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Stress in pregnancy - Implications for fetal BDNF in amniotic fluid at birth

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ABSTRACT

Introduction: At the maternal-fetal interface in pregnancy, stress during pregnancy can lead to an increased vulnerability to later psychopathology of the fetus. Potential mediators of this association have scarcely been studied and may include early alterations of fetal brain-derived neurotrophic factor (BDNF). Amniotic fluid is of particular interest for effects on fetal endocrine alterations, as the assessment in amniotic fluid allows for measurements over a time integral. This study hypothesized that maternal psychometrics, socioeconomic status and glucocorticoids are related to BDNF levels in amniotic fluid at birth. The association of fetal BDNF with newborn anthropometrics was tested.

Methods: Women near term who underwent elective cesarean section and their newborns were investigated ($n = 37$). Maternal psychometrics, socioeconomic status and glucocorticoids (the sum of cortisol and cortisone) in amniotic fluid at birth were analyzed for an association with fetal BDNF in amniotic fluid at birth. Newborn anthropometrics were assessed by length, weight, head circumference and gestational age at birth.

Results: In bivariate analysis, maternal psychometrics and socioeconomic status were not related to fetal BDNF in amniotic fluid at birth. The sum of cortisol and cortisone related to increased fetal BDNF in amniotic fluid at birth ($r = 0.745$, $p < 0.001$). BDNF in amniotic fluid was associated negatively with fetal birth weight per gestational age ($r = -0.519$, $p < 0.001$), length per gestational age ($r = -0.374$, $p = 0.023$), head circumference per gestational age ($r = -0.508$, $p = 0.001$), but not with gestational age at birth. In multiple regression analysis, the sum of cortisol and cortisone ($p < 0.001$) and birth weight per gestational age ($p = 0.012$) related to higher fetal BDNF levels in amniotic fluid at birth ($R^2 = 0.740$, $p < 0.001$) when controlling for fetal sex and maternal age. Head circumference per gestational age predicted fetal BDNF with borderline significance ($p = 0.058$) when controlling for confounders.

Conclusion: Glucocorticoids in amniotic fluid were positively associated with high fetal BDNF at birth, which may be an adaptive fetal response. Maternal psychological variables and socioeconomic status did not link to fetal BDNF. Birth weight and head circumference per gestational age were inversely associated with fetal BDNF at birth, which may represent a compensatory upregulation of BDNF in fetuses with low anthropometrics. Longitudinal studies are needed to assess the role of stress during pregnancy on later offspring development. The

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analysis of additional fetal growth factors and inflammation upon maternal stress in further biomaterials such as the placenta is warranted, to understand mechanistic alterations of how maternal stress links to fetal development and an increased vulnerability for psychopathology.

1. Introduction

At the maternal-fetal interface, an adverse environment and maternal stress may lead to early fetal alterations, such as altered levels of brain-derived neurotrophic factor (BDNF) (Deuschle et al., 2018; Lamadé et al., 2021a; Szczesny et al., 2014). BDNF is a neurotrophin that regulates neuronal development, survival and function, synaptic plasticity and neurotransmitter release in the fetus and is associated with psychopathology in later stages of life (Cirulli et al., 2020; Colla et al., 2021; Manji et al., 2003; Stapel et al., 2022). Identifying early fetal alterations upon stress during pregnancy may help unravel how stress during pregnancy contributes to a greater vulnerability for later psychopathology of the offspring.

An unfavorable early life, including early-life unpredictability associates with neuropsychiatric symptoms in adulthood (Spadoni et al., 2022). Stress during pregnancy links to later psychopathology of the offspring, including a depression-like phenotype in mice (Basta-Kaim et al., 2014), which may be mediated by early altered immune function (Chen et al., 2022), reduced growth factors such as insulin-like growth factor-1 in the hippocampus and frontal cortex of the adult offspring rats (Szczesny et al., 2014). In humans, depression and stress during pregnancy associate with low weight for gestational age at birth (Dunkel Schetter and Tanner, 2012; Gilles et al., 2018), which is a predictor for later neurodevelopmental difficulties (Eixarch et al., 2008), a delay in motor and mental development of three-months old offspring and more fear (Huizink et al., 2003) and psychopathology in two-months old offspring, displaying anxiety (Davis et al., 2007). This may be mediated by alterations in epigenetics (Lund et al., 2021) and early altered growth, shown by a lower left hippocampal and amygdala volume (Demers et al., 2022; Moog et al., 2021). Psychiatric diseases such as anxiety and depression strongly associate with neuroendocrine markers such as brain-derived neurotrophic factor (BDNF) in human adults (Notaras and van den Buuse, 2020; Wang et al., 2022). Hence early fetal alterations, in particular early altered BDNF, may not only link to distorted development in early stages of life but also contribute to an early vulnerability for later psychopathology in humans. The particular effect of maternal stress on specific fetal alterations such as altered fetal BDNF may depend on the timing and type of fetal biofluid investigated.

