Antenatal stress and impact on the fetus and the child

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National Institutes of Health
MRC EuroStress

Genesis Research Trust
The mother’s emotional state in pregnancy and in the early postnatal period can have a long lasting effect on her child
Depression: the most common major complication of maternity
DON'T LISTEN TO "OLD WIVES' TALES"
No shock can mark an unborn baby.
No horrible sight can deform him.

BUT
WORRY, FEAR and ANGER
may affect his mother's blood,
which supplies his food.

THEREFORE
she should be CALM, HAPPY
and SWEET-TEMPERED.
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.
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...
Links between maternal anxiety and fetal behaviour and heart rate

- Study shown that if pregnant mothers are asked to do a mental arithmetic and Stroop test, fetal heart rate goes up in the anxious group.

Monk et al
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
Causes of antenatal maternal anxiety /depression

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

• This effect is significantly stronger for women who knew the perpetrator.
Pregnancy specific anxiety

been found to be associated with

• having an unintended pregnancy,
• first birth,
• higher medical risk,
• higher perceived risk of complications
• job stress
  lower income
lower self-esteem
Prenatal stress associated with increased risk in child for:

- 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 associated with increased:

- Reduced birthweight and gestational age
- Mixed handedness
- Altered finger print pattern
- Decreased telomere length
- Asthma
- Altered immune function
- Altered microbiome
Altered microbiome affects gut brain axis, 5-HT, cytokines and mental health (Microbiome pattern different in Caucasians and non-Caucasians)
• Is it causal?
ALSPAC Study. Does antenatal stress affect child behaviour in humans?

• Aim of our study:
  • To determine the long term effects of prenatal depression or anxiety on the behavioural development of the child
  • Allowing for a wide range of confounders

Fetus age 20 weeks (18cm)

ALSPAC
Avon Longitudinal Study of Parents and Children

• Large prospective birth cohort
  ~14,000 pregnant women recruited around Bristol in 1990-1991
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
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
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.
Maternal anxiety at 32 weeks and 8 weeks postnatal and child SDQ (subscale) scores across childhood, after allowing for confounders.
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)
Links are similar with prenatal anxiety at 18 weeks gestation

Links are similar with depression

It is not just first trimester
• For top 15% of most anxious/depressed women in pregnancy, rate of probable mental disorder

• Doubled from about 6 to 12% at age 13 years (after multivariate analysis allowing for a wide range of possible confounders).

• Attributable load of probable mental disorder in whole population due to prenatal anxiety/depression/stress

• ~10%
• 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

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

(O’Donnell et al submitted for publication)

COMT rs4680

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

Maternal anxiety at 32 weeks gestation

O'Donnell et al submitted

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

15yr ADHD (parent 6-band computer prediction, DSM-IV)

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

transplacental passage cortisol

Proinflammatory cytokines

cortisol??

NR3C1

NR3C1

A1BHD2

Cortisol
The fetal-placental unit

Shams et al., 1999

Placental 11β-HSD2

CORTISONE

CORTISOL

Shams et al., 1999
1/11β-HSD2 ΔCT

Maternal Trait anxiety

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

stress

Maternal     Placenta     Fetal

cortisol

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 n=33 Non Caucasian (mainly Indian, Pakistani, Bangladeshi)
- Analysed for 11β-HSD2, NR3C1 (GR receptor) expression
Interaction between the number of maternal antenatal life events, 11β-HSD2 and ethnicity

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

$\beta = .249, \ p = .030$
PCA of **genetic variation** (SNPs) in GUSTO Cohort

Teh et al., 2014 Genome Research
Association of methylation with environment in one genotypic group.

Epigenetic effects depend on genetics too

Association between maternal prenatal depression and methylation pattern in infant cord blood

Ai Ling Teh et al. Genome Res. 2014;24:1064-1074
Maternal stress/anxiety/mental illness

transplacental passage cortisol

Proinflammatory cytokines

cortisol??

Cortisol

NR3C1

A18HSN2
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
• 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)

Sarkar et al (in prepn)
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?
Perinatal depression care
(from Gavin, Meltzer-Brody, Glover, and Gaynes in press)

- Prevalent PND Cases: 100%
- Recognized Clinically: 40
- Any Treatment: 24%
- Adequate Treatment: 10%
- Achieved Remission: 3%
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
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.

Nine-month infant outcomes showed several effects favouring the intervention including problem solving, self-regulation and stress reactivity, independent of maternal postnatal mood.

Treating severe depression and anxiety during pregnancy with a brief cognitive behavioural therapy (CBT) intervention appears feasible and worthwhile.
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