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Review

Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review

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Abstract

A direct link between antenatal maternal mood and fetal behaviour, as observed by ultrasound from 27 to 28 weeks of gestation onwards, is well established. Moreover, 14 independent prospective studies have shown a link between antenatal maternal anxiety/stress and cognitive, behavioural, and emotional problems in the child. This link generally persisted after controlling for post-natal maternal mood and other relevant confounders in the pre- and post-natal periods. Although some inconsistencies remain, the results in general support a fetal programming hypothesis. Several gestational ages have been reported to be vulnerable to the long-term effects of antenatal anxiety/stress and different mechanisms are likely to operate at different stages. Possible underlying mechanisms are just starting to be explored. Cortisol appears to cross the placenta and thus may affect the fetus and disturb ongoing developmental processes. The development of the HPA-axis, limbic system, and the prefrontal cortex are likely to be affected by antenatal maternal stress and anxiety. The magnitude of the long-term effects of antenatal maternal anxiety/stress on the child is substantial. Programs to reduce maternal stress in pregnancy are therefore warranted.

Keywords: Pregnancy; Stress; Programming; Cortisol; Fetal behaviour; Child behaviour; Developmental neuroscience; Review

Contents

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1. Introduction

> 'And surely we are all out of the computation of our age, and every man is some months elder than he bethinks him; for we live, move, have a being, and are subject to the actions of the elements, and the malices of diseases, in that other World, the truest Microcosm, the Womb of our Mother'(Sir Thomas Browne, Religio Medici, 1642) [1]

The question of the importance of prenatal environmental factors for development, behaviour and health, has been scientifically studied from the 1940s onwards in humans [1–4] and even earlier, from the 19th century onwards, in experimental embryology (see [5,6]). The fetal programming hypothesis states that the environment in utero can alter the development of the fetus during particular sensitive periods, with a permanent effect on the phenotype. In recent years, the work of Barker has given a great impetus to research in this particular field. He proposed "the fetal origins of adult disease hypothesis". This states that the physiological, neuroendocrine or metabolic adaptations that enable the fetus to adapt to changes in the early life environment result in a permanent programming (or reprogramming) of the developmental pattern of proliferation and differentiation events within key tissues and organ systems and can have pathological consequences in later life [7,8]. The key observation on which this was based was that weight at birth was a strong risk factor for coronary heart disease, diabetes mellitus, and obesity later in life. This finding has been reproduced in many independent studies, although it appears to be the ponderal index rather than birth weight that matters (for reviews see [9] for coronary heart disease; [10] for obesity). Most of the work on the possible mechanisms underlying these findings have focused on nutrition, although there is also evidence that the hypothalamic–pituitary–adrenal (HPA)-axis may be involved [8,11]. In parallel with this work in humans there has been a strong body of animal research linking prenatal stress and both HPA-axis dysfunction and the underlying neurotransmitter systems, and disturbed behaviour in animal offspring [12–15]. A consistent finding in the non-human primate work is that stressing the mother during pregnancy has a long-term adverse effect on attention span, neuromotor behaviour, and adaptiveness in novel and stress-inducing situations (e.g. enhanced anxiety) of the offspring [14,16].

Human studies on the long-term effects of prenatal stress are difficult. In 1893, Dr Alfred W. Wallace (cited in [1]) wrote to Nature: 'Changes in mode of life and in intellectual occupation are so frequent among all classes, that materials must exist for determining whether such changes during the prenatal period have any influence on the character of the offspring' ([1] p. 3). Joffe [1] concluded that, in human studies, obtaining sufficient control of genetic and post-natal environmental factors had been the major difficulty to enable the post-natal behavioural differences under investigation to be attributed conclusively to prenatal variables. However, he concluded that even if uncertainty about etiological relationships exists, human studies provide sufficient evidence to enable preventive action to be initiated with regard to a variety of childhood disorders, without waiting for the methodological issues to be unraveled… 'though the action may be more effective when they are' ([1] p. 308).

In humans, studies during the last two decades have provided continuing and mounting evidence that negative maternal emotions during pregnancy are associated with an adverse pregnancy outcome. The association between high antenatal anxiety/stress and preterm delivery and low birth weight for gestational age are the most replicated findings and have been discussed fully elsewhere (for recent reviews see [15,17–20]). A meta-analysis of 29 studies on work-related stress and adverse pregnancy outcome showed that occupational exposures significantly associated with preterm birth included physically demanding work, prolonged standing, shift and night work, and a high cumulative work fatigue score. Physically demanding work was also related to pregnancy-induced hypertension and preeclampsia [21]. Pregnancy-induced hypertension was shown to be related to

Trait Anxiety score (and maternal ponderal index) during the 7th month of pregnancy [22]. Hypertension and preeclampsia in turn, increase the rate of preterm delivery and small-for-gestational-age infants [23]. Hansen et al. [24] have shown that severe life events during pregnancy increased the frequency of cranial–neural-crest malformations in the child. Unexpected death of a child during the first trimester was associated with adjusted odds ratios of 8.4 (2.4–29.0) for cranial–neural-crest malformations and 3.6 (1.3–10.3) for other malformations.

In this paper, we review studies of the past two decades, concurrently or prospectively studying the link between antenatal maternal anxiety/stress on the one hand, and fetal behaviour and later development of the child on the other hand. Evidence for underlying physiological mechanisms in humans and possible effects of stress hormones on prenatal brain development are also reviewed. More specifically, the question is raised whether maternal anxiety, apart from affecting the HPA-axis and limbic system [17], may also affect the development of the prefrontal cortex, which is presumed to underlie behavioural alterations seen in children of mothers who were highly anxious/stressed during pregnancy. Finally, we formulate some suggestions for strengthening further research.

2. Antenatal maternal stress and anxiety and the human fetus

Reports from the pre-ultrasound era, both anecdotal and semi-scientific (i.e. non-controlled), have suggested that prenatal maternal stress, anxiety, and emotions affect fetal functioning, as evidenced by increased fetal heart rate (FHR) and motility [25]. Ultrasound techniques, enabling FHR monitoring and direct fetal behaviour observation for prolonged periods of time, have for two decades been used in longitudinal and cross-sectional studies of the effects of antenatal maternal anxiety and stress. Both observational and stress/emotion-induced study designs have been employed and the results will be reviewed here. The results can only be understood in the context of some background information on normal fetal neurobehavioural development [26–28].

2.1. Normal development of human fetal behaviour

A number of distinct fetal movement patterns has been distinguished, emerging at a well described time point during the first 15 weeks of gestation (post-menstrual age), including body movements, breathing movements, hiccups, and arm, leg, head, and mouth movements [26]. As pregnancy progresses, rest–activity cycles become increasingly linked to specific fetal heart rate patterns and to absence and presence of rapid eye movements (REM), respectively. These cycles finally develop into ultradian fetal behavioural states (sleep–wake cycles), which characterize stable temporal organisation near term [26,28]. Four distinct fetal states can be identified based on specific associations between the three variables mentioned (see legend to Table 1 for descriptions). Although some level of temporal organization is already present at 28–30 weeks, behavioural state organization progressively develops between 30 and 40 weeks, both in utero and in low-risk preterm born infants [26,29]. This developmental pattern, which parallels particular aspects of brain development, is characterized by a gradual increase in quiet sleep and awake states, and a profound decrease in indeterminate state, a gradual decrease over time in body movements and basal FHR, and an increase in FHR variability and fetal movement-FHR coupling (i.e. FHR accelerations associated with body movements) [26–31]. Besides macro-analysis of behavioural state organization, i.e. calculation of the % of time spent in each state, basal FHR, its variability, and the % incidence of body movements during episodes of states 1F and 2F (see Table 1) are often calculated (micro-analysis) to identify state-specific characteristics.

Table 1
Criteria to define episodes of each of four fetal behavioural states

	Behavioural state			
	1F	2F	3F	4F
Heart rate pattern (HRP)[26,29][a]	A	B	C	D
Body movements	Incidental	Periodic	Absent	Present
Eye movements	Absent	Present	Present	Present

States 1F and 2F are also called quiet sleep and active sleep, respectively; states 3F and 4F, quiet wakefulness and active wakefulness, respectively [28].

[a] HRP A is a stable heart rate with a narrow oscillation bandwidth; HRP B has a wider oscillation bandwidth with frequent accelerations during movements; HRP C is stable (no accelerations), but with a wider oscillation bandwidth than HRP A; HRP D is unstable, with large, long-lasting accelerations that are frequently fused into sustained tachycardia. If none of these combinations are met this is called no-coincidence (NoC) or indeterminate state.

Fetal behavioural states can be regarded as precursors of the adult sleep–wake states. Fetal and adult sleep states not only share comparable features of non-REM/REM, cardiovascular, respiratory, and (probably) metabolic control, but also share the neuronal substrate, neurotransmitters, and receptors that are believed to underlie sleep control from early in fetal life onward [32,33].

Recent studies on adult animals and humans have elucidated that the cyclic alternation between non-REM/REM states and wakefulness is a highly regulated process [33].

