpes [44]) may affect neurodevelopment indirectly by increasing the risk for preterm birth, which is independently associated with adverse neurodevelopment [10]. Early reports from the current COVID-19 pandemic have suggested an increased preterm birth rate in pregnant women with confirmed infections, without convincing evidence of vertical transmission [45,46]. This may to some extent reflect medical intervention in infected mothers and any longer term consequences for the offspring of COVID-19 infection in pregnant women remains to be seen. Vertical transmission of a viral pathogen to the fetus can be associated with serious neurodevelopmental consequences: Zika virus and cytomegalovirus infection in the first trimester have been associated with microcephaly [47]. Bacterial infections during pregnancy have also been associated with poor neurodevelopmental outcome in offspring. The Danish study reported a moderate association between bacterial infection during the second trimester and ASD in the offspring [40] and in a large American study, there was a marked increase in psychiatric disorders in the adult offspring of mothers who experienced a bacterial infection during pregnancy [48]. This was dependent on the severity of infection and a higher incidence was seen in males [48].

Inflammation induced by infection can be modelled in a number of ways, notably the use of agonists of the Toll-like receptor (TLR) family. TLR3 and TLR4 are the most commonly studied receptors with respect to maternal infection and are stimulated by the agonists Poly I:C (used to model viral infection) and lipopolysaccharide (LPS, a component of the bacterial cell wall which models bacterial infections) [49]. Studies of non-human primates during pregnancy have provided important insights into the mechanisms by which maternal infection impact on fetal neurodevelopment. In rhesus macaques, the offspring of mothers infected with influenza virus during pregnancy showed decreased white matter volume/density [50], while LPS exposure was associated with an increased white matter volume [51]. Again in rhesus macaques, exposure to the viral mimetic Poly I:C during pregnancy results in an altered inflammatory profile and stereotyped, repetitive behaviours during childhood [52,53]. In rodents, maternal immune activation with Poly I:C results in altered social interaction, communication and repetitive behaviours in adult offspring [54]. One potential mechanism which might mediate this is through maternal cytokine release; in mouse models, maternal interleukin (IL-)6 has been shown to mediate the effects of Poly I:C on fetal neurodevelopment [55]. A separate study indicated the maternal production of IL-17A in response to Poly I:C was involved in the pathogenesis of offspring neurodevelopmental disorders [56]. This leads to a hypothesised model in which maternal IL-6 is stimulated by a viral infection, which in turn activates TH17 cells to produce IL17A, which crosses the placenta to affect offspring neurodevelopment. Models of bacterial infection during pregnancy in rodents have also given important insights into atypical neurodevelopment induced by infection. Prenatal LPS in rodents results in an increase in repetitive behaviours [57], reduced social interaction [58], anxiety like behaviour [59] and spatial memory defects [60] in adult offspring. In rats, prenatal LPS is associated with an altered lipid profile in 8 week old offspring [61] and alterations in dopaminergic signalling [62], which has been hypothesised to be central in the aetiology of schizophrenia [63].

3. Maternal stress

Stress can be broadly described as an imbalance between the environment and an individual's perception of their resources to cope with that environment. Maternal stress can occur as a result of a diverse range of environmental perturbations and crucially, the experience of stress is highly individually specific. Therefore there are many domains of stress which can be associated with pregnancy [64]. While stress during pregnancy affects women worldwide, pregnancy-related stress in lower and middle income countries appears to be associated with a greater risk of adverse outcome in offspring [65].

Offspring exposed to high levels of prenatal maternal stress or

anxiety are at a higher risk of developing depression [66], ASD [67], schizophrenia [68] and ADHD [69] as well as various emotional and behavioural problems [70]; with the timing of stress and the sex of the fetus playing important roles in the outcome of these studies. There is also evidence to suggest that maternal antenatal depression and socioeconomic status can interact with a polygenic score for major depressive disorder to modulate risk [71]. Moreover, good maternal mental health during pregnancy is positively associated with cognitive abilities in the offspring at 2 years of age [72]. There are many factors that need to be accounted for in these studies. For instance some traditional metrics to assess stress may not be validated for use in pregnancy [64]. Further, studies typically focus on periods of increased stress and neglect, but fail to measure positive or uplifting experiences which may counterbalance these [73]. The questionnaires used to measure stress during pregnancy may also be sensitive to underlying personality traits, perhaps underscored by the substantial heritable component of stress as measured by these methods [74]. Moreover, stress experienced during pregnancy tends to continue during postnatal life, making assigning the importance of pre- and postnatal stress in mediating outcomes difficult [75,76]. To address this, some studies have focussed on the effects of short-lasting large-scale environmental perturbations during pregnancy. For example, stress associated with experiencing an earthquake during the first trimester has been associated with a shorter length of gestation [77]. There is also evidence for effects on neurodevelopmental outcome, as offspring born to mothers who were pregnant during the 1998 ice storm crisis in Quebec had lower cognitive and language abilities at 5.5 years of age when compared to control infants from pregnancies out with this period [78].