Amniotic fluid stems primarily from the fetus, with the fetus swallowing amounts of amniotic fluid, and secreting molecules into amniotic fluid via the urine (Cho et al., 2007; Underwood et al., 2005). Therefore, the amniotic fluid can be used to investigate fetal molecules. Maternal BDNF does not pass the placenta into fetal circulation in mice or in humans (Dingsdale et al., 2021). Therefore, BDNF in the fetal circulation including amniotic fluid can be regarded as of fetal origin. BDNF levels are known to be affected by the mode of delivery, with the lowest variation in elective cesarean section (Flock et al., 2016). Hence, only women who underwent elective cesarean sections were included in this study. Amniotic fluid may be of particular interest for studies assessing the effects of maternal stress on fetal proteins, as it allows for an investigating of fetal proteins over a time integral. Amniotic fluid can be investigated by amniocentesis during the second trimester of pregnancy and by assessing amniotic fluid at birth. The present study focused on amniotic fluid at birth, which can be most easily assessed with elective cesarean section as the mode of delivery. The frequency of amniocentesis in mid-pregnancy is dropping due to the advent of cell-free DNA and other prenatal tests, while the frequency of cesarean sections at birth is increasing, with nearly a third of all births in 2021 in Germany having been cesarean sections (Statistisches Bundesamt, 2023). Hence, assessing amniotic fluid at birth rather than at mid-pregnancy may of particular clinical relevance.

There are a few studies in animals and even fewer in humans that have investigated the effect of stress during pregnancy on fetal BDNF with overall conflicting results. In rats, prenatal stress leads to a decrease of brain cell proliferation directly after birth, with reduced BDNF in whole brain tissue, in the olfactory bulbs as well as the in male offspring in the days after birth (Van den Hove et al., 2006) and a depression-like phenotype with reduced BDNF levels in whole brain tissue of 5-month--old offspring (Enayati et al., 2020). This demonstrates that prenatal stress and BDNF regulation as well as the psychopathology of the offspring are related. Upon maternal infection during pregnancy, rats showed an acute increase of fetal cortex BDNF levels (Gilmore et al., 2003), which underlines the possibility of an acute protective BDNF elevation. Similarly, in rodents exposed to an early enriched environment, an environmental challenge results in acute upregulation of hippocampal BDNF, rather than showing alterations in BDNF baseline values or hours after the challenge (Branchi et al., 2011). Therefore, acute stress in rodents may be associated with transient rather than persistent BDNF alterations. In humans, only a few studies have assessed the effect of maternal stress on fetal BDNF, with most studies focusing on cord blood BDNF. Maternal psychopathology (diagnosed depression and generalized anxiety disorder) associates with lower serum BDNF in cord blood at birth (Sonmez et al., 2019; Uguz et al., 2013). Another study found no difference in serum BDNF levels in cord blood at birth in mothers without psychiatric disorders compared to mothers with major depressive disorder or anxiety disorder (Akbaba et al., 2018). One study found higher levels of fetal BDNF in cord blood at term in mothers with maternal depressive symptoms and those with lower net income per person in the household (Lamadé et al., 2024). To sum up, some studies suggest that upon acute stressors BDNF is elevated, while others suggest that maternal psychopathology is related to lower fetal BDNF, with some finding no effects on fetal BDNF. Hence, results on cord blood BDNF are overall conflicting. However, these studies focused solely on BDNF in cord blood. Research examining the impact of stress on fetal BDNF levels in amniotic fluid at birth is sparse. Amniotic fluid, which additionally gives information about fetal molecules over a time integral, might be particularly suitable to assess the impact of maternal distress during pregnancy on overall fetal BDNF levels.

To our knowledge, only one study has investigated the impact of maternal stress as well as glucocorticoids on fetal BDNF in amniotic fluid in humans so far, but focused on amniotic fluid derived from amniocentesis in mid-pregnancy. They found early life stress to associate with higher fetal BDNF in mid-pregnancy and found no significant association between glucocorticoids in amniotic fluid on fetal BDNF in mid-pregnancy (Deuschle et al., 2018). The maternal response to stress may be altered during the course of pregnancy and postpartum, with startle modulation during anticipation in the postpartum period being decreased when compared to the last trimester (Hellgren et al., 2012) and the fetus undergoing significant changes from mid-pregnancy to term (Wu et al., 2024). To our knowledge, no study has investigated the impact of stress during pregnancy on fetal BDNF levels in amniotic fluid at birth so far. This study aims to investigate whether stress assessed by maternal psychometrics, socioeconomic status and glucocorticoids affects fetal BDNF measurements in amniotic fluid at birth. Besides depression and anxiety (Deuschle et al., 2018), childhood trauma, low prenatal attachment to the unborn (Liu et al., 2022; Şanlı and Aypar Akbağ, 2022), low social support and low socioeconomic status (Bedaso et al., 2021), relate to high maternal stress and are therefore investigated in this study to assess stress during pregnancy. Additionally, the sum of cortisol and cortisone in amniotic fluid represents the overall