Several neuronal networks involving distinct mesopontine and hypothalamic brain areas and a variety of excitatory and inhibitory neurotransmitters, -modulators, and -peptides have been found to form an intricate web of interactions underlying sleep–wake control (for detailed reviews see [33–35]). Each behavioural state is now believed to result

from a specific balance between activities of wake-promoting and sleep-promoting neurons and the activities of many neurotransmitter systems (cholinergic, noradrenergic, serotonergic, GABA-ergic).

Processes during sleep have been found to be intimately related to memory and cognition in adult awake state [34]. Disturbed sleep–wake organization is a characteristic of neurological and psychopathological diseases (e.g. ADHD, autism, depression, schizophrenia). At least for some of these, exposure to prenatal maternal stress has been suggested as a causative factor. The sleep and stress control systems share particular brain loci, such as the locus coeruleus and forebrain centres. This brings us to the question of whether there are observable, objective effects of gestational stress on the developing human fetus. If so, which features of fetal behavioural development and organization are being affected, when do they emerge in relation to the timing of the stressor, are there differential effects on the fetus between different types of maternal stress, and which mechanisms may be involved?

2.2. Antenatal maternal stress and anxiety and fetal behaviour on ultrasound observation

An overview of the results obtained in 12 observational studies on the relationship between prenatal maternal psychological states and fetal behavioural development is presented in Table 2. All studies involved uncomplicated pregnancies, and healthy pregnant women (mainly nulliparous) and their newborns. The studies were also uniform regarding the demographic background of the participants, the majority being Caucasian, well-educated, and of middle SES-class. Maternal age, the number of participants, and fetal recording length on the other hand, varied largely among the studies. Most studies controlled for the possible effect of circadian rhythms and meals, and some also adjusted for potential confounders, including maternal age, SES, smoking, and alcohol intake. The levels of maternal anxiety and stress were assessed by using self-administered questionnaires, which are either widely used and validated or developed by the authors. The Spielberger State Trait Anxiety Inventory (STAI [36]) was used most frequently among the studies. It differentiates between current feelings of tension and apprehension (state anxiety) and an individual's relatively stable anxiety-proneness (trait anxiety). Some studies used measures of general stress, involving either stress-provoking (daily hassles, life events) or stress-resulting aspects (stress appraisal, perceived stress). Pregnancy-specific anxiety and affect were included in two studies (nos. 7, 8; Table 2). Similar definitions of fetal movement patterns and behavioural organization (when appropriate) were used across the studies, and fetal movements were observed and registered by a researcher, except for the studies by DiPietro et al. (nos. 5–8). These authors used an ultrasound device for automated detection of fetal motility (actograph) and analysed the 50-min records for total observation time only. Other groups provided results of macro- and/or micro-analyses for recordings that lasted at least 2 h.

Three studies that have evaluated the immediate relationship between maternal anxiety/stress and fetal behaviour in the first half of pregnancy found no observable effect on spontaneous motor activity (nos. 10–12). Four out of the five independent studies with a comparable study design (nos. 2–4, 9, 11) have reported evidence of increased arousal in near-term fetuses of high stress/anxious women, as reflected by an increase in fetal wakefulness, increased FHR variability and % of body movements during active (REM) sleep and state 4F, and a decrease in the amount of quiet (non-REM) sleep. The results of DiPietro et al. can be generally viewed to be in accordance with these findings, although no information is provided as to which fetal functional aspect was specifically involved. In two studies (nos. 7, 8) they showed overall increased % of body movements and FHR variability and accelerations (at 36 weeks in particular) in fetuses whose mothers reported higher levels of perceived stress and emotions, more pregnancy-related hassles, and a negative valence toward pregnancy. Results from earlier reports (nos. 5, 6), i.e. reduced FHR variability and poorer movement-FHR coupling in fetuses of women with high perceived stress, seem to be different from the later findings of this group. Of particular interest are the observations that fetuses of women with a positive vs. negative attitude toward pregnancy exhibit different overall levels of motor activity (reduced versus increased, respectively). As positive (pleasant) emotions and negative stressors are believed to have similar physiological effects (on the fetus), their observations deserve to be replicated in other studies.

The findings for maternal anxiety/stress on fetal performance are in line with the well-known report on hyperkinetic fetuses of acutely stressed women during an earthquake (no. 1), but are opposite to those described by Groome et al. for unknown reasons (no. 4). Their sample consisted for nearly 50% of black women, and fetuses of black women have been described to spend more time in quiet sleep than white fetuses [47]. As these data were not analysed by race, it remains unclear whether this confounder was a factor of importance with respect to the mentioned discrepancy in findings.

One study has reported that stress experienced in early pregnancy had an observable effect on fetal behaviour as early as at 28 weeks (no. 11). Only a few studies have focused explicitly upon the timing of gestational stress (nos. 3, 11). They have suggested that maternal anxiety/stress experienced during early pregnancy, but also during later stages of pregnancy, are associated with the above-mentioned fetal effects near term. The latter results suggest that maternal anxiety/stress-related mechanisms might affect the fetal nervous system during the first two trimesters of pregnancy. However, possible alterations have only been

Table 2
Ultrasound studies of the effect of prenatal maternal stress and anxiety on fetal behaviour

#	First author	Subjects	Stress measure	Fetal assessment	Analysis	Main results
1	Ianniruberto 1981 [37]	$n=28$ Age:–	Qualitative description: "panic stricken" women during earthquake	FM: observer FHR:– GA: 18–36 wk RL:–	Qualitative	Fetal hyperkinesia for 2–8 h, followed by a 24–72 h period of reduced motility
2	Van den Bergh 1989 [38]	$n=10$ Nulliparous: 70% Age: 26 (19–31) yr	STAI Administered on day of recording	FM: observer FHR: + GA: 36–40 wk RL: 120 min	Total rec. time; HRPs/states; Micro	Positive correlation between state anxiety and %FM (during total rec. time and during S2F-4F); No effect of induced maternal emotions
3	Van den Bergh 1990, 1992 [25,39]	$n=30$ Nulliparous: 100% Age: 24 (20–28) yr	STAI State scale administered on day of recording; State and Trait scales at 12–22 wk (T1) 23–31 (T2) and 32–40 wk (T3)	FM: observer FHR: + GA: 36–38 wk RL: 120 min	Total rec. time; HRPs/states; Micro	Negative correlation between state anx. (T3) and trait anx. (T1,T2,T3) and %S1F; Positive correlation between state anx. and %S4F and %FM (during total rec. time and during states 2F-4F)
4	Groome1995 [40]	$n=18$ Nulliparous:– Age:–	STAI Administered 3 days before fetal recording	FM: observer FHR: + GA: 38–40 wk RL: 240 min	HRPs/states; Micro	Positive correlation between state and trait anx. and %S1F; Negative correlation between state and trait anx. and %FM during state 2F
5	DiPietro1996 [31]	$n=31$ Nulliparous: 65% age: 29 (22–36) yr	Daily hassles (general) and uplifts expressed as one score (ratio) of perceived stress/stress appraisal; information over past 24 h	FM: actograph FHR: mean FHR and variability (SD) GA: 20–40 wk, 6 times at 4–wk interval RL: 50 min/session	Total rec. time	Greater perceived stress was associated with reduced FHR variability; No reported effects on %FM and % state concordance
6	DiPietro 1996 [30]	$n=31$ Nulliparous: 65% Age: 29 (22–36) yr	Daily hassles (general) and uplifts expressed as one score (ratio) of perceived stress/stress appraisal; information over past 24 h	FM: actograph FHR: baseline FHR FHR-FM coupling GA: 20–40 wk, 6 times at 4–wk interval RL: 50 min/session	Total rec. time	Higher reported stress was associated with less FHR-FM coupling
7	DiPietro 1999 [41]	$n=103$ Nulliparous:– age:–	(1) intensity of experienced emotions (trait index) (2) daily (general) stressors (perceived stress) (3) pregnancy-specific daily hassles and uplifts (frequency, intensity, ratio hassles to uplifts) (4) composite Z-score	FM: actograph FHR: # accelerations GA: 24, 30, 36 wk RL: 50 min/session	Total rec. time	Increased %FM and tendency toward more FHR accelerations in women who were more hassled or negative about their pregnancy (higher intensity of hassles relative to uplifts) and who reported more daily stressors;decreased %FM in women with high emotional intensity, but only for women in low-SES class

(*continued on next page*)

Table 2 (*continued*)

