

# Role of BDNF in the development of gestational complications: A scoping review

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**Abstract.** Brain-derived neurotrophic factor (BDNF) is a highly conserved member of the neurotrophin family, traditionally recognized for its essential role in neuronal survival and synaptic plasticity within the nervous system. Emerging evidence indicates that its biological functions extend far beyond neural tissues, highlighting its critical role in reproductive physiology and maternal-placental-foetal signalling networks. The present scoping review examines the molecular mechanisms underlying the role of BDNF during gestation and examines its dynamic changes in normal vs. pathological pregnancies. Under physiological conditions, maternal serum BDNF concentrations follow a predictable decline through the trimesters, which is influenced by maternal body mass index, gestational haemodilution and hormonal fluctuations. Conversely, compromised BDNF bioavailability is closely

linked to a triad of major obstetric disorders: Preeclampsia (PE), gestational diabetes mellitus (GDM), and foetal growth restriction (FGR). In PE, local neurotrophic deficiency is associated with defective trophoblast invasion, insufficient spiral artery remodelling, and an anti-angiogenic state marked by elevated soluble fms-like tyrosine kinase-1 levels. In GDM, chronic maternal hyperglycaemia directly suppresses systemic and neonatal BDNF production, accelerating metabolic decay. In FGR, depleted umbilical cord blood BDNF concentrations indicate systemic growth failure and exhausted foetal reserves, whereas elevated second-trimester amniotic fluid BDNF may serve as an endogenous adaptive 'brain-sparing' response to hypoxic-ischemic stress. Furthermore, premature termination of intrauterine development in preterm birth deprives the immature neonatal brain of essential neurotrophic support, increasing susceptibility to long-term neurodevelopmental impairments. Measuring BDNF concentrations in various biological sample sources provides a promising predictive tool for monitoring obstetric risk and understanding the long-term neurodevelopmental programming of the offspring.

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**Abbreviations:** AF-BDNF, amniotic fluid brain-derived neurotrophic factor; AGA, appropriate for gestational age; ASD, autism spectrum disorder; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BSID, Bayley scales of infant development; DBS, dried blood spots; eNOS, endothelial nitric oxide synthase; FGR, foetal growth restriction; GDM, gestational diabetes mellitus; HIE, hypoxic-ischemic encephalopathy; IMGD, infants of mothers with gestational diabetes; IUGR, intrauterine growth restriction; LGA, large for gestational age; MCI, mild cognitive impairment; MMP-9, matrix metalloproteinase-9; MSAF, meconium-stained amniotic fluid; NGF, nerve growth factor; NO, nitric oxide; NT-3, neurotrophin-3; PE, preeclampsia; PlGF, placental growth factor; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; PW, pregnant women; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age; SMD, standardized mean difference; TrkB, tropomyosin receptor kinase B; VDD, vitamin D deficiency; VDR, vitamin D receptor; VEGF, vascular endothelial growth factor

**Key words:** brain-derived neurotrophic factor, gestational complications, preeclampsia, gestational diabetes mellitus, foetal growth restriction, placental insufficiency, biomarker

## Introduction

Brain-derived neurotrophic factor (BDNF) is a highly conserved member of the neurotrophin family and a key regulator of mammalian development. Traditionally, BDNF has been recognised for its essential role in neuronal survival, differentiation, synaptic plasticity and the maintenance of neural networks within both the central and peripheral nervous systems. However, increasing evidence indicates that its biological functions extend far beyond neural tissues, highlighting its critical role in reproductive physiology and foetal development. The developmental origins of health and disease (DOHaD) paradigm emphasises the critical role of the intra-uterine environment in long-term health outcomes throughout lifespan. Within this framework, BDNF has emerged as a key molecular mediator linking maternal, placental and foetal physiology. In addition to its well-established neurotrophic functions, BDNF is widely expressed in reproductive tissues, including the uterus and placenta, where it participates in implantation, placental morphogenesis, angiogenesis and foetal neurodevelopment (1,2). Consequently, BDNF is increasingly recognised as a central component of the maternal-placental-foetal signalling network involved in developmental programming.

First discovered in 1982 and subsequently isolated in 1987, BDNF belongs to the neurotrophin family, which also comprises nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) (3). The biological versatility of BDNF is determined by its complex synthesis, post-translational processing and interactions with specific receptors. In a landmark experimental study, Kawamura *et al* (4) were the first to demonstrate that both BDNF and its high-affinity receptor, tropomyosin receptor kinase B (TrkB), are expressed in blastocyst trophoblast cells. The activation of the BDNF-TrkB signalling pathway promotes trophoblast invasion through phosphatidylinositol 3-kinase-dependent mechanisms and enhances trophoblast survival, thereby implicating BDNF in the earliest stages of implantation and placental development (4).

Historically, BDNF was recognised for its crucial role in the central nervous system, where it regulates neuronal differentiation, synaptic plasticity and cell survival, and has more recently emerged as a key molecular transducer of the intrauterine environment (5,6). The clinical study by Antonakopoulos *et al* (7) confirmed that second-trimester BDNF levels in amniotic fluid serve as a predictor of foetal growth restriction. The identification and quantitative characterisation of BDNF in second-trimester amniotic fluid have established a new avenue for investigating foetal neurodevelopment and pregnancy-related pathophysiology. The disruption of this neurotrophic regulatory network, resulting from genetic factors, maternal mental health conditions, or environmental toxicants, has been implicated in the development of adverse pregnancy outcomes and persistent neurodevelopmental disturbances in offspring (8).

BDNF is currently recognized as a systemic factor with profound implications in reproductive physiology and obstetric outcomes. The findings reported in the study by D'Souza *et al* (9), indicate that reduced maternal BDNF concentrations are linked to abnormalities in placental development and function; this suggests that BDNF may serve as a valuable biomarker for the identification of pregnancy complications (10,11). These complications, including preeclampsia (PE), gestational diabetes mellitus (GDM) and foetal growth restriction (FGR), represent a triad of gestational disorders often linked to placental insufficiency and metabolic stress. When BDNF bioavailability is compromised, the compensatory mechanisms of the placenta may fail, leading to endothelial dysfunction, impaired glucose homeostasis and suboptimal foetal growth (12). Mapping the existing literature is therefore essential to identify key biomarkers, understand the causal associations between neurotrophic deficit and obstetric pathology, and highlight the gaps in current clinical research that prevent the widespread adoption of BDNF as a predictive tool for maternal-foetal health.