glucocorticoid load in the amniotic fluid within the direct environment of the fetus (Beitins et al., 1973; Stirrat et al., 2018). Glucocorticoids rise throughout pregnancy (Castro-Quintas et al., 2024), which is essential for fetal maturation (Giannopoulos et al., 1982). Yet, excess glucocorticoids may be detrimental to the developing fetus (Cottrell et al., 2014). Prenatally administered glucocorticoids are associated with higher fetal BDNF values at birth (Rao et al., 2009), which may be a compensatory upregulation of fetal BDNF. To our knowledge, so far, no studies have investigated the association between endogenous glucocorticoids in amniotic fluid with fetal BDNF in amniotic fluid at birth. As birth represents a major stressor for both fetus and mother, birth may be window of particular interest for clinical research.

In fetuses small for gestational age during the second trimester of pregnancy, there is higher BDNF in amniotic fluid in the second trimester of pregnancy, when compared to fetuses with normal growth (Antonakopoulos et al., 2018). This shows that BDNF and fetal growth may be associated. This study therefore aims to investigate the association between fetal BDNF and newborn anthropometrics.

This study hypothesizes that maternal psychometrics, socioeconomic status and glucocorticoids in amniotic fluid are related to BDNF levels in amniotic fluid at birth. The association of fetal BDNF with newborn anthropometrics was tested. Maternal psychometrics included the evaluation of depressive symptoms, distress, experienced stress over the past month, anxiety, childhood trauma, prenatal attachment to the offspring and maternal social support. Glucocorticoids were assessed by measuring cortisol and cortisone in amniotic fluid. Additionally, this study assesses the association of BDNF in amniotic fluid with newborn anthropometrics, as assessed by birth weight, length and head circumference at birth (see Fig. 1).

2. Material and methods

2.1. Study population

This prospective study analyzed women pregnant in their third trimester who underwent elective cesarean section at the Marienhaus Klinikum Hetzelstift in Neustadt an der Weinstraße in Germany between 2018 and 2021 and their newborns at birth. Inclusion criteria ability to consent, maternal age ≥18 years and under 51 years of age and ability to speak German. Women with a drug- or alcohol addiction, a substitution therapy or with severe infections, such as hepatitis and HIV, or amniotic fluid samples contaminated with blood were excluded from the study. All women included in the study gave informed written consent. Initially, 49 women were included in the study, 6 were then excluded due to spontaneous delivery prior to planned elective cesarean section, 1 woman due to withdrawal of consent, 5 due to insufficiencies of collected biomaterial for measuring BDNF in amniotic fluid, so that 37 women were analyzed in this study.

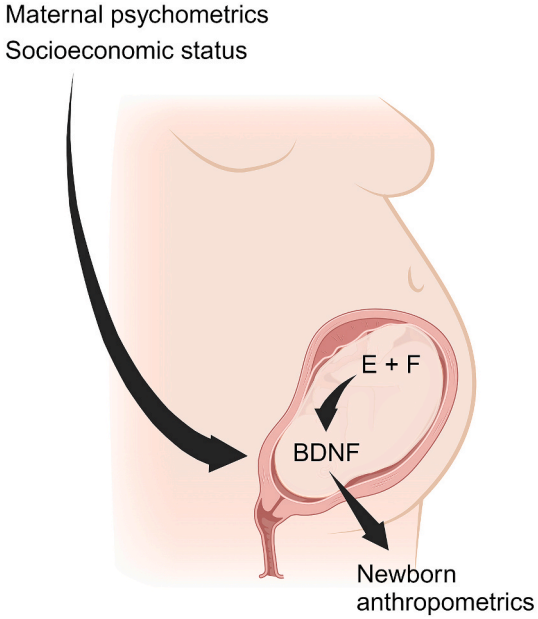

Fig. 1. Study design. This study tested the association of maternal psychometrics and socioeconomic status as well as the glucocorticoids cortisol (F) and cortisone (E) with fetal brain-derived neurotrophic factor (BDNF) in amniotic fluid at birth. The link of fetal BDNF at birth with newborn anthropometrics was tested.