#	First author	Subjects	Stress measure	Fetal assessment	Analysis	Main results
8	DiPietro 2002 [42]	$n=52$ Nulliparous: 63% Age: 30 (21–39) yr	(1) intensity of experienced emotions (trait index) (2) daily (general) stressors (perceived stress) (3) pregnancy-specific daily hassles and uplifts (frequency, intensity, ratio hassles to uplifts) (4) composite Z-score	FM: actograph FHR: mean FHR and variability (SD) GA: 24, 30, 36 wk RL: 50 min/session	Total rec. time	Decreased FHR at 36 wk in women who showed high emotional intensity; Increased FHR variability at 36 wk in women who had higher frequency of pregnancy-specific hassles; Increased %FM in women who reported greater emotional intensity, appraised their daily lives as more stressful, and who had more pregnancy-specific hassles and a more negative valence toward pregnancy; Decreased %FM in women who perceived their pregnancy to be more intensely and frequently uplifting and who had a positive emotional valence toward pregnancy
9	Sjöström 2002 [43]	$n=41$ Nulliparous: 100% Age: 26 (SD 4) yr	STAI Administered about 2 wk before fetal recording; the state anx. scale was considered to reflect perceived anxiety between 25 and 36 wk	FM: observer FHR: basal FHR and variability (estimated from paper chart) GA: 37–40 wk RL: 120 min	HRPs/states; Micro; Median split analysis	High anxiety group: tendency toward more %HRP-C (state anx.) and %HRP-D (state and trait anx.); tendency toward lower FHR variability in episodes of HRPs A and B (state anx.); lower FHR in HRP-C and increased FHR variability in HRP-D (state and trait anx.); positive correlation between state/trait anx. and %HRP-D; No effect of anxiety on %FM in each of the distinct fetal states
10	Bartha 2003 [44]	$n=20$ Nulliparous:– age:–	STAI Administered on day of recording	FM: observer FHR:– GA: 15 wk RL: 40 min	Total rec. time	No significant relationships between state or trait anxiety and %FM or other fetal movement patterns
11	Mulder 2003 [45]	$n=123$ Nulliparous: 100% Age: 31 (17–45) yr	STAI: state anx. scale before fetal recording;Life events (LE) and daily hassles (DH): frequencies reported over past 3 m; Administered at 15–17wk (T1), 27–28 wk (T2), and 37–39 wk (T3)	FM: observer (T1–T3) FHR: basal FHR and FHR variab. (T2, T3) GA: 15–17 wk, 27–28 wk, 37–39 wk RL: 60 min (T1, T2) and 120 min (T3)	Total rec. time; HRPs/states; Micro; Analysis: high-low contrasts (scores $>$P75 vs $<$ P25) and correlational	High numbers of LE and DH reported at T1 were not related to %FM at T1, but were sign. associated with increased %FM and FHR variability during episodes of HRP-B (S2F) at both T2 and T3, and, at T3, with an increase in %HRP-D (%S4F), a decrease in %HRP-A (%S1F) and a decrease in %NoC; Fetuses of high-stress women exhibited better state organization; No sign. effects of state/trait anxiety at T1–T3 on the near-term fetus
12	Niederhofer 2004 [46]	$n=227$ Low-risk population Age:–	Self-constructed questionnaire administered just before fetal observation	FM: arm, leg, head movements GA: 16–20 wk RL: 5 min (?)	Total rec. time	No relationship between maternal stress scores and the numbers of fetal arm, leg, and head movements

–information not provided or not applicable (e.g. FHR at early gestation, $<$24 wk); %FM: incidence of fetal (gross) body movements, expressed as % of time; FHR: fetal heart rate; HRP: fetal heart rate pattern; S1F-4F: fetal behavioural states 1F through 4F; %NoC: incidence of no-coincidence of state parameters (% of time); GA: gestational age; RL: record length; micro: micro-analysis of %FM and/or FHR and its variability during episodes of HRPs A–D or states 1F–4F.

observed so far with ultrasound from 28 weeks of gestation onwards.

A number of studies have recently investigated the effects of induced maternal stress, emotions, and hormonal changes on fetal functioning [48–52]. Changes in fetal heart rate and motility that occurred during a maternal cognitive challenge (arithmetic test or the Stroop colour-word matching test) were compared with values obtained during pre and post-test periods. The whole procedure was completed within about 15 min. The observed effects during testing compared with baseline were usually statistically significant but small, e.g. a 10% decrease in fetal movement and a 5 bpm increase in fetal heart rate [48,49].

The results of this kind of experiments are clearly of interest but have to be viewed with some caution because of potential methodological pitfalls. As pointed out above, the human fetus exhibits a large amount of spontaneous body movements occurring at a rate of about 0.4–5 per min [53]. Body movements are associated with FHR accelerations, such that it may increase from 130 to 160–170 bpm within a few seconds. Finally, fetal behaviour is organized in rest–activity or sleep–wake cycles. Both physiological variables and responsiveness to external stimuli depend on the state the fetus is in (input–output state relationship). Thus, for successful testing fetal responses to elicited maternal psychological challenges, stimulus-free control periods of the same duration as that of the test procedure are required. These control periods must be obtained from the same fetus during a comparable behavioural state [54]. In the only controlled (counterbalanced) study in this field to date (no. 2), the effect of induced emotion on fetal performance was studied by showing a film of a normal delivery to pregnant women at term during the second half hour of a 2-h fetal behaviour recording. Although this film evoked intense maternal emotions (some women were crying when watching) and a positive correlation was found between maternal state anxiety and fetal body movements, no differences in movement incidence and behavioural state distribution were revealed when comparing data of the experimental day with comparable data on a control day when no maternal emotions were induced. Further understanding of immediate maternal–fetal interactions awaits future studies that take into account the peculiarities of fetal behaviour.

To conclude, a link between antenatal maternal mood and ultrasonographically observed fetal behaviour is well established. Although two studies showed that maternal anxiety/stress measured at 12–21 and 15–17 weeks influenced near term fetal behaviour, an immediate link has in general only been observed from 27 to 28 weeks of pregnancy onwards. The mechanisms underlying these links are presently obscure.

3. The short and long term links between anxiety/stress during pregnancy and the development of the child

3.1. Overview of results

Evidence from earlier studies has been largely inconclusive but more recent methodologically improved studies support the notion of an overall relationship between negative maternal emotions during pregnancy and reproductive outcome [25]. The intensity and chronicity (or duration) of antenatal anxiety/stress and lack of appropriate coping mechanisms have been identified as critical factors [55,56]. A recent review suggests that antenatal maternal stress results in a general susceptibility to psychopathology [17].

We here review published or 'in press' prospective studies from the past 20 years, in which the assessment of maternal anxiety/stress was started during pregnancy (Table 3). The 17 studies-14 independent, one two-wave study (nos. 11, 14), and one three-wave study (nos. 6, 16, 17)—all with a different design are summarized. Studies are ordered by the age of the child at final assessment.

In general, the studies show that antenatal maternal anxiety/stress was positively related to regulation problems at the cognitive, behavioural, and emotional levels. These problems were assessed either by behavioural observations or recordings (nos. 1–6, 8–10, 16, 17), and/or by teachers' ratings (nos. 13, 15, 16), and/or by mother's ratings (nos. 4, 6–8, 11–16).

In *newborn babies*, regulation problems were expressed in less good scores for the Brazelton Neonatal Assessment Scale (nos. 1, 9), neurological examination (no. 2), cardiac vagal tone (no. 3) and behavioral states (no. 6).

Infants were rated by an observer as having less good interactions with their mother (no. 4), being highly reactive (no. 5), worse regulation of attention (no. 8) and having poorer language abilities (no. 10), and by their mother as having sleeping, feeding and activity problems (no. 6), and being irritable and difficult (nos. 6–8). Scores on the Bayley Scales of Infant Development were worse at 8 and 24 m (nos. 8–10), but not at 7 m (no. 6).

Pre-school children and children were rated by their mother (nos. 11–16), teachers (nos. 15, 16), an external observer (no. 16) or themselves (no. 16) as showing poorer attention, hyperactivity, behavioral and emotional problems, and they were rated by their teacher has having low school grades and bad behaviour (no. 13).

Finally, *adolescents* showed impulsive behaviour when performing computerized cognitive tasks and scored lower on intelligence subtests (no. 17). Unpublished results of Obel et al. (personal communication, [74]) indicate that stressful life events increased the risk for ADHD problems in pre-adolescents (9–11-year-olds). Unpublished results of Van den Bergh et al. [75] confirm a link between high antenatal anxiety and behavioural

Table 3
Prospective studies on the effect of prenatal maternal anxiety and stress on postnatal behavioural development[a]