The primary objectives of the present study were to provide a high-level scoping review of the molecular mechanisms governing BDNF action in gestation, delineate its fluctuations in normal vs. pathological pregnancies, and assess its utility as a biomarker. By synthesizing evidence from clinical trials, animal models and longitudinal cohort studies, the present scoping review aimed to provide a nuanced understanding of how neurotrophic support at the maternal-foetal interface dictates the trajectory of human life.

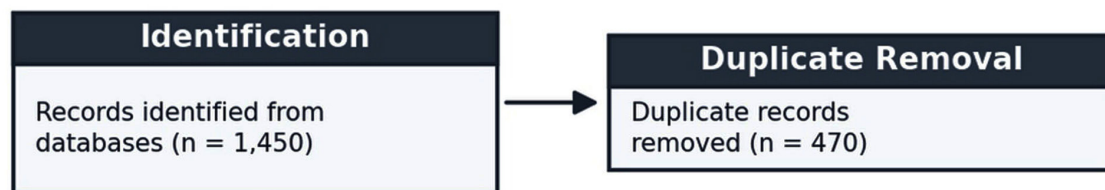
## Data and methods

The synthesis of evidence presented in the present scoping review follows a meticulous scoping review framework, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) recommendations, designed to map the breadth and depth of research regarding BDNF and gestational complications. Given the multidisciplinary nature of the available evidence, encompassing basic science, clinical obstetrics and psychiatric research, this approach provides an effective strategy for mapping the existing knowledge base. The scoping review methodology was implemented to ensure transparency in study selection, consistency in data extraction, and comprehensive coverage of the literature.

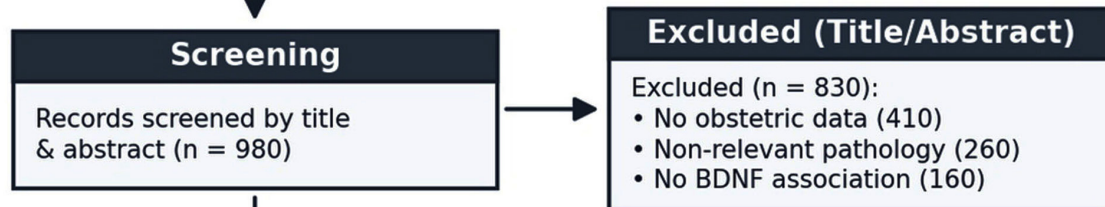
*Search strategy and evidence identification.* A comprehensive literature search was performed using the PubMed, Scopus and Web of Science databases, including studies published from January, 2010 to January, 2026. These databases were selected to capture a broad spectrum of evidence, ranging from fundamental molecular and signalling studies to translational research, clinical investigations, and population-based epidemiological cohorts. To maximise the retrieval of relevant literature and minimise the risk of publication omission, a backward citation-tracking (snowballing) strategy was additionally applied through manual screening of the reference lists of key review articles and original studies identified during the search process. Search strings were constructed using Boolean operators to combine terms related to neurotrophins, pregnancy and specific pathologies. The search strategy incorporated combinations of free-text terms and Medical Subject Headings (MeSH) reflecting obstetric pathology and the neurotrophic protein BDNF, including, but not limited to: 'Brain-Derived Neurotrophic Factor', 'BDNF', 'Pregnancy', 'Gestational', 'Maternal-Foetal Interface', 'Preeclampsia', 'Hypertensive Disorders of Pregnancy', 'Gestational Diabetes Mellitus', 'GDM', 'Insulin Resistance', 'Foetal Growth Restriction', 'FGR', 'Small for Gestational Age', 'Perinatal Depression', 'Neurodevelopmental Outcomes'. Logical operators AND/OR were used to construct the search queries, including combined queries of the following type: ('Pregnancy' OR 'Gestational' OR 'Maternal-Foetal Interface' OR 'Preeclampsia' OR 'Hypertensive Disorders of Pregnancy' OR 'Gestational Diabetes Mellitus' OR 'GDM' OR 'Insulin Resistance' OR 'Foetal Growth Restriction' OR 'FGR' OR 'Small for Gestational Age' OR 'Perinatal Depression' OR 'Neurodevelopmental Outcomes') AND 'BDNF'.

*Study selection and quantitative results.* The initial search retrieved 1,450 records. Following duplicate removal, 980 articles remained for screening. During title and abstract screening, 830 records were excluded as irrelevant due to the absence of obstetric data, focus on non-relevant pathologies, or lack of association with the neurotrophic protein BDNF. A total of 150 articles underwent full-text assessment. After applying predefined inclusion and exclusion criteria, 110 peer-reviewed publications were retained for the final analysis. These included: original clinical studies; reviews addressing the obstetrics-BDNF axis; studies examining psychiatric