Women included in the study were assessed for stress one to seven days prior to elective cesarean section by measuring maternal psychometrics, including maternal depressive symptoms, distress, experienced stress over the past month, anxiety, childhood trauma, prenatal attachment to the offspring, maternal social support using standardized psychometric questionnaires, and socioeconomic status, one to seven days prior to elective cesarean section. Amniotic fluid was collected at cesarean section for measuring fetal BDNF and glucocorticoids (cortisol and cortisone), and newborn anthropometrics at birth were recorded including length, weight, head circumference, and gestational age. Length, weight and head circumference per gestational age were calculated. This study was carried out in compliance with the Declaration of Helsinki and approved by the Ethics Committee of Medical Faculty Mannheim, University of Heidelberg.

Description of study participants are displayed in Table 1.

2.2. Assessment of psychometric data and socioeconomic status prior to elective cesarean section

Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EDPS). Measures of maternal psychometrics furthermore included the prenatal distress questionnaire (PDQ), perceived stress scale (PSS), childhood trauma questionnaire (CTQ), prenatal attachment to the offspring (PAI) and maternal social support (F-Sozu) as a resilience factor. The prenatal distress questionnaire (PDQ) investigated pregnancy-specific worries and concerns. The perceived stress scale (PSS) assessed the level of experienced stress over the past month and the total score of the childhood trauma questionnaire (CTQ) investigated maternal preconceptional trauma in childhood and adolescence. The prenatal attachment to the offspring (PAI) assessed the maternal attachment to the offspring over the past month and maternal social support (F-Sozu) measured the present perceived or anticipated social support by the mother. The Spielberger State Anxiety Inventory Scale (STAI-S) was used to assess maternal state anxiety, which is regarded as a more transient anxiety. The Spielberger Trait Anxiety Inventory Scale (STAI-T) measured maternal trait anxiety, which measured the more stable anxiety trait of the woman in general.

Different proxies for socioeconomic status of the household were used, including net income per person in the household as well as the average number of people living per room of the household as has been published before (Galobardes et al., 2006).

2.3. Assessments at elective cesarean section

Newborn anthropometrics were assessed at birth by newborn length, weight, head circumference and gestational age at birth, as stated in the maternity records. At birth, amniotic fluid was collected and frozen at −20 °C (<24 h), then stored at −80 °C until further analysis. BDNF in amniotic fluid was analyzed using a BDNF-ELISA as detailed elsewhere (Buchmann et al., 2013; Deuschle et al., 2018). Due to low BDNF concentration in amniotic fluid, samples were diluted 1:1 with the "block and sample buffer". Free cortisol (F) and free cortisone (E) in amniotic fluid were measured using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Sanchez-Guijo et al., 2014).

Table 1
Description of study participants.

	Min	Max	Mean	Standard Deviation
Maternal variables				
Age in years	23	40	31.59	4.56
Maternal pre-pregnancy BMI in kg/m^2	19.10	55.78	29.39	8.56
Maternal depressive symptoms (EDPS)	0	16	7.76	4.97
Maternal distress (PDQ)	1	30	11.27	6.70
Maternal experienced stress over the past month (PSS)	5	38	22.27	8.98
Maternal trait anxiety (STAI-T)	21	53	37.22	7.91
Maternal state anxiety (STAI-S)	20	65	40.59	10.61
maternal childhood trauma (CTQ)	25	74	34.81	11.00
prenatal attachment to the offspring (PAI)	22	58	39.76	9.79
maternal social support (F-Sozu)	18	56	49.32	7.04
Quantity of rooms lived in	2	9	5.39	1.77
People/room in the household	0.29	1.25	0.68	0.25
Net income in the household (21 categories)	3	20	14.25	3.66
Net income per person in the household (21 categories, from low to high income, per person)	1	9	4.77	2.15
Measurements in amniotic fluid				
BDNF amniotic fluid in pg/ml	0.49	400.28	104.07	106.97
Cortisone (E) in amniotic fluid ng/ml	4.72	26.05	15.14	4.74
Cortisol (F) in amniotic fluid ng/ml	12.90	94.76	31.64	20.89
E + F in amniotic fluid ng/ml	20.93	116.92	46.78	24.63
Newborn anthropometrics				
Length at birth in cm	47.00	61.00	53.19	2.98
Weight at birth in grams	2620.00	4270.00	3513.78	483.28
Head circumference at birth in cm	33.0	38.0	35.50	1.58
Gestational age in weeks	37.14	41.00	38.80	0.67
Length/gestational age	1.21	1.54	1.37	0.07
Weight/gestational age	67.42	111.11	90.50	11.94
Head circumference/gestational age	0.85	0.98	0.92	0.04

Note: BDNF: Brain-derived neurotrophic factor in amniotic fluid, E: cortisone and F: cortisol in amniotic fluid, BMI: Body-Mass Index, EDPS: Edinburgh postnatal depression inventory, PDQ: prenatal distress questionnaire, PSS: perceived stress scale, STAI-S/STAI-T: Spielberger State and Trait Anxiety Inventory, CTQ: childhood trauma questionnaire, PAI: prenatal attachment inventory, F-Sozu: maternal social support.