#	First author	Sample: Size at outcome, characteristics of pregnant women	Anxiety/stress measure in pregnancy: Timing; questionnaires; physiological measures	Outcome assessment: Child's age at outcome; gender; measures; observer	Statistical analyses: Method; confounders controlled for in analysis	Impact of antenatal anxiety/stress: Negative child outcome (normal letter); *positive and zero effect outcome (italic)*
1	Rieger [57]	$N=66$–87; nulliparous:– Age: 31 (18–40) yr No obstetrical or psychiatric pathology Singleton pregnancy	<20 wk; 30–34 wk Total distress score based on: Trier Inventory for the Assessment of Chronic Stress, Prenatal Distress Questionnaire, Perceived Stress Scale Life Experience Scale Morning cortisol: saliva samples $<$ 20 wk, 30–34 wk	3–5 days Neonatal Behavior Assessment (NBAS), by observer	Regression Controlled for: gestational age (Medical record data on birth)	Higher total distress score associated with more infant regulation problems on NBAS (e.g. alertness, cost of attention, state regulation…) Higher basal cortisol levels at 30–34 wk related to more infant difficulties in habituating to new or aversive stimuli
2	Lou 1994 [58]	$N=2382$ 70 most stressed versus 50 non-stressed (from cohort) Nulliparous:– Age:– Singleton pregnancy	Mid-gestation Questionnaire about life events, conditions at work (e.g., fatigue, chemicals), smoking, alcohol, drugs General Health Questionnaire (GHQ)	4–14 days Birth weight Head circumference Prechtl's neurological observation, by external observer	Linear and logistic regression Controlled for: maternal age, gestational age, educational level, social support, smoking, alcohol, tranquillizers, gender of child (Prechtl's Obstetric Optimality Score)	Moderate to severe stress associated with lower birth weight, smaller head circumference and lower Prechtl's neurological score
3	Ponirakis 1998 [59]	$N=27$ Nulliparous: 100% Age: 17.3 (13–19) yr No obstetrical risk or psychiatric pathology	$\leq$16 wk; 32–34 wk Negative trait emotionality (TE) based on: State Trait Anxiety Inventory (STAI)-trait, State Trait Anger Scale (STAS)-trait, and NEO-AC Personality Inventory depression, anxiety and hostility subscales Negative state emotionality (SE) based on: STAI-state, STAS-state, Beck Depression Inventory (BDI) Inventory of Socially Supportive Behaviors Saliva cortisol: 5 samples at 20 min intervals at $\leq$16 wk; 32–34 wk	Birth, 1 day, 3–4 wk Medical record data (e.g. Apgar 1', 5'; risk factors at birth and 24 h; no. of resuscitation methods required) Cardiac vagal tone at 3–4 wk (data analyzed from 10′ infant resting EKG according to Porges' method)	Correlations; regression	*Higher negative TE at $\leq$16 wk, associated with higher neonate Apgar 5′* and lower cardiac vagal tone Higher negative SE at 32–34 wk associated with more abnormalities on the newborn profile Social support mediated effect between TE at $\leq$16 wk and cardiac vagal tone Higher cortisol at $\leq$16 wk associated with lower neonate Apgar 1′, 5′ and increased need for resuscitation at birth *No effect of SE at $\leq$16 wk, TE at 32 wk, cortisol at 32–34 wk on measurs of infant outcome or cardiac vagal tone*
4	Field 1985 [60]	$N=24$ Nulliparous: 70% Age: 24 yr No obstetrical risk	Third trimester Pregnancy risk index (scale of Braverman and Roux on demographic characteristics, stress, depression)	3–5 m 10′ face-to-face play interactions (videotape), by external observer Colorado Child Temperament Inventory, by mother	T-tests –	High pregnancy risk index group had high postnatal maternal scores on BDI, STAI and Locus of Control scores; Depressed mothers have less optimal interactions (e.g. infant less relaxed, more fussiness, more drowsy state) and rate their infant as being more emotional

5	Davis [61]	*N*=22 Nulliparous: 54% Age: 28 (18–36) yr No psychiatric risksingleton pregnancy	32 wk STAI-state anxiety Center for Epidemiological Studies Depression Inventory	4 m 12 girls, 10 boys Harvard Infant Behavioral Reactivity Protocol (videotape), by external observer	Correlations; hierarchical linear regression Controlled for: anxiety and depression 8 wk after birth (Medical record data on medical risk and birth)	Higher antenatal anxiety and depression related to higher infant negative behavioral reactivity
6	Van den Bergh 1990 [25] 1992 [39]	*N*=70 Nulliparous: 100% Age: 18–30 yr No obstetrical risk or psychiatric pathology No medication	12–22 wk; 23–31 wk; 32–40 wk STAI (Important Life Event Scale, Daily Hassles Scale, Coping Scale, Social Support Scale, Pregnancy Anxiety Scale)	1 wk; 10 wk; 7 m Prechtl's neurological observation (1 wk) by external observer; 2 h behavioral state observation (1 wk) by observer Feeding score and mother-infant interaction during feeding (1 wk; 10 wk), by external observer Behavioral ratings (1 wk; 7 m), ITQ (10 wk; 7 m), ICQ (7 m), by mother BSID (7 m), by observer	Correlations; LISREL Controlled for: postnatal anxiety at 1 wk,10 wk,7 m (Educational level, smoking, birth weight for gestational age, gender of child, Prechtl's Obstetric Optimality Score)	Higher antenatal state and trait anxiety related to: more activity in state 2–4 and more crying at 1 wk; more difficult temperament at 10 wk and 7 m; more irregularity in feeding and sleeping, more activity at 7 m. *No effect of anxiety on Prechtl's neurological score, feeding score, MDI or PDI.* (Unpublished result: higher social support and expression of emotions associated with higher infant MDI and PDI)
7	Vaughn 1987 [62]	*N*=233 (study 3) Nulliparous: 100% Age: 28.6 yr	Near 21 wk; 35 wk STAI Personality Research Form Self-esteem (Epstein scale)	6 m ITQ-Revised, by mother	T-tests –	Mothers of infants with difficult temp. had higher STAI anxiety scores at 21 and 35 wk, were more defendant and impulsive, have less self-esteem than mothers of infants with easy temp.
		N=35–100 (study 4) Nulliparous: 62% Age: 29.7 yr No obstetrical risk or psychiatric pathology	26–34 wk (???) Institute for Personality Assessment and Testing (IPAT) anxiety scale; California Personality Inventory; (CPI); McGill Pain Inventory Cortisol, ACTH, β-endorphin: maternal and placental blood samples at 26–34 wk, during early and late labour)	4–8 m ITQ-Revised, by mother	Correlations; t-tests (Maternal age, Apgar score, education, parity, gender of infant, length of labour, birth weight)	Mothers of infants with difficult temp. had higher IPAT-anxiety and less optimal CPI personality scores during pregnancy than mothers of infants with easy temp. Maternal characteristics correlated with β-endorphin from placental blood sample (only 4 of 120 tests significant) Mothers of difficult infants had lower levels of β-endorphin during later stages of labor (only 1 of 15 tests significant)

(*continued on next page*)

Table 3 (*continued*)

#	First author	Sample: Size at outcome, characteristics of pregnant women	Anxiety/stress measure in pregnancy: Timing; questionnaires; physiological measures	Outcome assessment: Child's age at outcome; gender; measures; observer	Statistical analyses: Method; confounders controlled for in analysis	Impact of antenatal anxiety/stress: Negative child outcome (normal letter); *positive and zero effect outcome (italic)*
8	Huizink 2002 [63] 2003 [64]	$N=170$ Nulliparous: 100% Age: 31.3 yr No obstetrical risk No medication Singleton pregnancy	15–17 wk; 27–28 wk; 37–38 wk Daily hassles Pregnancy Related Anxieties Questionnaire-Revised (PRAQ-R) Perceived Stress Scale (Trait Anxiety, depression measure) Saliva cortisol: 7 samples every 2 h starting at 8 a.m, at 15–17 wk, 27–28 wk, 37–38 wk	10 days; 3 m; 8 m 86 girls, 84 boys BSID and IBR (3 m, 8 m), by external observer ICQ (3 m, 8 m) by mother (total score for adaptational problems and difficult behavior)	Correlation; logistic regression; MANCOVA Controlled for: postnatal perceived stress and depression at 3 m, 8 m, educational level, smoking, alcohol use, gender, breastfeeding) (SES, birth weight, gestational age at birth, obstetric risk, GHQ)	Higher fear of giving birth and having handicapped child at 15–17 wk associated with more infant attention-regulation problems at 3 and 8 m Higher perceived stress at 15–17 wk associated with more difficult infant behavior at 3 m and 8 m and infant attention-regulation problems at 8 m More daily hassles at 15–17 wk associated with lower infant MDI at 8 m Higher fear of giving birth at 27–28 wk related to lower infant MDI and PDI at 8 m High early morning salivary cortisol at 37–38 wk associated with lower infant MDI at 3 m and PDI at 3 and 8 m *No effects of daily hassles on attention regulation and difficult behavior*
9	Brouwers 2001 [65]	$N=105$ Nulliparous:– Age: 30.4 (21–38) yr No medical pathologysingleton pregnancy	32 wk STAI	3 wk; 12 m; 24 m 52 girls, 53 boys NBAS (3 wk), by observer BSID and IBR (1 and 2 yr), by observer	χ^2; linear regression; Controlled for: gender child, educational level, birth weight, type of feeding, parity, HOME-subscale, alcohol, smoking during pregnancy, postnatal maternal anxiety and depression symptoms	Higher anxiety associated with lower score on orientation cluster of NBAS at 3 wk and lower MDI at 24 m; χ^2 (without control for confounder); high anxiety associated with lower scores on task orientation and motor co-ordination on the IBR at 12 m, and lower MDI and PDI at 12 m and 24 m
10	Laplante 2004 [66]	$N=52$–58 Nulliparous: 19% Age: 30.6 (20–42) yr	1–3 m; 4–6 m; 7–9 m (within 6 m after ice storm, in many cases during pregnancy) Objective stress measure of disaster; treat, loss, scope and change Subjective stress measure: Impact of Event Scale Revised	24 m BSID-Mental scale by observer MacArthur Communicative Development Inventory (French adaptation)	Correlations; hierarchical linear regression Controlled for: birth weight, gender, month of gestation, age at testing (SES, pregnancy and birth complications, postpartum depression (EPDS))	More severe objective stress exposure associated with lower MDI and lower productive and receptive language abilities on MacArthur Inventory; effects on MDI only significant for stress during first six months of pregnancy *Subjective stress measure not related to MDI or language abilities*

