Prenatal stress, anxiety and depression: effects on the fetus and the child across the generations

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The mother’s emotional state in pregnancy and in the early postnatal period can have a long lasting effect on her child.
ORIGINAL ARTICLE

Grandmaternal stress during pregnancy and DNA methylation of the third generation: an epigenome-wide association study

F Serpeloni¹, K Radtke¹,², SG de Assis³, F Henning⁴, D Nätt⁵ and T Elbert¹

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 genomewide 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.

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INTRODUCTION

The impact of early-life adversity likely persists in subsequent generations and may influence the individual’s physiology and behavior. There is considerable evidence that exposure to prenatal grandmaternal pregnancy in the time of the Dutch Hunger Winter (1944–1945) on adiposity in grandchildren.⁹ There is growing support for the role of epigenetic mechanisms, especially DNA methylation, in the persistent effects of prenatal stress exposure.
Grand-maternal smoking in pregnancy and grandchild's autistic traits and diagnosed autism

Jean Golding¹, Genette Ellis¹, Steven Gregory¹, Karen Birmingham¹, Yasmin Iles-Caven¹, Dheeraj Rai² & Marcus Pembrey¹

Although there is considerable research into the genetic background of autism spectrum disorders, environmental factors are likely to contribute to the variation in prevalence over time. Rodent experiments indicate that environmental exposures can have effects on subsequent generations, and human studies indicate that parental prenatal exposures may play a part in developmental variation. Here we use the Avon Longitudinal Study of Parents and Children (ALSPAC) to test the hypothesis that if the mother or father (F1) had been exposed to their own mother's (F0) smoking during pregnancy, the offspring (F2) would be at increased risk of autism. We find an association between maternal grandmother smoking in pregnancy and granddaughters having adverse scores in Social Communication and Repetitive Behaviour measures that are independently predictive of diagnosed autism. In line with this, we show an association with actual diagnosis of autism in her grandchildren. Paternal grandmothers smoking in pregnancy showed no associations.

Autism and Autism Spectrum Disorder are terms given to children less able to interact with the world in the way that other children do. Autism spectrum disorders (ASD) are characterised by social-interaction difficulties, communication challenges and a tendency to engage in repetitive behaviours. Diagnosis is not simple and can depend on the experience and sensitivity of the examiner to the normal range of child behaviours, and the insistence of parents for a diagnosis for their child. In consequence there has been increasing interest in the aetiology of the...
Effects of prenatal stress in guinea pigs (Matthews personal communication)
Sex-specific, male-line transgenerational responses in humans

Marcus E Pembrey*,1,2, Lars Olov Bygren3,6, Gunnar Kaati4, Sören Edvinsson5, Kate Northstone2, Michael Sjöström9, Jean Golding2 and The ALSPAC Study Team2

1Clinical and Molecular Genetics Unit, Institute of Child Health, University College London, England, UK; 2Avon Longitudinal Study of Parents and Children, Bristol University, England, UK; 3Department of Community Medicine and Rehabilitation, Social Medicine, Umeå University, Umeå, Sweden; 4Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; 5Demographic Database, Umeå University, Umeå, Sweden; 6Department of Biosciences, Preventive Nutrition Karolinska Institute, Karolinska, Sweden

Transgenerational effects of maternal nutrition or other environmental ‘exposures’ are well recognised, but the possibility of exposure in the male influencing development and health in the next generation(s) is rarely considered. However, historical associations of longevity with paternal ancestors’ food supply in the slow growth period (SGP) in mid childhood have been reported. Using the Avon Longitudinal Study of Parents and Children (ALSPAC), we identified 166 fathers who reported starting smoking before age 11 years and compared the growth of their offspring with those with a later paternal onset of smoking, after correcting for confounders. We analysed food supply effects on offspring and grandchild mortality risk ratios (RR) using 303 probands and their 1818 parents and grandparents from the 1890, 1905 and 1920 Överkalix cohorts, northern Sweden. After appropriate adjustment, early paternal smoking is associated with greater body mass index (BMI) at 9 years in sons, but not daughters. Sex-specific effects were also shown in the Överkalix data; paternal grandfather’s food supply was only linked to the mortality RR of grandsons, while paternal grandmother’s food supply was only associated with the granddaughters’ mortality RR. These transgenerational effects were observed with smoking in the SGP (BMI at ages 9 years, age at menarche, and height in adulthood) but not in girls.
Sex differences in effects of prenatal stress on offspring

- Females more anxious
- Males more aggressive and more cognitive deficits
- Sex differences being found in human infants
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...
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, interpersonal violence
- 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
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
Causes of antenatal maternal anxiety /depression

( New ALSPAC study in prepn )

• Early childhood trauma-adverse childhood experiences (ACES)

• 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.
- Interpersonal violence
- War
- Refugees/migrants
- Natural disasters (e.g. earthquake in Tibet)
Prenatal stress associated with increased:

- 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
• 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
Multivariate Analysis

Cohort with complete data

$n = 7,363$

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

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>4</th>
<th>7</th>
<th>9</th>
<th>11.5</th>
<th>13</th>
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<tbody>
<tr>
<td>Population prevalence %</td>
<td>13.5</td>
<td>7.5</td>
<td>9.5</td>
<td>11.5</td>
<td>13.0</td>
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(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

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

Maternal anxiety at 32 weeks gestation

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

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

COMT rs4680

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

cortisol

cortisol?