2.4. Statistical analysis

The Shapiro-Wilk test was used for testing for the distribution of normality in metric variables. In bivariate analyses, the association between maternal psychometrics, socioeconomic status, and glucocorticoids in amniotic fluid with fetal BDNF levels in amniotic fluid was tested. Spearman's and Pearson's regression analyses were used where appropriate.

There were no BDNF outliers ($\geq$ or $\leq$ 3 SD). As BDNF in amniotic fluid was not normally distributed, Spearman's regression analysis was used for bivariate analysis where appropriate. As the newborn anthropometrics length/gestational age, weight/gestational age and head circumference/gestational age were normally distributed, the Person's regression analysis was used to test for intercorrelation of these variables. Maternal depressive symptoms, maternal childhood trauma, prenatal attachment to the offspring, maternal social support, cortisol, the sum of cortisol and cortisone, head circumference, and gestational age were not normally distributed variables. Maternal distress, maternal experienced stress over the past month, maternal state and trait anxiety, cortisone, length and birth weight of the newborn at birth were normally distributed variables. The variables assessing the socioeconomic status, net income per person in the household and the average number of people living per room of the household, were ordinal variables.

Multiple regression analyses were calculated to examine the contribution of the sum of cortisol and cortisone (E + F) and newborn anthropometrics in predicting BDNF in amniotic fluid while controlling for the confounders fetal sex and maternal age. The selection of covariates was theory-driven. As the newborn anthropometrics weight/gestational age, length/gestational age and head circumference/gestational age at birth were strongly intercorrelated, three separate regression analyses were calculated, including one of the three newborn anthropometrics in each model (see Tables 2–4).

A power analysis was calculated using G-power, with a power of 0.90, $\alpha = 0.05$, $R^2 = 0.708$, an effect size $f^2 = 2.43$ and four predictors. A sample size of n = 8 was calculated. All statistical analyses were calculated using IBM SPSS, Version 29. The significance level was set to $p < 0.05$.

3. Results

Women near term with an average age of 31.6 years and their newborns at birth were analyzed in this study (n = 37 mother-newborn dyads). The newborns were on average 53.19 cm long, with 3513.78 g and a head circumference of 35.50 cm at birth (for descriptive statistics see Table 1).

The different measures for maternal psychometric data correlated with each other. Maternal depressive symptoms significantly correlated with state ($r = 0.498$, $p = 0.002$) and trait ($r = 0.628$, $p < 0.001$) anxiety. Maternal distress correlated positively with maternal trait ($r = 0.377$, $p = 0.022$) anxiety. Maternal state anxiety correlated positively with maternal trait anxiety ($r = 0.752$, $p < 0.001$). For the other intercorrelations, see Supplemental Table 1.

3.1. Bivariate analyses

BDNF in amniotic fluid did not associate with maternal depressive symptoms ($r = 0.012$, $p = 0.943$), prenatal distress ($r = 0.077$, $p = 0.652$), maternal experienced stress over the past month ($r = 0.002$, $p = 0.990$), state anxiety ($r = -0.068$, $p = 0.690$), trait anxiety ($r = -0.182$, $p = 0.280$), maternal childhood trauma ($r = 0.106$, $p = 0.539$), prenatal attachment to the offspring ($r = -0.068$, $p = 0.688$) nor maternal social support ($r = 0.179$, $p = 0.290$).

Regarding socioeconomic status and fetal BDNF at birth, neither net income per person in the household ($r = -0.037$, $p = 0.834$) nor the average number of people living per room of the household ($r = 0.037$, $p = 0.827$) were associated with fetal BDNF in amniotic fluid at birth.

BDNF in amniotic fluid correlated positively with cortisol (F) ($r = 0.744$, $p < 0.001$) and cortisone (E) ($r = 0.630$, $p < 0.001$) as well as the sum of cortisol and cortisone (E + F) ($r = 0.745$, $p < 0.001$) in amniotic fluid (see Fig. 2).

BDNF in amniotic fluid correlated negatively with fetal newborn anthropometrics at birth, including weight ($r = -0.506$, $p = 0.001$), length ($r = -0.400$, $p = 0.014$), head circumference ($r = -0.564$, $p <$

Table 2
Multiple regression analysis for prediction of brain-derived neurotrophic factor (BDNF) in amniotic fluid, including weight/gestational age at birth of the newborn.

Covariates	Standardized coefficient Beta	p-value
Fetal sex	−0.065	0.514
Maternal age	0.032	0.741
E + F	0.775	**< 0.001**
Weight/gestational age	−0.256	**0.012**

Note: Abbrevations: E + F: sum of cortisol and cortisone. Bold represents significant results.