11	O'Connor 2002 [67]	$N=7447$ (from cohort) Nulliparous: 45% Age: 28 (14–46) yr	18 wk; 32 wk Anxiety items of the Crown-Crisp Index	3 yr 11 m 3595 girls, 3853 boys Strengths and Difficulties Questionnaire (SDQ), by mother	Logistic regressioncontrolled for: timing of prenatal anxiety, birth weight for gestational age, mode of delivery, parity, smoking, alcohol, SES, maternal age, postnatal anxiety and depression (EDPS)	High levels of anxiety at 32 wk associated with more inattention/hyperactivity and emotional problems in boys and with more emotional and conduct problems in girls High levels of anxiety at 18 wk associated with more emotional problems in girls
12	Martin 1999 [69]	$N=527$–1297 (6 m) and $N=389$–900 (5 yr) (from cohort) Nulliparous: 61% Age: 27 yr	1–16 wk; 17–28 wk; 29–40 wk Self-construct pregnancy questionnaire on psychological distress (anxiety/depression and mood lability)	6 m; 5 yr 50% male (6 m) 54% male (5 yr) ITQ and Preschool Temperament Questionnaire (adapted), by mother	Correlations; latent variable path analysis Controlled for: somatic illness, nausea, maternal age	Psychological distress modestly related to negative temperament at 6 m.; strongest for psychological distress at 1–16 wk Higher psychological distress at 1–16 wk related to higher negative emotionality at 5 yr; strongest for males
13	Niederhofer 2004 [46]	$N=247$ Nulliparous:– Age:–	16–20 wk Self-construct questionnaire	6 m; 6 yr Infant temperament questionnaire (self-construct), by mother (6 m) School grades and marks for behavior in school, by two teachers (6 yr)	Correlations –	More risks during pregnancy associated with lower school grades and more negative behavior in school at 6 yr
14	O'Connor 2003 [70]	$N=6204$–6493 (from cohort) Nulliparous: 45% Age: 28 (14–46) yr	18 wk; 32 wk Anxiety items of the Crown-Crisp Index	6 yr 9 m 3000 girls, 3204 boys SDQ, by mother	Logistic regression Controlled for: timing of prenatal anxiety, birth weight for gestational age, mode of delivery, parity, smoking, alcohol, SES, maternal age, postnatal anxiety and depression (EDPS)	High levels of anxiety at 32 wk associated with more behavioural/emotional problems in both boys and girls High levels of anxiety at 18 wk associated with more behavioural/emotional problems in girls (effect of 18 wk stronger than effect of 32 wk in girls)
15	Rodriguez [71]	$N=208$–290 Nulliparous:– Age: 27 yr	10; 12; 20; 28; 32; 36 wk Swedish 10-item version of Perceived Stress Scale	7 yr 8 m 146 girls, 142 boys 18 symptoms (DSM-IV criteria for ADHD), by mother and teacher Impact item of the SDQ, by mother	Correlations, linear and logistic regression Controlled for: smoking, timing of stress and smoking, maternal education and civil status, presence and salary of father figure	High stress and heavy smoking independently associated with more ADHD symptoms; fulfillment of diagnostic criteria for ADHD related to prenatal stress Week 10 accounted for the largest portion of the variance

(*continued on next page*)

Table 3 (*continued*)

#	First author	Sample: Size at outcome, characteristics of pregnant women	Anxiety/stress measure in pregnancy: Timing; questionnaires; physiological measures	Outcome assessment: Child's age at outcome; gender; measures; observer	Statistical analyses: Method; confounders controlled for in analysis	Impact of antenatal anxiety/stress: Negative child outcome (normal letter); *positive and zero effect outcome (italic)*
16	Van den Bergh 2004 [72]	*N*=71 (72 children) Nulliparous: 100% Age: 18–30 yr No medical or psychiatric pathology No medication	12–22 wk; 23–31 wk; 32–40 wk STAI-state anxiety	8–9 yr 34 girls, 38 boys Composite score for ADHD symptoms, externalizing and internalizing problems based on: CBCL, by mother and teacher; Conners' Abbreviated Teacher Rating Scale, by mother and teacher; Groninger Behaviour Observation Scale, by external observer STAIC, by child	Correlations, hierarchical linear regression Controlled for: timing of prenatal anxiety, postnatal trait anxiety, educational level, smoking, birth weight for gestational age, gender of child (Prechtl's Obstetric Optimality Score)	Higher anxiety at 12–22 wk associated with more ADHD symptoms and externalizing problems and with higher self report anxiety on STAIC *Anxiety at 32–40 wk not a significant independent predictor of childhood disorders*
17	Van den Bergh 2005 [73]	*N*=57–68 Nulliparous: 100% Age: 18–30 yr No medical or psychiatric pathology No medication	12–22 wk; 23–31 wk, 32–40 wk STAI	14–15 yr 28 girls, 29 boys Performance of child on computerized Encoding Task and Stop Task Vocabulary and Block Design of Wisc-R intelligence test	Correlations; MANCOVA's Controlled for: timing of prenatal anxiety, postnatal trait anxiety (Educational level, birth weight for gestational age, smoking, Prechtl's Obstetric Optimality Score)	High state anxiety at 12–22 wk is related to impulsive cognitive style (reacting faster but making more errors) in the Encoding task and to lower scores on the intelligence subtests, *but not to Stop Task performance.* *No effect of trait anxiety and no effect of state anxiety at 23–31 and 32–40 wk on encoding, Stop Task, or intelligence subtests*

wk, week(s); m, month(s); ACTH, adrenocorticotrophic hormone; ADHD, Attention-Deficit Hyperactivity Disorder; SES, Socio-Economic Status; temp., temperament. Abbreviation of Scales: BDI, Beck Depression Inventory; BSID, Bayley Scales of Infant Development; CBCL, Child Behavior Checklist; EPDS, Edinburgh Postnatal Depression Scale; GHQ, General Health Questionnaire; IBR, Infant Behavioral Records; ICQ, Infant Characteristics Questionnaire; ITQ, Infant Temperament Questionnaire; MDI, Mental Developmental Index; NBAS, Neonatal Behavior Assessment Scale; PDI, Psychomotor Developmental Index; STAI, State Trait Anxiety Inventory; STAIC, State Trait Anxiety Inventory for Children; SDQ, Strengths and Difficulties Questionnaire; [a]All studies in this table are prospective follow-up studies of the period 1985–2004. Under the heading 'Sample' characteristics of the mothers are given out of which eligibility criteria can be inferred. Under the headings 'Anxiety/stress measures in pregnancy' and 'Outcome assessment' those variables are given that were reported in the articles (between brackets: variables not used in the statistical analyses). Under the heading 'Statistical analyses' the variables are listed that were controlled for in the described statistical analysis method (between brackets: confounders not used in the statistical analyses). Under the heading 'Impact of antenatal anxiety/stress' only those negative, positive and zero effects are presented that were reported in the article.

disorders measured with the Child Behavior Checklist up to 14–15 years of age.

3.2. Controlling for the effect of confounders

It is important to ask whether the good evidence for a link between antenatal maternal anxiety/stress and regulation problems in the child, also implies fetal programming induced directly by maternal anxiety/stress. The link may be mediated by other prenatal or post-natal environmental factors, such as smoking during pregnancy or post-natal maternal anxiety, or may be explained by rater bias. There may also be a genetic vulnerability passed directly from mother to child. The underlying mechanism is likely to be a prenatal programming one if the link can be shown to be specifically with antenatal and not post-natal anxiety/stress, if it cannot be explained by rater bias, and if the link persists after controlling for the effect of other prenatal environmental factors. Several studies have attempted to control for these confounders.

For measuring anxiety or stress during pregnancy all studies used mother's self rating of symptoms or events, rather than a clinical diagnosis. Studies 1, 3, 7, and 8 also included stress hormone measures (Table 3). Some studies have analyzed specific pregnancy anxieties (no. 8) or the number of life events and/or appraisal of recently experienced life events (nos. 1, 2, 8) or disaster (no. 10) during pregnancy, which indicates that the anxiety and stress are likely to be more specific to the antenatal period. Most other studies used standardized scales (nos. 3, 5–11, and 14–17) or assembled a scale (nos. 4, 12, 13) to measure perceived anxiety and stress confined to the prenatal period. As the perception of anxiety in pre- and post-natal periods are significantly correlated [15,72,74], associations found between antenatal anxiety/stress and child's outcome can be spurious. However, studies nos. 5, 6, 8, 9, 11, 14, 16, and 17 used a multivariate analysis including measures of perceived post-natal anxiety and/or depression and/or stress as confounding variables, and still found strong links between antenatal maternal anxiety and regulation problems in the child.

Studies nos. 2, 11, and 14 have used large numbers, which gives a good opportunity to not only control for post-natal but also for antenatal confounding variables, e.g. for educational level and income, smoking, parity, birth weight, gestational age, and gender of the child. The other studies, using smaller numbers, controlled in their statistical analyses at least for confounders shown in their own sample to be influential (nos. 1, 5–10, 12, 15–17). Moreover, potential confounders were also controlled by using strict eligibility criteria, e.g. for parity, age, medical, obstetrical and psychiatric risks (see nos. 1, 3, 5–9, 16, 17). Only study nos. 3, 4, 7, and 13, and one report of study no. 6 [25], showed insufficient control for confounders in their design or statistical analyses.

