Infant mental health and effects of prenatal stress, anxiety and depression on the developing fetus and the child

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MRC EuroStress
The mother’s emotional state both in pregnancy and in the early postnatal period can have a long lasting effect on her child.
• 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.
From fetus

To child
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...
Long term effects of prenatal stress on neurodevelopment
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
- Distress caused by 6 day war in Israel, 1967
- 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
Prenatal stress associated with Increased child:

- Anxiety and Depression
- Behavioural problems—ADHD, conduct disorder
- Impaired cognitive development
- Sleep problems in infants
- Neonatal behaviour
- More difficult infant temperament
- Victimisation in childhood
- Schizophrenia, Autism?
Prenatal stress in humans associated with increased:

- Reduced birthweight and gestational age
- Mixed handedness
- Altered fingerprint pattern
- Decreased telomere length
- Asthma
- Altered immune function
• Is it causal?
ALSPAC
Avon Longitudinal Study of Parents and Children

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

• Detailed information on children at 4, 7, 11 and 13 years
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

O’Donnell et al 2014
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.
ALSPAC child data

- COMT genotype
- IQ and Working memory at 8 years
- ADHD at 4 (SDQ) and 15 years (DAWBA)
- Controlled for birthweight, gestational age, maternal education, maternal age, household crowding, maternal smoking, alcohol consumption, postnatal mood and parenting
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 submitted)

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

P<0.01

COMT rs4680

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

O’Donnell et al in prep

COMT rs4680

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

P<0.05

Maternal anxiety at 32 weeks gestation
Underlying mechanisms
Maternal stress/anxiety/mental illness

transplacental passage cortisol/5HT

Cortisol

MAO A
11B-HSD2
NR3C1

Cortisol/5HT

NR3C1
The fetoplacental unit

Shams et al., 1999

CORTISONE

CORTISOL
Maternal Trait anxiety

Males $r = -0.39$, $p = 0.040$
Females $r = -0.40$, $p = 0.034$
n = 28

$1/11\beta$-HSD2 ΔCT

O’Donnell et al 2011

significant correlation with State anxiety trend with depression

$r = 0.40$, $p<0.01^{**}$
11-βHSD2

stress

Maternal Placenta Fetal

cortisol
cortisone
cortisone
cortisol
Placental study
Capron, Ramchandani, Glover in prep

- 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
- Placenta collected and dissected within 1 hour. 5 samples pooled.
- Analysed for $11\beta$-HSD2, NR3C1 (GR receptor) and MAO A mRNA expression
Maternal Antenatal Life Events

$^{11}\beta$-HSD2 gene expression

Rs -0.418  p=0.003
MAO-A gene expression

Maternal Antenatal Depression

Rs -0.26 p=0.07
NR3 C1 gene expression

Maternal Antenatal Trait Anxiety

Rs 0.370  p=0.01
Interactions with prenatal maternal mood, placental gene expression and ethnicity

Caucasian/non Caucasian

• NR3C1

• Interaction between Trait Anxiety and ethnicity $\beta=0.249$ $p=0.03$

• $11\beta$-HSD2

• Interaction between Life events and ethnicity $\beta=-0.385$ $p=0.02$

• MAO A

• Interaction between Depression and ethnicity $\beta=-0.385$ $p=0.02$
Maternal stress/anxiety/mental illness

transplacental passage cortisol/5HT

Cortisol

MAO A
11βHSD2
NR3C1

Cortisol/5HT
Spielberger state and trait Anxiety questionnaire

Blood sample

cortisol

Amniotic fluid
cortisol
Bayley Scales of Infant Development (BSID-II)

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

$r = -0.245$  $n=125$  $p=0.006$

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

Bergman et al 2010
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)

Sarkar et al (in prep)
Evolutionary reason for effects of prenatal stress on the child in the wild?

• Anxiety/fear reactivity - beneficial effects of more vigilance
• ADHD - shifting attention helps if predators about
What should be done?
Perinatal depression care
(from Gavin, Meltzer-Brody, Glover, and Gaynes 2015)

- 100% of Cases Recognized Clinically
- 40% have received any treatment
- 24% have received adequate treatment
- 10% have achieved remission
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
£8bn cost of mental illness in maternity

Report shows huge annual toll of inadequate care for new mothers

Peter Walker

Substandard mental health care for pregnant women and new mothers is creating long-term costs of more than £8bn every...
Of these costs
28% relate to the mother
72% relate to the child

Costs vs improvement
The cost to the public sector of perinatal mental health problems is 5 times the cost of improving services.
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
www.beginbeforebirth.org