Table 3
Multiple regression analysis for prediction of brain-derived neurotrophic factor (BDNF) in amniotic fluid, including length/gestational age at birth of the newborn.

Covariates	Standardized coefficient Beta	p-value
Fetal sex	−0.046	0.666
Maternal age	0.021	0.842
E + F	0.805	< **0.001**
Length/gestational age	−0.151	0.144

Note: E + F: sum of cortisol and cortisone. Bold represents significant results.

Table 4
Multiple regression analysis for prediction of brain-derived neurotrophic factor (BDNF) in amniotic fluid, including head circumference/gestational age at birth of the newborn.

Covariates	Standardized coefficient Beta	p-value
Fetal sex	−0.060	0.568
Maternal age	0.030	0.765
E + F	0.758	< **0.001**
Head circumference/gestational age	−0.207	0.058

Note: E + F: sum of cortisol and cortisone. Bold represents significant results. Results with borderline significance $p < 0.1$ are underlined.

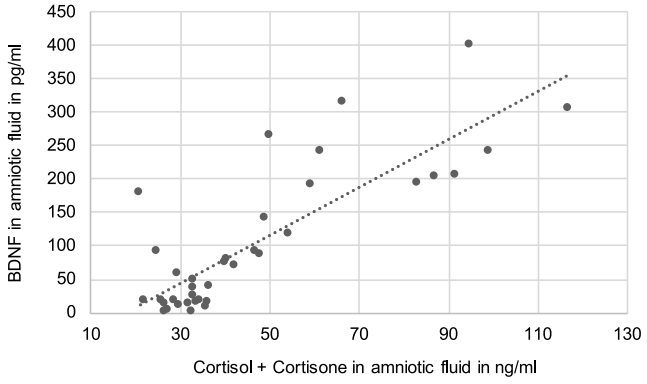

Fig. 2. The sum of glucocorticoids and brain-derived neurotrophic factor (BDNF) in amniotic fluid. The positive correlation between the sum of cortisol and cortisone in amniotic fluid and BDNF in amniotic fluid is shown ($r = 0.745$, $p < 0.001$).

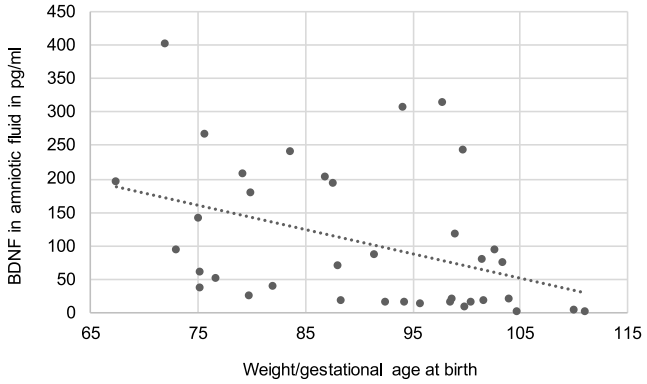

Fig. 3. Brain-derived neurotrophic factor (BDNF) in amniotic fluid and weight per gestational age of the newborn. The negative correlation between BDNF and weight per gestational age of the newborn at birth is shown ($r = -0.519$, $p < 0.001$).

0.001) as well as weight/gestational age ($r = -0.519$, $p < 0.001$) (see Fig. 3), length/gestational age ($r = -0.374$, $p = 0.023$), head circumference/gestational age at birth ($r = -0.508$, $p = 0.001$) but not with gestational age at birth ($r = -0.172$, $p = 0.308$).

As weight/gestational age strongly intercorrelated with length/gestational age at birth ($r = 0.724$, $p < 0.001$) and head circumference/gestational age ($r = 0.708$, $p < 0.001$), and head circumference/gestational age strongly correlated with length/gestational age at birth ($r = 0.634$, $p < 0.001$) three separate regression analyses were run, including each of the newborn anthropometrics separately (see Tables 2–4).

3.2. Multiple regression analyses

We conducted multiple regression analyses to examine the contribution of E + F and newborn anthropometrics in predicting BDNF while controlling for confounders.

In multiple regression analysis including fetal sex, maternal age, the sum of cortisol and cortisone and weight/gestational age at birth as covariates, a higher sum of cortisol and cortisone (E + F) and lower weight/gestational age at birth predicted higher BDNF in amniotic fluid ($R^2 = 0.740$, adjusted $R^2 = 0.708$, $p < 0.001$), see Table 2.

In multiple regression analysis including length/gestational age as a covariate, higher E + F but not length/gestational age stayed predicted higher BDNF in amniotic fluid when controlling for fetal sex and maternal age ($R^2 = 0.703$, adjusted $R^2 = 0.665$, $p < 0.001$), see Table 3.