We can conclude that the fact that in most studies the link between antenatal maternal emotions and later infant or child behaviour persisted even after controlling for potential confounders in the pre and/or post-natal period, lends support to the idea that fetal programming by antenatal anxiety/stress is occurring in humans, as in the animal models. It is likely that the effects of the changed prenatal environment interact with genetic factors in defining the phenotype at birth [76,77]. Those studies, which have examined the same sample at two or more times, show the same effects persisting with the same magnitude over 3 (nos. 11, 14) and 9 years (nos. 6, 16). Although more research is needed to study the potential modulating effect of other post-natal factors than post-natal mood (e.g. attachment and parenting style) [78,79], all these long-term results again support a prenatal programming hypothesis.

3.3. Timing of gestational stress

Studies are inconsistent with regard to the gestational age at which the effects of antenatal maternal anxiety/stress are most pronounced. Rodriguez and Bohlin (no. 15; Table 3) concluded that stress at week 10 accounted for the largest proportion of the variance in ADHD-symptoms at age 7, and Martin et al. (no. 12) found the strongest effect on negative emotionality in 5-years-old for psychological distress during the first three months of pregnancy. Laplante et al. (no. 10) found that high levels of objective stress exposure (measured within 6 m after an ice storm) affected intellectual capacities at age 2 only when the stress occurred in the first six months of pregnancy. Van den Bergh (nos. 16, 17) found that effects on childhood disorders at age 8–9 and cognitive functioning at age 14–15 were confined to maternal anxiety at 12–22 weeks of pregnancy. Huizink and colleagues (no. 8) found more pronounced effects for maternal anxiety/stress at 15–17 weeks and pregnancy-specific anxieties at 27–28 weeks, while early morning cortisol levels at 37–38 weeks had a small effect. O'Connor et al. (nos. 11, 14) found that anxiety at week 32 was a stronger predictor of behavioural/emotional problems at age 4 and 7 than anxiety at 18 weeks.

The fact that several gestational ages have been reported to be vulnerable to the long-term effects of antenatal anxiety/stress may indicate that different mechanisms are operating at different stages. However, observed differences in effects of timing may also be due to differences between the studies, including the scales used for dependent and independent variables (see Table 3), the exact timing of the anxiety measurements, the time period to which they refer, as well as to the intensity of anxiety and the actual persistence of anxiety throughout pregnancy [80]. In addition, genetic differences and differences in psychological, medical–obstetrical, and environmental factors controlled for and not controlled for might be relevant [18,19,66,72,79]. This is clearly an area that needs more attention in future research.

3.4. Magnitude of the effect

It is important to assess the amount of variance in outcome that may be related to antenatal maternal emotions. Several of the studies show associations large enough to be of clinical significance (nos. 10, 11, 14–16; Table 3). For example, in study no. 10, maternal stress exposure to an ice storm at 0–12 weeks and 13–24 weeks of pregnancy explained 27.5 and 41.1% of the variance in the Bayley MDI scores at age 2, respectively. In studies nos. 11 and 14, being in the top 15% for antenatal anxiety at 32 weeks of gestation, approximately doubled the risk for having a son with ADHD symptoms at age 4 and 7, even after allowing for a wide range of covariates including post-natal anxiety up to 33 m. Study no. 6 indicates that maternal anxiety at 12–22 weeks explained 15 and 22% of the variance in externalizing problems and ADHD symptoms at age 8–9, respectively. Other studies show more modest effects. In study no. 8, for instance, 3–8% of the variance in behavioural regulation and mental and motor development at 3 and 8 m was explained, mainly by specific anxiety/stress at 15–17 and 27–28 weeks of gestation [64], and no effect of state or trait anxiety during these periods was found [80].

Differences in the amount of explained variance may be related to the timing of anxiety/stress (see above) or to a difference in the degree of anxiety/stress experienced by the pregnant women across the different studies. For instance, in study no. 8, mean state anxiety was 32.9 (SD = 7.8) at 15–17 weeks and 31.1 (SD = 8.4) at 37–38 weeks of gestation [81]. These values equal decile 4, thus below the mean, of a Dutch female norm population [82]. In study no. 6, mean state anxiety in comparable gestation periods was 38.7 (SD = 7.7) and 36.1 (SD = 8.8), equaling decile 6 and decile 5 of the same norm population, respectively.

3.5. Effects of antenatal maternal depression, a co-morbid symptom of anxiety

Much more research has been done on the effects of antenatal anxiety than depression, although it is well established that there is a strong co-morbidity between the two [78]. Field's group has performed a range of studies on the outcome for the newborn baby with mothers who were depressed during pregnancy [83,84]. They showed that maternal depression during pregnancy was significantly associated with less than optimal scores on many subscales of the Brazelton Neonatal Assessment Scale (e.g. habituation, orientation, autonomic stability), with lower vagal tone, and with a greater relative right frontal EEG activation. Elevated cortisol and norepinephrine, and lower dopamine and serotonin levels in the newborn were also found [83,84]. A structural equation model indicated that the less than optimal neonatal behavioural profile, in which 8–21% of the variance was explained, was related to antenatal maternal depression and to cortisol and epinephrine levels and not to the higher rates of low birth weight and prematurity [83]. Zuckerman et al. [85] observed that babies of women with depressive symptoms ($N = 1123$) cried excessively at 8–72 h after birth and were difficult to console; no effects were found on neurological state. Dawson and colleagues have found that during mother–infant interaction, children of depressed mothers showed increased autonomic arousal (higher than normal heart rates and cortisol levels), and reduced activity in brain regions that mediate positive approach behaviour [86]. The authors indicate that there is suggestive evidence from their follow-up study ($N = 159$ at 13–15 m; partial follow-up to 42 m [87]) that the post-natal experience with the mother had more effect on infant frontal EEG than prenatal factors.

O' Connor et al. [68] examined antenatal depression as well as anxiety, using the self-rating Edinburgh Post-natal Depression Scale antenatally as well as post-natally. Antenatal depression had a somewhat weaker effect on child outcome than antenatal anxiety. When both were used together in a multivariate analysis, the effects of antenatal anxiety were apparent but not those of antenatal depression. In contrast, the effects of post-natal depression were found to be separate but additive to those of antenatal anxiety [68]. Mäki et al. [88] in a prospective epidemiological study ($N = 12{,}059$), found that in the male offspring of antenatally depressed mothers there was a significant but only slight increase in criminality.

3.6. Effects of antenatal anxiety/stress on handedness

Studies that looked at handedness [89,90] have shown that antenatal life events or anxiety are associated with a greater incidence of mixed handedness in the child. This was defined as the child using either hand for a range of task such as drawing or throwing a ball. While in itself not a behavioural problem, mixed handedness has been shown to be associated with a range of neurodevelopmental problems such as dyslexia, autism, and ADHD. This mild adverse effect would again fit with the animal research in which a wide range of disturbances have been found in the offspring, including a disturbance of laterality [15,17].

3.7. Weaknesses of the studies

One weakness of many or most of the studies concerns the outcome measures. Researchers did not use specific marker tasks for testing specific cognitive functions (e.g. attention, inhibition, working memory, processing speed). Nor did they use neuro-imaging techniques, such as electro-encephalogram, event related potentials, and (functional) magnetic resonance imaging, or neuroendocrine measures. In some studies of infants, the Bayley Scales of Infant Development were used. Although these instruments are useful as descriptive instruments and allow identification of certain sensorimotor deficits, they are rather global measures. In addition, scores on these tests have proved to

be largely unrelated to scores on intelligence tests in later childhood ([91] p. 33). Marker tasks provide more specific outcome measures. They are used in developmental cognitive neurosciences [92] and behavioural teratology research [93] to indirectly identify which underlying structure–function relations are altered. Neuro-imaging techniques could elucidate some of the altered structure–function relations and underlying mechanism in a more direct manner. Using neuroendocrine measures, especially under stress-inducing situations, has the potential to elucidate if and how the stress-regulating system is involved in the regulation problems of the offspring.

A *second* weakness is that it is not always clear whether or not women were excluded who took medication such as antidepressants during pregnancy [94].

Third, although maternal coping mechanisms and characteristics such as optimism [95–97] can interact with anxiety/stress or have an independent effect, only a few of the studies have included these measures. For instance, an unpublished result of study no. 6 revealed that use of emotion-focused coping (i.e. subscales expression of emotions and social support of the Utrecht Coping list [56]), had a positive effect on both psychomotor development ($B=6.13$, $p<0.0001$) and mental development ($B=2.76$, $p=0.044$) and uniquely explained 17.8 and 6.5% of the variance, respectively, after control for the confounders listed under study no. 6 (Table 3). State anxiety was unrelated to this coping style (r [70] $=0.030$; $p=0.80$).

A *fourth* concern is that most of the studies have not looked for gender effects. Those studies that did (nos. 11, 12, 14–17) found some suggestion that boys were more susceptible to the influence of maternal anxiety and stress.

