The effects of prenatal stress, anxiety and depression on the fetus and the child - a global perspective

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MRC EuroStress
The mother’s emotional state in pregnancy can have a long lasting effect on her child.
Depression: the most common major complication of maternity
Anxiety and depression
the scale of the problem

• The single biggest cause of misery in our community is mental illness
• 40% of all disability is due to mental illness

% of population

• Anxiety and depression 8.8
• Generalised anxiety 4.4
• Depression 2.6

LSE report 2006 (Lord Layard)
• Women have as many symptoms of depression and anxiety during pregnancy as postnatally

• Pregnancy can also be a time of increased domestic abuse and relationship strain
Fetal programming

Environment in the womb, during different sensitive periods for specific outcomes, can alter the development of the fetus, with a long lasting effect on the child.
Sensitive early mothering helps attachment, and can counteract some of what happens in the womb.
The Fetal Brain is “Under Construction”

- 3 mm long neural tube – whole brain with 100 billion neurons and 100 trillion connections
- 250,000 neurons/minute – all through gestation
- Proliferation: 5 wks gestation through 18 months after birth
- Migration
- Differentiation
- Synaptogenesis
- Neural pruning: continues till puberty...
Examples of prenatal stress reported to be associated with changes in development and behavior

- Maternal anxiety and depression
- Maternal daily hassles
- Pregnancy specific anxiety
- Partner or family discord
- Experience of acute disasters, e.g. freezing ice storm, hurricane or 9/11

- It’s not just extreme or toxic stress or diagnosed mental illness—but can be dose related
Causes of antenatal maternal anxiety /depression (New ALSPAC study in prep)

• Early childhood trauma-adverse childhood experiences (ACES)

• Maternal history of sexual abuse predicts elevated anxiety/depression from pregnancy to 33months.
PTSD

Simple

Complex
Prenatal stress associated with increased risk of child:

- Anxiety and Depression
- Behavioural problems-ADHD, conduct disorder
- Impaired cognitive development
- Sleep problems in infants
- More difficult infant temperament
- Victimisation in childhood
- Schizophrenia,
- Autism Spectrum
Prenatal stress associated with increased risk of:

- Reduced birthweight and gestational age, increased risk of preterm delivery
- Decreased telomere length
- Altered immune function and increased risk of asthma
- Altered microbiome
Altered microbiome affects gut brain axis, 5-HT, cytokines and mental health
(Microbiome pattern different in Caucasians and non Caucasians)
Mean EPDS score was 9.9 ± 4.5

54.6% of women were at risk of probable depression

Consistent with WHO estimates that perinatal depression is much more prevalent in LMICs

Often about double
Polygyny

- 17% of women in rural areas of Zambia in polygynous marriages

- Women in polygamous relationships were more likely to be moderately-severely depressed than their monogamous counterparts
Global reasons for prenatal stress

• Interpersonal violence can be high in LMIC
  (in Afghanistan 90.2% of women thought that 'wife-beating' was justified)
• War
• Refugees
• Natural disasters
  (e.g. earthquake in Tibet)
Anxiety about maternal or infant mortality
Interactions, especially in LIMC

• Can be interactions with infections e.g HIV

• Dietary deficiencies e.g iodine or iron
Transgenerational effects

- Children of women exposed to stress during pregnancy may be more aggressive themselves and perpetuate problems in society
• Are Associations Causal?
ALSPAC
Avon Longitudinal Study of Parents and Children

• Large prospective birth cohort
  ~14,000 pregnant women
  recruited around Bristol in 1990-1991

95% Caucasian
Multivariate Analysis

Cohort with complete data
\[ n = 7,363 \]

- Maternal Postnatal anxiety and depression
- Paternal pre and postnatal anxiety/depression
- Parenting
- Maternal age
- Birthweight
- Gestational age
- Smoking
- Alcohol
- Psychosocial factors: crowding (SES)
- Maternal education
ALSPAC study

Maternal anxiety—at 18 and 32 weeks of pregnancy
Compared children of 15% most anxious or depressed mothers with the rest

Child behaviour
–maternal report at from 4 to 13 years old.
Strengths and Difficulties questionnaire.
Attention deficit/hyperactivity;
anxiety and depression;
conduct disorder
Total SDQ scores and maternal anxiety at 32 weeks - allowing for BW, GA, maternal age, maternal education, postnatal depression, postnatal anxiety, SES, maternal substance use, parenting, paternal anxiety etc.