In multiple regression analysis, including head circumference/gestational age as a covariate, higher E + F and lower head circumference/gestational age with borderline significance, predicted higher BDNF in amniotic fluid when controlling for fetal sex and maternal age ($R^2 = 0.716$, adjusted $R^2 = 0.681$, $p < 0.001$), see Table 4.

4. Discussion

To our knowledge, this is the first study to investigate the effect of stress near term, including maternal psychometrics, socioeconomic status, and glucocorticoids in amniotic fluid, on fetal BDNF in amniotic fluid at birth. The association of fetal BDNF with newborn anthropometrics was tested. This study demonstrates the role of higher glucocorticoids in amniotic fluid and lower newborn anthropometrics in predicting higher fetal BDNF. Maternal psychometrics or socioeconomic status were not associated with fetal BDNF in amniotic fluid.

4.1. Maternal psychometrics, socioeconomic status and fetal BDNF in amniotic fluid

This study found no correlation between maternal psychometrics or socioeconomic status with fetal BDNF in amniotic fluid. There are a few studies in humans that have examined the role of maternal stress during pregnancy on fetal BDNF, but they have focused mainly on cord blood with overall conflicting results (Akbaba et al., 2018; Dingsdale et al., 2021; Lamadé et al., 2024; Sonmez et al., 2019; Uguz et al., 2013). One study has investigated fetal BDNF in mid-pregnancy and found a positive association between maternal early life stress and higher BDNF in amniotic fluid (Deuschle et al., 2018). However, they have focused on amniotic fluid in mid-pregnancy, where small effects of stress on BDNF values over time in the absence of a major stressor such as at birth, may be more pronounced. In rodents, there is some evidence that BDNF upregulation upon acute stress is an adaptive mechanism in response to acute environmental stress in pregnancy upon infection (Gilmore et al., 2003) or challenge to a new environment, with no difference in baseline BDNF levels or at 3 h after the challenge in animals (Branchi et al., 2011). Hence, BDNF levels in cord blood may reflect an acute up- or downregulation, but BDNF in amniotic fluid at birth represents a more stable measurement over time where acute and less pronounced alterations of BDNF are not represented well, which may explain the negative findings regarding maternal psychometrics and fetal BDNF in our study.

The fetus is capable to protect itself from high levels of maternal stress and cortisol during pregnancy by acute up- or downregulation of proteins such as fetoplacental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (La Marca-Ghaemmaghami et al., 2015; Lamadé et al., 2021b) and possibly BDNF, as shown in animal models and in cord blood (Branchi et al., 2011; Lamadé et al., 2024). Maternal psychometrics and socioeconomic status do not seem to alter BDNF values over a time integral as measured in amniotic fluid. The stress of birth itself, with increases in cortisol near term and under cesarean section, seems to exceed the effect of maternal psychometrics upon fetal BDNF in amniotic fluid at birth.

This study took place during the COVID-19 pandemic, which saw significant changes, including overall higher levels of stress, depression, and anxiety during pregnancy (Lebel et al., 2020). This is reflected in higher mean values of maternal depressive symptoms, anxiety and stress scores and lower socioeconomic status in participants from this study when compared to another pregnancy cohort from Germany from before the pandemic (Deuschle et al., 2018). Hence, effects of elevated maternal psychometrics may be even more pronounced in our cohort. This underlines that maternal stress as measured by psychometrics, even when pronounced, does not link to altered BDNF levels over time as measured in amniotic fluid at birth.

There have been contradicting results regarding the possibility that a fraction of the BDNF measured within the fetal circulation may be of maternal origin. An older study showed that injection of BDNF into maternal circulation associated with a dose-dependent elevation of fetal BDNF, which may suggest a transfer of BDNF from the mother to the offspring (Kodomari et al., 2009). A more recent study found no evidence of such a transfer via the placenta to the offspring (Dingsdale et al., 2021). Furthermore, most studies have found merely a moderate correlation between maternal BDNF and fetal BDNF (Dingsdale et al., 2021; Flock et al., 2016). Hence, amniotic fluid BDNF can be regarded as of fetal origin.

4.2. Glucocorticoids and fetal BDNF in amniotic fluid

To our knowledge, this study investigated for the first time the role of endogenous glucocorticoids in amniotic fluid on fetal BDNF in amniotic fluid at birth. We found glucocorticoids to be positively related to higher fetal BDNF at birth. Interestingly, the only study that has investigated the role of glucocorticoids and BDNF in amniotic fluid so far, found no association between the two (Deuschle et al., 2018). However, they investigated the second trimester of pregnancy. Cortisol increases throughout pregnancy (Giannopoulos et al., 1982), which is essential for fetal maturation. Therefore, the positive association that we found at birth may be a physiological response of the fetus at birth in response to increasing glucocorticoids and birth. Fetal levels of cortisol in cord blood as well as placentas at birth are even higher in spontaneous births when compared to cesarean sections (Huebner et al., 2021; Jin et al., 2023). Hence the impact of the surgery in cesarean sections on cortisol levels is lower than the impact of spontaneous birth on cortisol. Investigating women with vaginal deliveries may have led to an even greater association of cortisol and BDNF.