To conclude, the evidence for a link between antenatal maternal anxiety/stress and regulation problems at the cognitive, behavioural, and emotional levels in the child is persuasive because this link has been replicated in 14 independent studies, with children ranging from birth up to 15-years-old. Moreover, this link generally persisted after controlling for post-natal maternal mood and/or other potentially important pre- and post-natal confounders. The study of the timing, intensity and chronicity of anxiety/stress, of maternal coping mechanisms and gender of the child on a variety of neurodevelopmental aspects (including handedness) needs more attention. The use of marker tasks of specific cognitive functions, neuro-imaging techniques, and neuroendocrine measures could elucidate some of the altered structure–function relationships and some underlying mechanisms.

4. Two physiological mechanisms by which the maternal affective state may affect the fetus in humans

Two mechanisms of transmission of anxiety/stress from mother to fetus in humans have been suggested. One hypothesis is that maternal stress hormones, and in particular, glucocorticoids, are transmitted across the placenta [98]. A second possible mechanism is via an effect on uterine artery blood flow [99,100].

4.1. Transfer of hormones across the placenta

In utero exposure to abnormally high levels of maternal glucocorticoids is one plausible mechanism by which maternal stress may affect the fetus. However, the placenta is an effective barrier between the maternal and fetal hormonal environments in humans, being rich in protective enzymes such as monoamine oxidase A, peptidases, and 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to inactive products such as cortisone [101]. The impact of maternal stress on this enzyme is not known; there is some evidence that it is reduced in intrauterine growth restricted pregnancies [102].

The links between maternal and fetal hormonal levels have been examined by studying the correlation between maternal and fetal plasma levels for a range of hormones (Table 4). Comparing levels of cortisol in paired maternal and fetal plasma samples, showed that fetal concentrations were linearly related to maternal concentrations [98,103]. As maternal concentrations are substantially higher than fetal (over 10-fold), this is compatible with substantial (80–90%) metabolism of maternal cortisol during passage across the placenta, and is in accord with in vivo [104] and ex vivo studies [105]. However, it does suggest that if the mother is stressed in a way that increases her own cortisol level, this will be reflected in the hormonal milieu of the fetus. This mechanism cannot underlie the immediate links that have been observed between changes in maternal mood, e.g. in anxiety while doing a cognitive test, and fetal behaviour [47–49,51] as plasma cortisol takes about 10 min to respond to a stressor.

With both β-endorphin [98] and noradrenaline [107] there was no significant correlation between maternal and fetal plasma levels. Neither β-endorphin nor noradrenaline is lipophilic, and neither would be expected to cross cell membranes as readily as the steroid, cortisol. Corticotrophin releasing hormone (CRH) is correlated in the maternal and fetal compartments of the placenta [106], but to a lesser

Table 4
Correlations between maternal and fetal hormone levels

Hormone	Correlation	Maternal–fetal ratio	Reference
Cortisol	0.58 $p<0.01$	11.8	Gitau 2001 [98]
β-endorphin	−0.20 ns	0.6	Gitau 2001 [98]
CRH	0.36 $p=0.03$	1.7	Gitau 2004 [106]
Noradrenaline	0.08 ns	10.5	Giannakoulopoulos 1999 [107]
Testosterone	0.42 $p<0.01$	1.3	Gitau [108]

degree than cortisol. Being a peptide, it is unlikely to cross from mother to fetus, and it is therefore more probable that CRH is secreted into both compartments from the placenta, under some partial form of joint control. Testosterone, a steroid like cortisol, is highly correlated in the two compartments, and it is plausible that there is some direct transfer from mother to fetus. Recently, it has also been shown that, unlike the norm in the adult, there is a positive correlation between fetal plasma cortisol and testosterone levels [108]. Cortisol and testosterone in the fetus are clearly not under identical control; there are likely to be several different determinants of fetal testosterone levels. Fetal testosterone levels are higher in males than females but there is no difference in cortisol in the two sexes. Whereas there is an increase in testosterone with gestational age in females there is no such increase in cortisol over this age range. However, the mechanism of inter-related control of the HPA axis and testosterone production is different in the fetus compared with the adult. Thus it may be that in the fetus some of the factors that cause raised fetal cortisol level may also cause an increase in testosterone level. This is compatible with a mechanism by which maternal stress may influence fetal development in ways associated with a more masculine profile, including an increase in mixed handedness, ADHD and learning disabilities.

There have been very few studies examining the function of the maternal HPA-axis during pregnancy in relation to her emotional state. Obel [74] observed that evening, but not morning salivary cortisol was raised in women with high perceived life stress at 30 weeks, but not at 16 weeks of gestation. Rieger et al. [57] found no significant influence of perceived maternal stress on awakening cortisol response, neither in the first, nor in the third trimester. Cortisol rises markedly at the end of gestation, and the mother's HPA-axis becomes desensitized to stressors as her pregnancy develops [109,110], presumably due to the large amounts of CRH which are released from the placenta. We do not know exactly when, and by how much this desensitization occurs.

4.2. Impaired uterine blood flow

The hypothesis that anxiety in pregnant women is associated with abnormal blood flow in the uterine arteries was tested using colour Doppler ultrasound to measure the blood flow pattern and an according to standard procedures calculated Resistance Index (RI) [100]. A high RI indicates a greater resistance to blood flow, and is known to be associated with adverse obstetric outcome, particularly intrauterine growth restriction and preeclampsia. The resulting lack of oxygen may also cause a direct stress to the fetus. Significant associations between the RI in the uterine artery and both state and trait anxiety were found in a sample of hundred women with singleton pregnancies, measured between 28 and 32 weeks of gestation. Women in the highest anxiety groups (Spielberger's state anxiety score of 40 and more) had significantly worse uterine flow velocity waveform patterns than those in the lower anxiety groups. This finding on abnormal uterine blood flow parameters in highly anxious women was recently confirmed in a larger cohort where an association between maternal anxiety and uterine blood flow was present at 30 but not at 20 weeks of gestation (Jackson, Fisk and Glover; unpublished observations).

A study by Sjöström and colleagues [99], aimed at determining whether fetal circulation was affected by maternal anxiety, found that, in the third trimester, fetuses of women with high trait anxiety scores had higher indices of blood flow in the umbilical artery, and lower values in the fetal middle cerebral artery, suggesting a change in blood distribution in favour of brain circulation in the fetus. These results indicate that raised maternal anxiety, even within a normal population, had an influence on fetal cerebral circulation.

We do not know whether these associations between anxiety and Doppler patterns are acute or chronic. Further work is needed to determine whether overall anxiety during pregnancy or even prior to or at conception, might affect later uterine artery blood flow patterns, or instead, whether the association is only with the current emotional state. We also need to determine whether the magnitude of the link between maternal anxiety and uterine blood flow is sufficient to be of clinical significance.

In pregnant sheep infusion of noradrenaline decreased uterine blood flow, indicating the possibility that high anxiety can cause acute changes in uterine artery blood flow [111]. In addition, in sheep, reproductive tissues including the uterus are more sensitive to the vasoconstrictive effects of noradrenaline than other body tissues. However, other animal studies have also indicated the possibility that maternal stress or anxiety, early in gestation, might affect the later uterine blood flow. In a rat model study cold stress early in pregnancy decreased trophoblastic invasion. This was followed by increased blood pressure, raised blood catecholamine levels, and proteinuria in later pregnancy [112]. The authors suggest they have produced a model for preeclampsia, mediated by increased catecholamines causing decreased trophoblastic invasion.

To conclude, there is good evidence for a strong correlation between maternal and fetal cortisol levels. Thus if the mother is stressed in such a way as to raise fetal cortisol, the fetal environment may be changed in a way that could have long term effects. However, this mechanism cannot underlie the immediate links between maternal mood and fetal behaviour. Noradrenaline, which can respond in seconds, does not appear to cross from mother to fetus, but may have an indirect effect via changes in the maternal muscular or vascular tone. This in turn may cause stress to the fetus and raise cortisol levels. However, much remains to be understood. We need to know more about the biochemical correlates of normal variations and of high anxiety, stress and the response to

life events in the pregnant woman at different periods of gestation. We also need to know what happens when cortisol levels are raised in the fetus. How does this affect the development of the nervous system and of other systems, infant growth, age at delivery, and later behaviour? We need to be aware that these may all be affected by different mechanisms.

5. Stress hormones and the developing fetal nervous system: how are they related to behavioural/emotional regulation problems in infants and children?

There is evidence that complex functions such as behavioural and emotional regulation, are mediated through the prefrontal cortex (PFC). The PFC has many subdivisions and collectively these areas have extensive and reciprocal connections with all sensory systems, cortical and subcortical motor system structures, subcortical arousal and attention functions, and with limbic and midbrain structures involved in affect, memory, and reward [113]. Behavioural functions are not localized in the PFC, rather the PFC (through the action of its subdivisions) seems to be essential for the control of organized, integrated functioning [114]. For example, the medial part, including the anterior cingulate cortex (ACC), controls a range of functions, such as motivation, drive to perform, response selection, working memory, and novelty detection [115–117]. It is therefore of interest to determine how prenatal stress may affect the development of the PFC and ACC and of areas related to these regions.