Results similar with prenatal depression.
The combined effects of raised anxiety both antenatally (32 weeks) and postnatally (33 months) on child outcome up to 13 years. Similar results with depression.
ALSPAC. Predicted population prevalence of a probable mental health disorder in children born to high (top 15%: open bars) and low prenatal anxiety (full bars) mothers. Based on SDQ scores. Results similar with prenatal depression.

(O’Donnell et al 2014)
• Why are some children affected and not others?

• Why are they affected in different ways?

• Gene-environment interactions?
COMT inactivates catecholamines – dopamine, adrenaline and noradrenaline - gene variants associated with working memory and ADHD
Working memory at age 8

Birthweight, gestational age, maternal education, maternal age, household crowding, maternal smoking, alcohol consumption, postnatal mood and parenting controlled for

(O’Donnell et al 2017)

GG: N=1126
AA: N=1259
AG: N=2310

P<0.01

Maternal anxiety at 32 weeks gestation
Child ADHD (DAWBA) at age 15

COMT rs4680

Maternal anxiety at 32 weeks gestation

GG: N=761
AA: N=857
AG: N=1543

P<0.05
Underlying mechanisms
Maternal stress/anxiety/mental illness

Proinflammatory cytokines

cortisol?

transplacental passage

cortisol

Cortisol

NR3C1

11βHSD2

?
The fetal-placental unit

Shams et al., 1999

Placental 11βHSD2

CORTISONE

CORTISOL

Shams et al., 1999
Spielberger state and trait Anxiety questionnaire

Blood sample

cortisol

Amniotic fluid
cortisol
Correlation between maternal plasma and amniotic fluid cortisol with increasing maternal anxiety

P=0.01

Glover et al 2009
Males: $r = -0.39$, $p = 0.040$, $n = 28$
Females: $r = -0.40$, $p = 0.034$, $n = 28$

significant correlation with State anxiety
trend with depression

O’Donnell et al 2011
11-βHSD2

stressed

Maternal Placenta Fetal

cortisol
cortisone
cortisol
Placental study
Capron, Ramchandani, Glover submitted

• Women(n=81) recruited day before elective caesarean. Filled in self rating psychometric questionnaires EPDS (depression) and Spielberger(anxiety) and Life Events.

• N=48 Caucasian n= 33 Non Caucasian

• (mainly Indian, Pakistani, Bangladeshi)

• Analysed for 11β-HSD2
Interaction between the number of maternal antenatal life events, $11b$-HSD2 and ethnicity

$\beta = -0.385, \ p = 0.020$
Interaction between trait anxiety, GR expression and ethnicity

\[ \beta = 0.249, \ p = 0.030 \]
Genetic variation (SNPs) in GUSTO Cohort in Singapore

Teh et al., 2014 Genome Research
Questions for the future

• Are there ethnic differences in the effects of prenatal stress on the placenta?
• Which ethnic groups differ from Caucasians and how?
• Are there different effects of prenatal stress on the fetus and the child among different ethnic groups?
• Are some more resilient?
Maternal stress/anxiety/mental illness

transplacental passage cortisol

Cortisol

NR3C1

11βHSD2

Cortisol

Cortisol
Spielberger state and trait Anxiety questionnaire
Bayley Scales of Infant Development (BSID-II)

Study child’s cognitive (MDI) development at 17 months
Correlation between amniotic fluid cortisol and cognitive development

\[ r = -0.245 \quad n=125 \quad p=0.006 \]

Bergman et al 2010
Ainsworth's 'Strange Situation' Assessment

1. Parent and child are alone in a room.

2. Child explores the room without parental participation.

3. Stranger enters the room, talks to the parent, and approaches the child.

4. Parent quietly leaves the room.

5. Parent then returns and comforts the child.
Effect of Maternal Attachment on association between AF cortisol and Cognitive Development

Insecure

Secure

Bayley Mental Development Index

Ln AF cortisol

Bergman et al 2010
• Higher in utero exposure to cortisol is associated with lower cognitive function

• Sensitive early mothering can reverse the effects of high in utero exposure to cortisol
Antenatal in utero cortisol and fMRI sustained attention response in children age 6-9 years
n=32 (areas with a significant correlation p<0.01)

Regions where in utero cortisol correlated with non-rewarded attention (positively - A): brainstem, superior temporal gyrus/insula/amygdala, caudate, and cingulate gyrus; and (negatively - B): middle temporal gyrus/hippocampus, middle occipital gyrus, precuneus, and middle frontal gyrus. Z coordinates are provided above each figure.