Similarly to results found in this study, external administration of prenatal glucocorticoids associates with increased fetal serum BDNF at birth in literature, with higher overall doses of prenatal glucocorticoids leading to higher fetal BDNF values (Rao et al., 2009). Animal studies demonstrated that particularly those animals who have been brought up in a stimulating social environment, show an elevation of BDNF levels in response to a stressor (Branchi et al., 2011). Values of cortisol and cortisone in amniotic fluid are much higher at birth when compared to values in amniotic fluid in mid-pregnancy (Deuschle et al., 2018). Birth represents a major stressor for both mother and child. Hence, the increased BDNF found in amniotic fluid may represent a healthy response to an increased glucocorticoid burden at birth.

4.3. Newborn anthropometrics

This study found BDNF in amniotic fluid to correlate negatively with fetal newborn anthropometrics at birth, particularly weight per gestational age and head circumference per gestational age. Although BDNF is mainly known as a neurotrophin, some studies have shown an inverse relationship between anthropometrics and fetal BDNF in amniotic fluid in mid-pregnancy and in cord blood at birth (Antonakopoulos et al., 2018; Wang and Ye, 2008). Prenatal stress itself is associated with decreased newborn anthropometrics (Gilles et al., 2018), which may increase the risk for neurodevelopmental deficits (Eixarch et al., 2008). The brain-sparing effect, enabling sufficient neurodevelopment even in cases of stress (Malamitsi-Puchner et al., 2006), may explain the inverse relationship found in this study. Hence, higher levels of BDNF may be a compensatory upregulation in fetuses with low anthropometrics.

4.4. Limitations

Amniotic fluid samples macroscopically contaminated with blood represented an exclusion criterion in this study. However, we did not rule out the microscopic contamination of the samples with blood, which may increase BDNF values. Amniotic fluid may be of particular interest for studies assessing the effects of maternal stress on fetal proteins, as it allows for an investigating of proteins over a time integral. We did not investigate women with other modes of delivery (spontaneous birth or emergency cesarean sections). As the neuronal and behavioral development of the offspring may be different in vaginal delivery compared to cesarean sections (Cabré et al., 2022), the pre-selection of elective cesarean sections as the mode of delivery may have resulted in a bias and may limit the generalizability of the findings. The effect of maternal stress on specific fetal alterations may depend on the timing and type of fetal biofluid or tissue investigated. Further studies investigating the effect of stress during pregnancy on early fetal alterations including analysis of further growth factors and inflammation in other biomaterials such as placental tissue are warranted.

5. Conclusions

Taken together, the findings of this study show that higher glucocorticoids in amniotic fluid predict higher fetal BDNF at birth after controlling for confounders. These findings demonstrate for the first time that endogenous glucocorticoids in amniotic fluid associate with higher fetal BDNF at birth, which may be an adaptive response of the fetus. This expands on previous studies that had shown the effect of externally administered glucocorticoids on higher fetal BDNF at birth. Newborn anthropometrics, in particular lower birth weight and head circumference per gestational age at birth associated with higher fetal BDNF at birth. This may be a compensatory upregulation of fetal BDNF in fetuses with smaller anthropometrics. To unravel mechanistic alterations of how maternal stress links to fetal development, the analysis of further growth factors as well as fetal inflammatory response upon stress in further biomaterials such as the placenta is needed. As BDNF is associated with psychopathology, further longitudinal studies are needed to explore the impact of early BDNF alterations on subsequent developmental outcomes.

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CRediT authorship contribution statement

Eva Kathrin Lamadé: Writing – original draft, Visualization, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bruno Pedraz-Petrozzi:** Writing – review & editing, Visualization, Formal analysis. **Ole Lindner:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Pascal Meininger:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Antonia Pisters:** Writing – review & editing, Methodology, Formal analysis. **Maria Gilles:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Stephanie H. Witt:** Writing – review & editing, Resources, Methodology, Conceptualization. **Marcella Rietschel:** Writing – review & editing, Methodology, Conceptualization. **Helene Dukal:** Writing – review & editing, Resources, Methodology. **Fabian Schunk:** Writing – review & editing, Visualization, Methodology. **Michaela Coenen:** Writing – review & editing, Visualization, Resources, Methodology. **Stefan A. Wudy:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Conceptualization. **Rainer Hellweg:** Validation, Resources, Methodology, Investigation. **Michael Deuschle:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

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Data availability

Data will be made available upon reasonable request and upon permission of our ethical commitee.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100658.

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