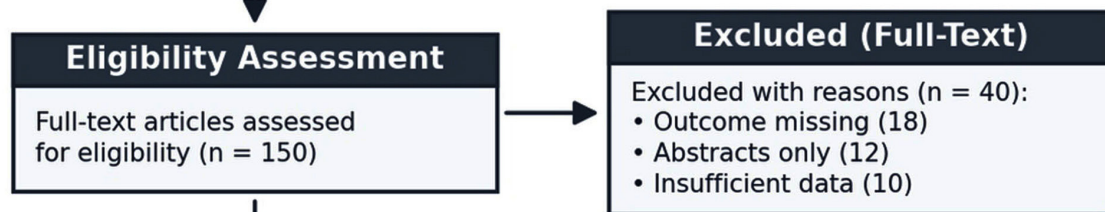
## IDENTIFICATION



## SCREENING



## ELIGIBILITY



## INCLUDED

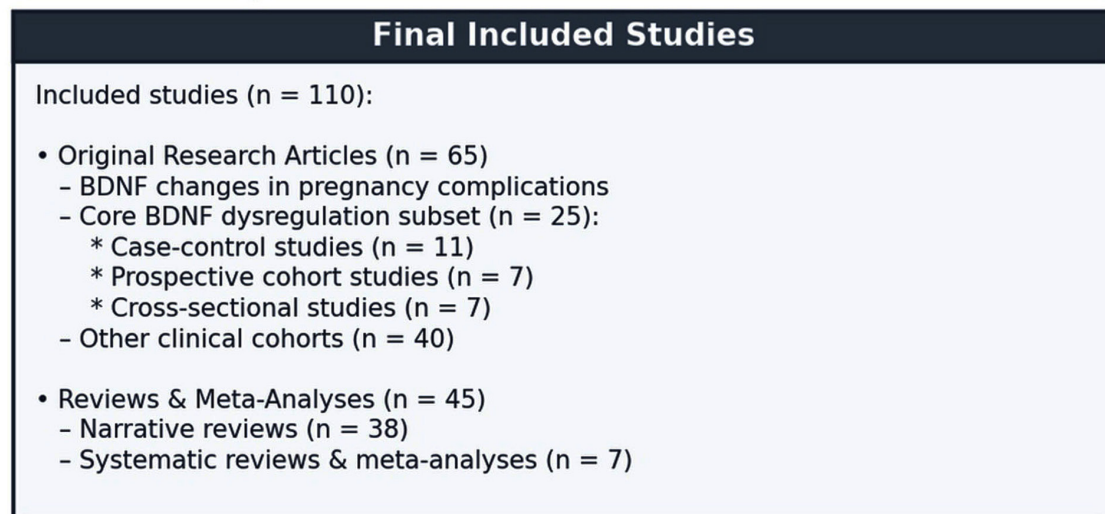


Figure 1. PRISMA-ScR flow diagram of the literature search and study selection process.

complications during pregnancy in relation to BDNF; research involving cohorts of pregnancies complicated by growth restriction; publications exploring associations between BDNF and metabolic disorders in pregnancy. A simplified PRISMA-ScR flow diagram illustrating the study selection process is presented in Fig. 1.

*Inclusion and exclusion criteria.* Eligible studies comprised peer-reviewed publications in English or Russian, including original clinical research (cohort studies, case-control studies and case series), as well as narrative and systematic reviews and clinical guidelines that examined the association between BDNF and physiological changes during pregnancy, obstetric

complications, or maternal mental health. Sources were excluded if they lacked peer review (except official international clinical guidelines), including conference abstracts, non-reviewed preprints, and publications that did not report obstetric-related data.

**Data extraction and synthesis of results.** Study selection was conducted in a multi-stage process, beginning with the screening of titles and abstracts, followed by full-text assessment of potentially eligible articles. From the included studies, data were extracted on study design, population characteristics (including gestational age), type of gestational complication (e.g., PE, GDM, preterm birth, foetal growth restriction), methods used to quantify BDNF levels, as well as reported associations, proposed pathophysiological mechanisms and clinical implications.

In accordance with the PRISMA-ScR framework, a formal assessment of methodological quality and risk of bias was not performed, reflecting the exploratory nature of a scoping review and representing an inherent limitation of the present study. Current evidence suggests a consistent association between disrupted BDNF regulation, maternal physiological responses and gestational disorders; however, differences in methodological frameworks across studies complicate direct comparisons and may contribute to variability in reported findings. Variations in biological sample sources (serum, plasma, cord blood, placental tissue, and amniotic fluid), assay methodologies and the timing of specimen collection may lead to inconsistencies in reported BDNF concentrations and limit direct comparisons between studies. Additional sources of potential bias include the predominance of studies conducted in large academic and research centres, a geographical concentration of evidence from high-income and English-speaking countries, and the possible underrepresentation of studies reporting null or negative findings. To address these limitations, particular attention was paid to the consistency and reproducibility of findings across independent investigations and diverse study populations. Despite these methodological challenges, the collective evidence identifies BDNF as a central biological mediator linking placental function, maternal adaptation and foetal neurodevelopment, highlighting its potential role as both a biomarker and a mechanistic contributor to obstetric pathophysiology.

Data synthesis was performed narratively, with emphasis on epidemiological associations between BDNF levels and gestational complications, the exploration of underlying pathophysiological pathways (including neuroendocrine regulation, inflammatory processes, and placental dysfunction), and characterisation of clinical phenotypes. The findings were integrated into a conceptual, clinically oriented framework outlining the potential role of BDNF in the development and progression of pregnancy-related complications.

**Source type delineation.** The evidence base for the present scoping review consisted exclusively peer-reviewed scientific literature from obstetrics, neonatology, endocrinology, reproductive biology and related biomedical disciplines. These publications were systematically analysed to characterise the epidemiological relevance, biological functions, and clinical implications of BDNF across normal and complicated preg-

nancies. Particular attention was paid to its involvement in placental development, maternal adaptation to pregnancy, foetal growth, neurodevelopmental programming and the pathogenesis of major obstetric disorders, including PE, GDM and FGR.

## Results

From the 110 articles identified in the search (1-110), 38 were reviews, and 7 were systematic reviews (meta-analyses). Of the 65 remaining articles, the majority described changes in BDNF levels in major pregnancy complications, focusing primarily on maternal and neonatal outcomes. Several studies ( $n=25$ ) linked altered BDNF concentrations to pregnancy pathologies, suggesting that BDNF dysregulation contributes to their pathobiology. Methodologically, this core subset comprised 10 case-control studies (26,41,42,46,47,49,59,60,62,68,93), 8 prospective longitudinal cohort studies (11,17,26,27,73,74,100) and 7 cross-sectional studies (3,6,12,14,28,32,101). The studies were derived from all regions of the world including, Asia, Europe and America. Research studies were derived from last 16 years, i.e., 2010-2026. The studies were obtained from Google Scholar (50%), Science Direct (35%) and other (15%) databases, i.e., PubMed. The key clinical and experimental studies that shaped the understanding of BDNF as a pivotal factor in gestational vascular biology and pregnancy pathologies are detailed and summarized in Table I.