Sarkar et al (in prepn)
Epigenetic modifications - basis for fetal programming

Epigenetic changes are functionally relevant modifications to the genome that do not involve a change in nucleotide sequence. Can persist to grandchild generation.
Stress during pregnancy may impact subsequent generations, which is demonstrated by an increased susceptibility to childhood and adulthood health problems in the children and grandchildren. Although the importance of the prenatal environment is well reported with regards to future physical and emotional outcomes, little is known about the molecular mechanisms that mediate the long-term consequences of early stress across generations. Recent studies have identified DNA methylation as a possible mediator of the impact of prenatal stress in the offspring. Whether psychosocial stress during pregnancy also affects DNA methylation of the grandchildren is still not known. In the present study we examined the multigenerational hypothesis, that is, grandmaternal exposure to psychosocial stress during pregnancy affecting DNA methylation of the grandchildren. We determined the genome-wide DNA methylation profile in 121 children (65 females and 56 males) and tested for associations with exposure to grandmaternal interpersonal violence during pregnancy. We observed methylation variations of five CpG sites significantly (FDR < 0.05) associated with the grandmother’s report of exposure to violence while pregnant with the mothers of the children. The results revealed differential methylation of genes previously shown to be involved in circulatory system processes (FDR < 0.05). This study provides support for DNA methylation as a biological mechanism involved in the transmission of stress across generations and motivates further investigations to examine prenatal-dependent DNA methylation as a potential biomarker for health problems.
Why?
Predictive adaptive value of changes due to prenatal stress in a stressful environment in the wild?

- Anxiety/fear reactivity - beneficial effects of more vigilance
- ADHD - shifting attention helps if predators about
Other findings explained by evolutionary perspective

Sex differences

– females stay to look after offspring - more anxiety/vigilance
  -- males explore and fight, more conduct disorder, aggression, ADHD

Effects of stress across the range

- dose response effect to respond to the degree of stress in the environment

Children not all affected in the same way

- genetic variation basis for natural selection
• What should be done?
Public health implications of reducing stress/anxiety/depression in pregnancy

• More than one million children in UK suffer from emotional, behavioural, and cognitive developmental problems
• Attributable load of such problems due to prenatal stress ~10 %
• Potential to reduce number of affected children in the UK by 100,000
Feasibility study and pilot randomised trial of an antenatal depression treatment with infant follow-up

Jeannette Milgrom & Charlene Holt & Christopher J. Holt & Jessica Ross & Jennifer Ericksen & Alan W. Gemmill

Treatment was 8 one to one sessions of CBT.


Treating severe depression and anxiety during pregnancy with CBT intervention appears feasible and worthwhile.
Perinatal depression care
(from Gavin, Meltzer-Brody, Glover, and Gaynes 2016)

<table>
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<th>Cases</th>
<th>Recognised Clinically</th>
<th>Any Treatment</th>
<th>Adequate Treatment</th>
<th>Achieved Remission</th>
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<td>Prevalent PND Cases</td>
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<td>40</td>
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Lena

“Emphasis of maternity service was 98% medical physical thing and 2% emotional”

Anne

“They’re more interested in you medically-have you got any lumps and bumps and pain?….They’re not asking how are you feeling at the moment?-are you coping?”

in Zoe Darwin PhD
Role of Professionals

• Detect and treat anxiety and depression both in pregnancy and postnatally
  – Psychological interventions (eg CBT)
  – Pharmacological intervention if needed

• Help with relationship problems or domestic abuse

• Help to create more social support

• Practical help with housing etc

• Help to teach sensitive mothering – video feedback
Ask about ACES at booking

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<tr>
<th>ABUSE</th>
<th>NEGLECT</th>
<th>HOUSEHOLD DYSFUNCTION</th>
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<td>Substance Abuse</td>
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<td>Divorce</td>
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How we can all help support pregnant women

- Fathers
- Employers
- Grandparents
- Friends
- Education in schools
How women can help themselves

- take time for themselves each day to relax
- yoga
- massage
- music
Effect of listening to Jennnie Muskett lullabies or control relaxation on anxiety in pregnant women

(Nwebebe, Glover and Stewart 2017)
www.beginbeforebirth.org