Proinflammatory cytokines

transplacental passage cortisol

11βHSD2
NR3C1

Cortisol
The fetal-placental unit

Placental 11β-HSD2

CORTISONE

CORTISOL

Shams et al., 1999
$1/11\beta$-HSD2 $\Delta$CT

Maternal Trait anxiety

Males $r = -0.39$  
$p = 0.040$  
n = 28

Females $r = -0.40$  
$p = 0.034$  
n = 28

O’Donnell et al 2011

significant correlation with State anxiety  
trend with depression
11-βHSD2

stress

Maternal  Placenta  Fetal

cortisol  cortisol

cortisone
New 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, NR3C1 (GR receptor) expression
Interaction between the number of maternal antenatal life events, 11b-HSD2 and ethnicity

\[ \beta = -0.385, \ p = 0.020 \]
PCA of **genetic variation** (SNPs) in GUSTO Cohort

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?
Maternal stress/anxiety/mental illness

transplacental passage cortisol

Proinflammatory cytokines

cortisol?
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
Effect of Maternal Attachment on association between AF cortisol and Cognitive Development

Insecure
Secure

Bayley Mental Development Index vs. Ln AF cortisol

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 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.
What should be done?
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

<table>
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<tr>
<th>ABUSE</th>
<th>NEGLECT</th>
<th>HOUSEHOLD DYSFUNCTION</th>
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<tbody>
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<td>Physical</td>
<td>Physical</td>
<td>Mental Illness</td>
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<td>Emotional</td>
<td>Mother treated violently</td>
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<td>Divorce</td>
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<td>Incarcerated Relative</td>
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<td>Substance Abuse</td>
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Feasibility study and pilot randomised trial of an antenatal depression treatment with infant follow-up

Abstract

Substantial evidence links antenatal depression, anxiety and stress with negative effects on foetal development, resulting in enduring problems in child development. Despite this, there is a paucity of research on intervention programmes designed to address depression and
Prenatal anxiety, maternal stroking in infancy, and symptoms of emotional and behavioral disorders at 3.5 years

Andrew Pickles1 · Helen Sharp2 · Jennifer Hellier1 · Jonathan Hill3

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Abstract Animal findings of long-term effects of maternal behaviors mediated via altered GR gene expression will, if translated into humans, have far reaching implications for our understanding of child and adolescent psychopathology. We have previously shown that mothers’ self-reported stroking of their infants modifies associations between prenatal depression and anxiety and child outcomes at 29 weeks and 2.5 years. Here, we examine whether the effect of early maternal stroking is evident at 3.5 years, and in a much larger sample than in previous publications. A general population sample of 1233 first-time mothers completed anxiety measures at 20 weeks gestation, 865 reported on infant stroking at 9 weeks, and 813 on child symptoms at 3.5 years. Maternal stroking moderated the effect of prenatal anxiety on child symptoms, and also modified the relationship between maternal depression and child symptoms. These findings have implications for interventions to reduce child emotional and behavioral problems, including the potential for stroking, modifying associations between prenatal anxiety and child emotional and behavioral symptoms.

Keywords Fetal programming · Prenatal anxiety · Tactile stimulation · Epigenetics · Emotional · Behavioral disorders

Introduction

In animal models, prenatal stress causes long lasting ‘fetal programming’ increases in anxiety and depression type behaviors and hypothalamo-pituitary axis (HPA) reactivity, mediated via decreased hippocampal glucocorticoid receptors (GluRs) and increased glucocorticoid receptor expression (GR). Maternal behaviors can also influence child outcomes, with maternal care behaviors associated with lower anxiety in offspring [1, 2]. This is reflected in animal studies, where maternal care modifies the HPA response to stress [3]. In humans, maternal care behaviors were associated with fetal cortisol levels [4]. Early maternal care behaviors also appeared to modulate the effects of prenatal stress on offspring anxiety and depression, with mothers who stroked their newborn infants at 9 weeks post-partum having children who were less anxious and depressed compared to those who did not stroke their infants [5]. This finding has implications for interventions to reduce child emotional and behavioral problems, including the potential for stroking, modifying associations between prenatal anxiety and child emotional and behavioral symptoms.
Effect of listening to Jennnie Muskett lullabies or control relaxation on anxiety in pregnant women

Spielberger Trait

Trait anxiety

Time

Baseline, Week 4, Week 8, Week 12

P<0.01

N=20

N=16

lullaby

relax
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