**Biomarker matrices and molecular targets.** The selected studies displayed distinct biological matrices and analytical targets, as follows:

**Protein quantification.** In total, 21 of 25 studies quantified total BDNF [representing unseparated pro-BDNF and mature BDNF (mBDNF) isoforms] in serum (6,26-28,41,60,73,74,93,100), plasma (32,47), or cord blood (42,46,59,68,98), paired maternal-neonatal blood (12,14), alternative biological matrices: blood spots (11) and amniotic fluid (26).

**Genetics and epigenetics.** A total of 4 studies evaluated single nucleotide polymorphisms (SNPs) of the *BDNF* gene (e.g., Val66Met/rs6265) in cord blood or oral swabs (3,26,49,62), and 3 studies examined *BDNF* mRNA expression or DNA methylation patterns in cord blood or placental tissue (3,14,101).

**Clinical pregnancy pathologies and perinatal outcomes.** BDNF dysregulation was strongly implicated across major obstetric, metabolic and psychiatric pathologies:

**Hypertensive disorders and PE.** Maternal serum and plasma BDNF concentrations were significantly reduced in PE compared to normotensive pregnancies (28,46,47), with cord blood BDNF exhibiting gestational age-dependent variation (elevated in term PE, reduced in preterm PE) (46). Severe hypertensive complications demonstrated a compensatory surge in serum BDNF (41). Maternal-foetal pairing analysis of the Val66Met polymorphism revealed no transmission disequilibrium in PE (49).

**Foetal growth and metabolic pathologies.** Cord blood BDNF expression was downregulated in GDM regardless of foetal growth pattern (59), exhibiting a downward gradient from healthy controls to dietary GDM and insulin-dependent

Table I. The landmark clinical and experimental studies that shaped the understanding of BDNF.

| Study no. | First author, year of publication | Study design       | Study objective                                                                                                                         | Size and characteristics of population                                                                                        | Conclusions                                                                                                                                                                                                      | (Refs.) |
|-----------|-----------------------------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1         | D'Souza, 2014                     | Case-control study | To examine the levels of maternal and cord BDNF in women with PE                                                                        | 106 Full-term and 46 preterm with PE and 95 normotensive women delivering at term                                             | Maternal BDNF levels were lower in PE when compared to normotensive women. Cord BDNF levels were higher in women with PE delivering at term, while it was lower in women delivering preterm.                     | (46)    |
| 2         | Briana, 2018                      | Case-control study | To determine BDNF, NGF and NT-4 are expressed in cord blood samples at birth in LGA, IUGR and AGA offspring of diabetic mothers         | 80 cord blood samples from 15 LGA, 12 IUGR and 33 AGA diabetic, as well as from AGA 20 normal singleton full-term pregnancies | BDNF is down-regulated in the fetus exposed to GDM, independently of the fetal growth pattern/                                                                                                                   | (59)    |
| 3         | Perucci, 2017                     | Case-control study | To investigate BDNF plasma concentrations in PE and to compare with BDNF concentrations from normotensive PW                            | 38 women with PE (17 early-onset and 21 late-onset) and in 20 normotensive PW                                                 | Lower BDNF plasma concentrations and cross-talk between BDNF and AnxA1 signaling pathways might be involved in PE pathogenesis.                                                                                  | (47)    |
| 4         | Ardiani, 2019                     | Case-control study | To determine differences in BDNF and moderately mature MMP-9 between normal birth weight and IUGR.                                      | Umbilical cord blood of appropriate gestational age neonate with normal birth weight (31 neonates) and IUGR (31 neonates)     | BDNF of moderately mature neonates was significantly higher in normal birth weight compared to IUGR, and the moderately high MMP-9 neonates were significantly higher in IUGR compared with normal birth weight. | (68)    |
| 5         | Sonmez, 2019                      | Case control study | To assess the association between cord blood BDNF concentration and maternal depression during pregnancy                                | 48 PW, 23 women with depression during pregnancy and the control group included 25 PW without depression during pregnancy     | Cord blood BDNF concentration was significantly lower in babies born to mothers with major depression as compared with those in the control group.                                                               | (98)    |
| 6         | Guan, 2020                        | Case-control study | Correlation of Val66Met variation in BDNF and PE                                                                                        | 1,138 Cases of the PE group and 1342 cases of the control group                                                               | The analysis of maternal-fetal pairing showed the transitivity of BDNF Val66Met have no significant difference between the case group and the control group                                                      | (49)    |
| 7         | Kondratiuk, 2021                  | Case-control study | To investigate quantitative serum brain-derived neurotrophic factor as a possible predictor of the severity of PE and its complications | 88 Pregnant women at 22 to 42 weeks of gestation were examined, 77 of them with hypertensive disorders                        | In severe complications of hypertensive disorders, a reliable increase of BDNF in blood serum was revealed.                                                                                                      | (41)    |

Table I. Continued.