Proper timing and guidance of neurogenesis, neuronal differentiation and migration, apoptosis, synaptogenesis and myelination, are critical for the appropriate organization and functioning of the neocortex. These processes are controlled by mechanisms intrinsic to the cell and processes extrinsic to the cell, i.e. by genes and their products, by cell–cell interactions, by interactions of cells with early neurotransmitters and neuromodulators acting as growth factors [118]. It is important to note that, although before 23 weeks of gestation these developmental processes are not driven by activity that is modulated by sensory input, they nevertheless can be altered [119]. This happens when environmental factors (e.g. viruses, tobacco, cocaine, cortisol) modulate the influence of intracellular and extracellular developmental signals. In general, the earlier the disturbance occurs, the greater its potential influence on subsequently occurring events and maturation, and finally, on the mature structure–function relationship [32,118–121].

Although region-by-region differences in timing exist, neurogenesis, neuronal differentiation and migration occur before the 7th month of gestation for most parts of the nervous system. Knowledge of these differences is important for delineating which cortical layers or areas (and hence processes) might have been altered by a disturbing environmental agent, acting during a particular gestational period. In lower parts of the brain (e.g. in the nuclei of the brainstem and reticular formation) the first neurons are produced in the 4th week after conception (6th week postmenstrual age). The basal ganglia become visible during the 6th postconceptional week, when the ganglionic eminence develops [114]. In the cerebral cortex, almost all neurons are generated at 6–18 weeks after conception. After their birth, neurons start migrating; the last born neurons arrive at their final place in the cortex at about 23–24 weeks of gestation [118,122–124]. During migration, differentiation of the neuron starts, resulting in the final phenotype of the neuron. The prefrontal cortex differentiates rather late: only at 26–34 weeks of gestation is its basic 6-layered cytoarchitectonic pattern established [125]. In contrast, in the limbic system (e.g., the hippocampus, amygdala) and limbic regions of the cortex (e.g. anterior cingulate cortex) the major nuclei are already formed during the third and fourth month; at 16 weeks the hippocampal area begins to differentiate into the hippocampus proper and the dentate gyrus [114]. Although differentiated early, the dentate gyrus displays continued post-natal proliferation of granule cells; about 85% is formed at birth [126]. Proliferation of granule cells continues also in the cerebellum for several months after birth [127].

Synaptic maturation includes the growth of axons and dendrites, axonal projections, synaptogenesis and myelination. Correct timing and exclusion of inappropriate connections (‘synaptic pruning’) are essential for the maturation of synaptic connections. Also apoptosis, or programmed cell death, is necessary for proper development of the central nervous system, as about 50% of all generated neurons die. In the neocortex, the first synapses are formed around 8 weeks of gestation, although at a very low density [125]. Different genes and their products (e.g. various transcription factors and growth factors) are involved in early axon guidance [128–130]. Until 23–24 weeks of gestation intrinsic (experience-independent) processes guide axonal growth and synaptogenesis; at 23–24 weeks thalamocortical circuits become functional and from then onwards (and throughout life) experience-dependent processes are important, first in expanding and afterwards in fine-tuning the neuronal circuits. Experience also induces modifications in glial cells and cerebrovasculature [131–135]. Clusters of genes are exclusively expressed in correlation with high levels of developmental plasticity (e.g. in the visual cortex [136]); this again illustrates the importance of the interaction between genes and environment (in casu experience) for developmental cortical plasticity [137].

In animal models, glucocorticoids are known to be involved in fetal programming of the HPA-axis and neurotransmitter systems (for a review see [15,17,137], and Owen et al. [138]). Antenatal maternal treatment with synthetic glucocorticoids, such as betamethasone and dexamethasone, has been shown to have a range of long-term effects on child behaviour and cognitive development [139–142]. However, we currently know very little of

the influence of stress hormones on the developing human fetal nervous system. It is clear that, although cortisol is essential for normal brain development, exposure to excessive amounts has long-lasting effects on neuroendocrine functioning and on behaviour. Glucocorticoids (cortisol in humans) are known to have profound effects upon the developing brain and spinal cord; they can modulate cell proliferation and differentiation and synaptic development in various brain regions [143–146]. If for instance, in the third or fourth month of gestation, a teratogen such as cortisol modulates the influence of developmental signals and disrupts neuronal migration, this may result in abnormal cell density and cell position in the different layers of the anterior cingulate cortex. This pattern, which has been reported in postmortem cases of schizophrenia and bipolar disorders [147], results in alterations of different neurotransmitter systems in the corticolimbic region [148]. During the onset of differentiation (e.g. at about 16 weeks in the hippocampus and between 26–34 weeks in the prefrontal cortex) disturbances by teratogens can alter the timetable of the expression of several neurotransmitters, neuropeptides (e.g. CRH), and their receptors. This in turn can alter receptor sensitivity as well as dendritic outgrowth and formation of synapses, and change the balance between excitatory and inhibitory brain circuits [15,120,137,149,150].

Two recent studies are of interest in the context of perinatal programming. Roberts et al. have recently examined the relationship between the striatal dopamine system integrity and behaviour in 5-to 7-year-old rhesus monkeys born from mothers that were exposed to stress during late pregnancy [13]. They have previously shown altered HPA-axis function and behaviour in such offspring. In their new study, subjects from prenatal stress conditions showed an increase in the ratio of striatal dopamine D2 receptors and DA synthesis compared to controls, in a way which they conclude supports a hypothesis linking striatal function to behavioural inhibitory control. Lou et al. found a link between high dopamine D2/3 receptor availability (examined with positron emission tomography) and inhibition failure (expressed in increased reaction time and reaction time variability during a computerized attention task) in 27 prematurely born adolescents with ADHD [151]. Interestingly, high dopamine receptor availability was predicted by low neonatal cerebral blood flow. This could contribute to a persistent deficiency in dopaminergic neurotransmission. Results of these studies are congruent with results of Durston et al. in which event-related functional magnetic resonance imaging indicated that children with ADHD did not activate fronto-striatal regions during go/no-go tasks in the same manner as control children, but rather relied on a more diffuse network of regions [152].

To conclude, disturbance of the delicate balance of factors guiding the precisely timed neocortical neurogenesis and synaptogenesis during gestation can have long-term consequences. Prenatal programming of the HPA-axis and of structure–function relationships controlled by the prefrontal cortex may contribute to regulation problems at the cognitive, behavioural, and emotional level of children of mothers with high anxiety/stress during pregnancy. The disturbance of the particular developmental processes taking place in specific brain layers and areas at the time of antenatal maternal stress hormone release, in interaction with the genetic susceptibility of the offspring and mediated by later pre and post-natal environmental factors, will determine the way in which cognitive, motor, arousal, and emotional structure–function relationships are altered [153–155]. The ways in which the PFC integrates these altered processes presumably underlie the kind of behavioural/emotional regulation problems these children will eventually develop [137,149].

6. General conclusions

This review shows that there is good evidence for a direct link between antenatal anxiety/stress and fetal behaviour observed by ultrasound from 27 to 28 weeks postmenstrual age onwards. There is also accumulating evidence that there are links between maternal mood during pregnancy and the long-term behaviour of her child. The fact that maternal anxiety/stress during pregnancy is linked with later behaviour, even after controlling for effects of post-natal maternal mood and other relevant prenatal and post-natal confounders, does suggest that, as in animal models, a programming effect on the fetal brain is taking place. It is clear that many different underlying mechanisms and systems are involved in perinatal programming. Based on the available evidence it seems plausible that fetal programming of the HPA-axis, limbic system, and prefrontal cortex may contribute to the regulation problems found in children of mothers who were highly anxious/stressed during pregnancy. Many questions remain on exactly how fetal programming works in humans, and in which specific ways the timing, kind, intensity, and duration of environmental disturbances are related to altered neurobehavioural development. The mechanisms underlying either direct links or fetal programming in humans are only just starting to be understood.

However, there is enough evidence now to warrant active research into prevention, intervention, and support programs to reduce stress or anxiety during pregnancy and their effects on child outcome. These programs could include stress reduction instructions (e.g. [156]) and cognitive-behavioural treatments to reduce anxiety from early gestation on, or even before conception (e.g. [157]). Research on underlying mechanisms, on the effect of the timing, intensity and duration of anxiety/stress, and the effect of gender, can be carried out in parallel, and actually would be helped by successful intervention strategies.

It would also be of interest to use physiologically based measures of anxiety/stress and coping mechanisms during different gestational periods, and of regulation problems in the children after birth. The use of neuro-imaging techniques and of different marker tasks for cognitive development that can be reliably used from 7 to 8 m after birth [92,93], would enable one to link the prenatal stress research in humans with behavioural teratology research and cognitive developmental neuroscience.

There is evidence that up to 22% of the variance in several behavioural problems is linked with prenatal anxiety, stress, or depression. Mothers in the top 15% for symptoms of antenatal anxiety have a doubled risk for ADHD in their child at age 7. It is better to prevent these developmental problems from arising than trying to treat them once established. A program to reduce maternal stress or anxiety in pregnancy may help.

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