There are a number of rodent models of maternal stress during pregnancy including exposure to a lactating female, forced swimming, noise and restraint stress [79] and the first rodent experiments describing altered behaviour in the offspring of stressed mothers was published more than 60 years ago [80]. In this study the adult offspring showed increased activity in the open field (a preclinical proxy of anxiety like behaviour), a finding which has been replicated in many subsequent studies (see Weinstock 2017 for a full review [79]). Prenatal stress in rodent models has also been shown to affect other cognitive domains in offspring, such as spatial memory [81,82] and social behaviour [83]. To account for the effects of pre- and postnatal stress, offspring cross-fostering studies have been performed. Cross-fostering the offspring of stressed mothers onto a control non-stressed mother at birth results in no differences in anxiety or social related behaviours in stress-exposed offspring and controls, suggesting that the postnatal environment is important for some effects [84,85], but differences in learning memory, novel object recognition, long-term potentiation and risk of depression remain [86–88].

Many of the effects of maternal stress on the fetus may be attributable to fetal glucocorticoid overexposure [89]. The enzyme 11β-hydroxysteroid dehydrogenase type 2 is present within the placenta and is responsible for converting active glucocorticoids in the maternal circulation (cortisol in humans, corticosterone in rodents) into an inactive form (cortisone or 11-dehydrocorticosterone). However, the enzyme has finite capacity and some active glucocorticoid may cross to the fetus, particularly in the presence of the increased maternal circulating glucocorticoid concentrations which may occur in stressful situations [90]. The administration of synthetic glucocorticoids, which bypass this enzyme, is commonplace in the management of women at risk of preterm birth and significantly improves morbidity and mortality in preterm babies [91]. However, there have been concerns about the deleterious effects of exposure to excess glucocorticoids (endogenous or exogenous) on the developing brain, with clinical studies reporting long-term effects on the function of the hypothalamic-pituitary-adrenal axis and behaviour in exposed children [92–96]. This is supported by data from a number of animal studies (reviewed by McGowan and Matthews [95]). Although evidence from both human and animal studies suggests that excess fetal exposure to glucocorticoids can have adverse consequences on the brain, the effects of pregnancy related stress cannot be entirely attributed to glucocorticoid exposure [97]. Maternal stress in rodents is also associated with an accumulation of catecholamines in the fetal circulation [98], an increase in kynurenic acid in the placenta and fetal brain [99], changes in oxytocin signalling [83], and an altered maternal microbiome and associated *in utero* cytokine levels [100]. Finally, maternal stress may interact with other factors *e.g.* infection to modulate offspring neurodevelopmental outcome. For example concurrent infection and stress during the second trimester result in a higher adolescent depression score in offspring then either alone [101].

4. Transgenerational effects

A growing number of studies suggest that 'programmed' effects might not be limited to the first generation offspring *i.e.* those directly exposed *in utero*, but may be transmitted to a number of subsequent generations. Human epidemiological studies have demonstrated evidence for such 'transgenerational' effects on birth weight and cardiovascular risk [102–105]. Animal studies have confirmed that diverse prenatal insults can indeed influence the health of future generations, including effects on neurodevelopment and behaviour [106,107]. The transmission of programmed effects on neurodevelopment through the maternal line could occur through a number of mechanisms including i) continued exposure to an adverse environment; ii) re-exposure *via* programmed alterations in maternal physiology which impact on the development of the next generation *e.g.* through increased maternal glucocorticoid levels; or iii) changes in maternal behaviour leading to the development of similar behavioural phenotypes in her own children.

Many studies have suggested that the early life environment influences the health of the offspring through induced changes in epigenetic marks and there has been much recent interest in the possibility that the transmission of effects (from both mother and father) could occur through epigenetic effects that are transmitted through the germline. Although there is no universal definition of the term 'epigenetic' [108,109], in the DOHaD field the term has often been used to include DNA methylation, histone modifications and/or non-coding RNA. Many animal and human studies reporting associations between the early life environment and disease risk have reported differences in such epigenetic marks in the offspring [110] although there is, as yet, little evidence that these differences are causative of disease. Although studies suggest that similar alterations occur in the germline epigenome and that these changes may be responsible for the transmission of effects across generations, the data in support of such transgenerational epigenetic inheritance in mammals remain limited [111].

5. Conclusions

Factors such as poor nutrition, stress and infection during pregnancy have all been associated with adverse effects on fetal neurodevelopment. One important consideration is that the long-term risks associated with exposure to an adverse intra-uterine environment are not evenly distributed across society. Low socio-economic status (SES) is associated with an array of adverse pregnancy outcomes even in countries with established antenatal care programs [112,113] which may in part be due to a reduced awareness of service provision [114]. Women of lower SES have an increased likelihood of exposure to risk factors during pregnancy [115] and SES is independently associated with future cognition [115,116]. In higher [117] as well as lower- and middle-income countries [118] lower SES is associated with measures of unhealthy behaviour for example poor nutrition, smoking and low levels of physical activity, including amongst women of reproductive age [119]. Increased levels of infections have been seen in pregnant women with a lower SES. For instance, an increased presence of the infectious bacterium *H. pylori* [120] (which has been linked with

hyperemesis gravidarum [121]) and an increase in urinary tract infections [122]. This is important for public health policy since many of the behaviours associated with lower SES are potentially amenable to change. For example, income supplementation, independent of a changing family dynamic or characteristic can reduce the prevalence of clinically relevant externalising behaviours in a low income population [123]. Increasing the provision of support for families in lower socioeconomic brackets may be one crucial step in mitigating some of the antenatal risk factors associated with atypical brain development. Such interventions also have the potential to improve help in future generations.

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