| Study no. | First author, year of publication | Study design       | Study objective                                                                                                                                      | Size and characteristics of population                                                                                                                                                       | Conclusions                                                                                                                                                                                        | (Refs.) |
|-----------|-----------------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 8         | Pascual-Mancho, 2022              | Case-control study | To analyze the blood levels of BDNF in the cord blood from fetuses with FGR in comparison to those with weight appropriate for gestational age (AGA) | 130 Subjects were recruited: 91 in AGA fetuses; 39 (16 FGR fetuses with exclusively middle cerebral artery pulsatility index <5th percentile and 23 with umbilical artery >95th percentile). | Significant decrease in cord blood levels of BDNF in FGR and more prominently in those with UA PI >95th percentile in comparison to AGA.                                                           | (42)    |
| 9         | Huang, 2024                       | Case-control study | To investigate the roles of BDNF and the Val66Met polymorphism in MCI in patients with type 2 diabetes mellitus (T2DM).                              | 169 Patients with T2DM were involved and divided into long-term (>10 years) and short-term (≤10 years) diabetes, and in each group, the patients were separated as MCI and the control       | Elevated peripheral BDNF level associated with declined islet function, when combined with its Val66Met polymorphism, may forecast memory dysfunction in patients with long-term T2DM.             | (62)    |
| 10        | Firdaws, 2025                     | Case-control study | To investigate the association between poor neonatal outcomes of MSAF and serum BDNF.                                                                | 90 PW. The case group-45 PW who underwent cesarean section due to fetal distress with MSAF, and the control group-45 PW cesarean section due to fetal distress without MSAF.                 | The maternal BDNF cutoff for predicting meconium-stained liquor fetal distress was 1.76 ng/ml, showing an acceptable validity finding with sensitivity 100%, specificity 95.6% and accuracy 98.5%. | (93)    |
| 11        | Su, 2021                          | Longitudinal       | To investigate the possible relationship between the serum BDNF levels of IMGD and neuro-developmental outcomes using the BSID-III.                  | 24 Candidates, including 8 IMGD and 16 healthy infants                                                                                                                                       | The BDNF content was significantly higher in the non-IMGD than in the IMGD group at 12 months of age.                                                                                              | (60)    |
| 12        | Cattaneo, 2010                    | Longitudinal       | Functional polymorphism (Val66Met) in the pro-region of BDNF                                                                                         | In amniotic fluids (AF) obtained from 139 healthy women during 15-17 weeks of pregnancy                                                                                                      | Significant BDNF protein levels reduction in 55 Met carriers as compared to 84 non carriers, and no effect of fetus gender, maternal age or gestation week on BDNF levels.                         | (26)    |
| 13        | Fung, 2015                        | Longitudinal       | BDNF in the pathophysiology of depression                                                                                                            | 968 Pregnant women                                                                                                                                                                           | Lower maternal serum BDNF levels in early pregnancy are associated with antepartum depression.                                                                                                     | (100)   |
| 14        | Gao, 2016                         | Longitudinal       | To determine whether there is an association between serum BDNF and PPD                                                                              | 340 women were enrolled: 37 women (10.9%) were considered as meeting criteria for PPD.                                                                                                       | Serum BDNF levels in women without PPD were significantly higher than those in women with PPD.                                                                                                     | (74)    |

Table I. Continued.

| Study no. | First author, year of publication | Study design          | Study objective                                                                                                 | Size and characteristics of population                                                                | Conclusions                                                                                                                                                                                               | (Refs.) |
|-----------|-----------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 15        | Christian, 2016                   | Longitudinal          | The predictive value of serum BDNF in pregnancy                                                                 | During each trimester and 4-11 weeks postpartum among 139 women (77 of African origin, 62 Caucasian). | Serum BDNF declines considerably across pregnancy in women of African origin and Caucasians, with overall higher levels in those of African origin.                                                       | (11)    |
| 16        | Ghassabian, 2017                  | Longitudinal          | Mothers rated children's development in five domains repeatedly through age 3 years                             | BDNF measured in 2,637 newborns dried blood spots                                                     | BDNF levels in neonates may be impacted by maternal lifestyle characteristics.                                                                                                                            | (17)    |
| 17        | Dingsdale, 2022                   | Longitudinal          | Serum BDNF levels in mothers and their newborns correlate with sex-specific outcomes at 1 year.                 | 355 Women with children                                                                               | Reduced serum BDNF levels at birth are linked to an increased risk for neuro-developmental disorders.                                                                                                     | (73)    |
| 18        | Zhang, 2025                       | Longitudinal          | Depressive symptoms in the first and third trimester                                                            | Depressive symptoms in the first and third trimester                                                  | Serum BDNF shows promise as a predictive biomarker for antenatal depressive symptoms across all trimesters.                                                                                               | (27)    |
| 19        | Saenen, 2015                      | Cross-sectional study | Adaptive responses of the placenta to the maternal environment may influence central nervous system development | Placental tissue of 90 mother-infant pairs                                                            | Placental expression of <i>BDNF</i> and <i>SYN1</i> , two genes implicated in normal neuro-developmental trajectories, decreased with increasing <i>in utero</i> exposure to PM2.5.                       | (101)   |
| 20        | Yang, 2017                        | Cross-sectional study | To examine the correlates of early pregnancy serum BDNF concentrations                                          | 982 Women attending prenatal care                                                                     | Serum BDNF concentrations were positively associated with maternal age and early pregnancy BMI, but inversely correlated with gestational age at sample collection and C-reactive protein concentrations. | (6)     |
| 21        | Zaw, 2019                         | Cross-sectional study | metals [lead (Pb), mercury (Hg), cadmium (Cd) and arsenic (As)] were measured in plasma BDNF level              | 108 with Myanmar migrant pregnancy with a single viable fetus of 0 to 14 gestation weeks              | Women with a higher blood total arsenic level were more likely to have lower BDNF in early pregnancy. Heavy metals could aggravate the BDNF level.                                                        | (32)    |
| 22        | Mayuliani, 2021                   | Cross-sectional study | To analyze the correlation between BDNF and perinatal outcomes in PE.                                           | 73 Pregnant women with PE.                                                                            | BDNF level in PE was lower than normal pregnancy, positive correlation between BDNF and perinatal outcomes.                                                                                               | (28)    |
| 23        | Flóck, 2022                       | Cross-sectional study | The importance of BDNF acting at the foeto-placental interface.                                                 | 109 Maternal blood-amniotic fluid pairs (including 66 maternal blood-fetal blood-amniotic fluid trios | Correlate AF-BDNF samples with the corresponding maternal and fetal blood-BDNF samples.                                                                                                                   | (14)    |

Table I. Continued.

| Study no. | First author, year of publication | Study design          | Study objective                                                                                              | Size and characteristics of population                        | Conclusions                                                                                                                                       | (Refs.) |
|-----------|-----------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 24        | Jaskolski, 2022                   | Cross-sectional study | The influence of dietary (dGDM) and insulin-dependent (iGDM) gestational diabetes (GDM) on BDNF blood levels | Blood samples from 293 maternal-neonatal pairs were analyzed. | Maternal and neonatal BDNF levels were lowest in the iGDM group, followed by the dGDM group and healthy controls.                                 | (12)    |
| 25        | Granitzer, 2024                   | Cross-sectional study | Determine whether BDNF and KISS-1 levels can be used as biomarkers                                           | 65 Pregnant women                                             | Pb exposure and iron status modulate BDNF and KISS-1 levels. The correlations between maternal BDNF and KISS-1 levels, placental gene expression. | (3)     |

BDNF, brain-derived neurotrophic factor; BSID-III, Bayley Scales of Infant Development III PE, preeclampsia; NGF, nerve growth factor; NT, neurotrophin; LGA, large for gestational age; IUGR, intrauterine growth restriction; AGA, appropriate for gestational age; GDM, gestational diabetes mellitus; PW, pregnant women; MMP, matrix metalloproteinase; IMGD, infants of mothers with gestational diabetes; FGR, foetal growth restriction; T2DM, type 2 diabetes mellitus; MCI, mild cognitive impairment; MSAF, meconium-stained amniotic fluid; PPD, postpartum depression.

GDM (12). FGR/intrauterine growth restriction (IUGR) was significantly associated with reduced cord BDNF levels (42,68), particularly in foetuses presenting with an umbilical artery pulsatility index exceeding the 95th percentile (42).

*Perinatal mental health.* Declining maternal serum BDNF levels across trimesters were associated with antepartum (27,100) and postpartum depression (74). Furthermore, maternal major depressive disorder significantly reduced offspring cord blood BDNF concentrations (98).

*Environmental toxicants and gene-environment interactions.* Exposomic investigations demonstrated a high sensitivity of BDNF signalling to environmental stressors:

*Air pollution.* Prenatal exposure to fine particle air pollution with a diameter  $\leq 2.5 \mu\text{m}$  (PM2.5) reduced placental BDNF expression (101).

*Heavy metals.* Heavy metal exposures, including arsenic and lead, modulated maternal and cord blood BDNF concentrations (3,32).

*Diagnostic significance.* BDNF demonstrated utility as a predictive clinical biomarker; a maternal serum BDNF cut-off level of 1.76 ng/ml accurately predicted meconium-stained amniotic fluid (MSAF)-associated foetal distress (sensitivity, 100%; specificity, 95.6%) (93).

## Discussion

*BDNF in normal gestation.* In a population-based cohort study that applied a comprehensive mother-placenta-foetus sampling approach, Flöck *et al* (14) reported dynamic changes in maternal circulating BDNF concentrations throughout pregnancy. Mean maternal serum BDNF levels were  $11.3 \pm 3.5$  pg/ml during the first trimester, decreased to  $10.6 \pm 3.8$  pg/ml in the second trimester and remained relatively stable at  $11.0 \pm 4.1$  pg/ml in the third trimester. Analysis of matched maternal blood, amniotic fluid and foetal blood samples further demonstrated a positive association between amniotic fluid BDNF (AF-BDNF) levels and corresponding maternal and foetal circulating concentrations, suggesting coordinated regulation of neurotrophic signalling across the maternal-foetal interface (14).

Notably, Flöck *et al* (14) also identified that pre-pregnancy maternal BMI exhibits a strong inverse association with maternal BDNF levels. Furthermore, maternal obesity, particularly when accompanied by lower baseline BDNF concentrations, was associated with a greater probability of AF-BDNF levels falling below the analytical detection threshold (14). Together, these empirical findings highlight the potential influence of maternal metabolic status on the intra-uterine neurotrophic environment and suggest that maternal adiposity may contribute to alterations in foetal neurodevelopmental programming through modulation of BDNF availability (13,14).

A thorough understanding of the involvement of BDNF in pregnancy-related disorders requires an examination of its physiological dynamics during uncomplicated gestation. Under normal reproductive conditions, BDNF functions as a key regulatory molecule from the earliest stages of development, contributing to folliculogenesis, oocyte maturation, embryo implantation and placental formation (4,15). In a

longitudinal cohort study involving 139 women from diverse racial backgrounds, Christian *et al* (11) observed a progressive decline in maternal serum BDNF concentrations across pregnancy, from the first trimester ( $12.0 \pm 1.89$  weeks) to the second ( $21.7 \pm 2.2$  weeks) and third trimesters ( $30.3 \pm 2.0$  weeks), followed by a marked increase during the postpartum period (4-11 weeks following delivery). Several physiological mechanisms have been proposed to explain this temporal pattern, including gestational haemodilution, increasing placental uptake and utilization of neurotrophic factors, and the modulatory effects of pregnancy-associated hormones, such as progesterone and oestradiol (11,15,16). Notably, BDNF is capable of crossing the uteroplacental barrier, and experimental evidence indicates a close association between maternal circulating BDNF concentrations and foetal brain levels. These findings suggest that the maternal neurotrophic status may directly influence foetal neurodevelopment and support the concept of BDNF as a critical mediator of maternal-foetal communication during pregnancy (13).

Determinants of maternal and neonatal BDNF levels are complex and encompass socioeconomic, lifestyle and demographic factors. In population-based cohorts, lower neonatal BDNF measured via dried blood spots has been found to be associated with maternal smoking and alcohol consumption during pregnancy, as well as pre-pregnancy obesity (17-19). It is synthesized within the trophoblast of the blastocyst and remains a persistent factor in the development of both the maternal decidua and the foetal placental structures throughout the three trimesters (20). Furthermore, BDNF serves as a potent pro-angiogenic factor, promoting the survival of endothelial cells and facilitating the complex process of uterine spiral artery remodelling (21,22).

*Molecular architecture and genetic regulation of BDNF.* The *BDNF* gene locus is characterized by high evolutionary complexity and conservation of the coding sequence; however, the structure of its regulatory elements has undergone significant sophistication in primates and humans compared to rodents (23). Located on chromosome 11p13, the gene consists of 11 exons and utilizes nine distinct promoters that are regulated in a tissue-specific and activity-dependent manner (3,24). The recent study by Esvald *et al* (25) substantially refined the transcriptional landscape of the *BDNF* gene in cultured rat cortical and hippocampal neurons.

According to Granitzer *et al* (3), BDNF is a highly conserved neurotrophin synthesized as the precursor protein pro-BDNF (~32 kDa), which is subsequently cleaved into the biologically active mBDNF form. This maturation process contributes to the functional versatility of BDNF in various physiological processes. This 32-kDa protein is synthesized in the endoplasmic reticulum and subsequently transported to the Golgi apparatus, where it undergoes proteolytic cleavage by enzymes, such as furin or proprotein convertases to generate the 14-kDa mBDNF isoform (3). During pregnancy, the balance between these two isoforms is essential for maintaining placental health and guiding the delicate processes of brain morphogenesis.

The seminal study by Cattaneo *et al* (26) provided critical insight into the molecular consequences of the BDNF Val66Met polymorphism, elucidating how this functional genetic variant

alters intracellular trafficking and activity-dependent release of BDNF. Carriers of the Met allele exhibit reduced neurotrophin secretion in response to neuronal stimulation, which has been associated with structural alterations in brain regions involved in learning, memory, and emotional regulation, particularly the hippocampus. These neurobiological changes have also been linked to an increased vulnerability to a range of neuropsychiatric conditions. During pregnancy, the Val66Met polymorphism may further modulate maternal-foetal neurotrophic signalling. Evidence suggests that the presence of the Met allele in either the mother or the foetus can influence BDNF concentrations within the intrauterine environment and may modify the impact of maternal psychological stress on the development of foetal limbic structures, including the amygdala and hippocampus (26).

In addition, extravillous trophoblasts, which are responsible for maternal decidual invasion and spiral artery transformation, also express components of the BDNF signalling pathway. This observation supports the hypothesis that BDNF may regulate trophoblast migration and invasion through both autocrine and paracrine mechanisms. As gestation advances, the distribution of BDNF receptors undergoes substantial changes. Near term, the expression of TrkB and p75NTR within trophoblastic layers declines, whereas receptor localization becomes increasingly prominent within the villous stromal compartment of the placenta, suggesting a shift in the functional role of neurotrophin signalling during late pregnancy (27). In their study, Mayuliani *et al* (28) further emphasized the importance of BDNF in placental development by demonstrating that inadequate cytotrophoblast invasion and incomplete remodelling of the maternal spiral arteries contribute to placental ischemia and persistent hypoxic stress at the maternal-foetal interface. These findings indicate that the oxidative environment characteristic of PE suppresses placental BDNF gene expression throughout gestation, providing a potential link between impaired neurotrophin signalling with the pathophysiology of placental dysfunction and hypertensive disorders of pregnancy (28,29).

According to D'Souza *et al* (29), maternal plasma BDNF levels are altered prior to the clinical onset of PE, establishing the potential of BDNF as an early gestational biomarker. They connected the placental neurotrophin axis to one-carbon metabolism and maternal nutrition. They demonstrated that maternal micronutrient imbalances [such as folate and vitamin B12 deficiencies combined with low docosahexaenoic acid (DHA)] disrupt placental global DNA methylation, thereby epigenetically downregulating the expression of placental BDNF and TrkB; this leads to impaired placental development and intrauterine growth restriction (29,30).

As demonstrated by Dingsdale *et al* (64), there is a sex-specific maternal-foetal a involving maternal anxiety and serum BDNF levels. In a large cohort of pregnant women, they found that maternal symptoms of anxiety correlate with significantly elevated serum BDNF exclusively in mothers carrying male foetuses, while maternal depression shows no such correlation. To determine the physiological path of this elevated BDNF, they developed a novel mouse model that demonstrated that maternal BDNF does not cross the placental barrier into the foetal circulation (64). Based on these findings, it was concluded that the placenta serves as an active barrier,

shielding the developing foetus from fluctuating maternal serum neurotrophin levels that could otherwise interfere with controlled and endogenous foetal neurodevelopment (31).

The longitudinal profile of serum BDNF in healthy pregnancies reveals a characteristic and statistically significant decline as gestation progresses. According to Christian *et al* (11), serum BDNF concentrations declined progressively from the first to the third trimester of pregnancy, followed by a rapid rebound in the postpartum period. They documented that women of African origin exhibit significantly higher circulating BDNF during the first two trimesters and postpartum compared to Caucasian women, as well as lower corresponding cortisol levels. In addition, they demonstrated that lower maternal serum BDNF in late pregnancy was strongly associated with high levels of maternal depressive symptoms and a significantly increased risk of delivering low-birth-weight (<2,500 g) infants, emphasizing the clinical value of within-race prenatal monitoring (11). For the developing foetus, BDNF is critically required starting from the third week of gestation, when active differentiation of neural progenitor cells occurs (32,33).

As the pregnancy advances into the second and third trimesters, these levels decline considerably, often reaching a nadir in late pregnancy that is 30 to 50% lower than levels observed in non-pregnant women (27). Of note, the postpartum period is marked by a rapid and substantial rebound in maternal serum BDNF levels, typically measured between 4 and 11 weeks after delivery. This rebound may be associated with the neurobiological recovery and remodelling required for the transition to maternal caregiving (34).

**BDNF and gestational complications.** PE remains a primary driver of maternal and neonatal morbidity, affecting ~2-8% of pregnancies globally (35).

In a landmark study, D'Souza *et al* (9) demonstrated that women with PE exhibit substantially reduced BDNF concentrations in maternal plasma, placental tissue and umbilical cord blood, with levels ~40-50% lower than those observed in normotensive pregnancies. These reductions were closely associated with the severity of endothelial dysfunction, indicating a critical role for BDNF in the pathophysiology of PE. Notably, this decrease was associated with both the severity of maternal hypertension and the extent of placental ischemic injury, suggesting a disruption of compensatory angiogenic pathways that are essential for maintaining placental function (9). Under hypoxic conditions, the ischemic placenta overproduces and secretes soluble decoy receptors into the maternal bloodstream. Of note, Liao *et al* (36) proposed a 'self-defence' hypothesis, demonstrating that foetal trophoblasts overexpress soluble fms-like tyrosine kinase-1 (sFlt-1) to shield the foetus from excessive maternal decidual VEGF, though this feedback loop ultimately compromises the maternal vasculature. There is also evidence of a regulatory interplay between BDNF and established angiogenic markers, such as placental growth factor (PlGF) and sFlt-1 (37).

According to Nelson *et al* (38), reduced BDNF availability may intensify placental dysfunction by compromising endothelial cell proliferation, vascular remodelling and vasoregulatory mechanisms that are essential for maintaining adequate uteroplacental perfusion. As a result, a pathogenic feedback loop may emerge whereby placental ischemia reduces

BDNF production, while decreased neurotrophic signalling further aggravates vascular impairment and hypoxic stress. Ultimately, this disruption of the placental neurotrophic environment may restrict the delivery of critical developmental signals to the foetus during vulnerable stages of brain maturation, which may increase susceptibility to hypoxia-related neurodevelopmental injury (38).

Further findings reported by Cinkajzlova *et al* (39) indicated that in pregnancies complicated by both PE and diabetes mellitus, reduced BDNF levels are accompanied by elevated concentrations of P-selectin and interferon gamma receptor 1, contributing to the progression of placental microvascular dysfunction. Similarly, Meakin *et al* (40) demonstrated that reduced BDNF concentrations in PE may not simply result from placental ischemia, but may also predict early postnatal neurocognitive impairment in offspring, probably due to the reduced capacity of the placenta to buffer foetal exposure to hypoxic stress. The aetiology of PE is closely linked to defective trophoblast invasion and inadequate remodelling of the maternal spiral arteries, leading to placental hypoxia and the systemic release of anti-angiogenic factors. Research indicates that BDNF plays a pivotal role in this process, with significant alterations in its maternal serum levels and placental expression observed in preeclamptic pregnancies (29,41). This reduction in local BDNF availability may contribute to the shallow trophoblast invasion observed in PE by failing to sufficiently stimulate matrix metalloproteinase (MMP)-9 production and other pro-invasive signalling pathways (29,42). In PE, the increase in the levels of sFlt-1, a decoy receptor that sequesters VEGF and PlGF, leads to an anti-angiogenic state. The concurrent reduction in BDNF levels further compromises the angiogenic potential of the placenta, reinforcing a state of chronic hypoxia and endothelial stress (9,29,43).

The clinical phenotypes of PE differ substantially, as demonstrated by Marzioni *et al* (44), who highlighted the critical regulatory role of the STAT3 signalling pathway. Early-onset PE (developing prior to 34 weeks of gestation) is strongly associated with deficient spiral artery remodelling, severe placental hypoxia and FGR. Conversely, late-onset PE (manifesting at or after 34 weeks) is more closely linked to pre-existing maternal metabolic or cardiovascular predispositions and primary endothelial susceptibility (44-49). The interplay between BDNF and endothelial cells is highly cooperative and relies on autocrine and paracrine signalling loops. Healthy vascular endothelial cells express both the ligand BDNF and its high-affinity TrkB receptor. Under normal blood flow conditions, physiological fluid shear stress stimulates the vesicular exocytosis of BDNF from endothelial cells (50).

The maintenance of endothelial barrier integrity also depends on nitric oxide (NO). Under normal conditions, the generation of NO via endothelial nitric oxide synthase (eNOS) phosphorylation at Ser1177 serves as a key driver of BDNF synthesis and release in the vascular network. Maternal endothelial dysfunction is the ultimate common pathway in PE, characterized by downregulated eNOS expression, NO deficiency, reduced prostacyclin synthesis, elevated vasoconstrictor production (such as endothelin-1) and the accumulation of reactive oxygen species (ROS). Experimental models indicate that the pharmacological blockade of eNOS via L-NAME markedly decreases endothelial BDNF production, whereas

the application of NO donors, such as glyceryl trinitrate completely restores BDNF expression (51). In PE, this feed-forward loop is broken. Excessive anti-angiogenic factors (such as sFlt-1) lead to the downregulated expression of eNOS and reduced NO bioavailability, leading to endothelial BDNF depletion and vascular wall breakdown.

To systematically evaluate the degree of systemic endothelial cell activation and stress, the Endothelial Activation and Stress Index (EASIX) has been proposed (n=986):  $EASIX = LDH \times \text{creatinine} / \text{platelets}$ . This index has exhibited strong prognostic power in stratifying maternal and perinatal risk, particularly in patients diagnosed with early-onset PE (51).

Recent neuropathophysiological concepts classify severe PE as a gestational proteinopathy with impaired autophagy, sharing common pathways with neurodegenerative disorders. Endothelial injury and anti-angiogenic stress cause blood-brain barrier leakage, neuroinflammation and the loss of cerebral autoregulation. Indeed, >70% of maternal PE deaths stem from acute neurological complications, such as eclampsia, cerebral oedema and stroke (52). Against this clinical background, serum BDNF serves as a powerful predictive biomarker. In mild or moderate PE, circulating BDNF is systemically reduced due to endothelial depletion and impaired placental synthesis.

*Metabolic complications: Insulin resistance and BDNF in GDM.* GDM is one of the most common medical complications of pregnancy, affecting ~14 to 16.5% of pregnancies worldwide, with an increasing prevalence due to the global epidemics of maternal obesity and delayed childbearing (54). In a normoglycemic gestation, maternal pancreatic  $\beta$ -cells undergo robust compensatory hypertrophy and hyperplasia to increase insulin secretion by 60 to 70% (53). However, in pregnancies predisposed by genetic susceptibility, an advanced maternal age, or pre-existing obesity, this compensatory capacity fails, culminating in persistent hyperglycaemia, foetal hyperinsulinemia and a state of chronic subclinical systemic inflammation (12,54).

During the first trimester, elevated concentrations of oestrogen and human chorionic gonadotropin enhance peripheral insulin sensitivity by ~20%, encouraging maternal lipid and glycogen deposition. Beyond the 10th to 12th weeks of gestation, as the placenta assumes dominant endocrine control, a significant increase in maternal insulin resistance occurs. By the third trimester, peak levels of human placental lactogen, human placental growth hormone, cortisol and progesterone cause a 40 to 50% decrease in systemic insulin sensitivity (55,56). In patients with GDM, chronic maternal hyperglycaemia leads to a persistent, systemic depletion of circulating BDNF, which deprives peripheral tissues of its insulin-mimetic, protective functions and accelerates maternal metabolic decay (12,57).

Jaskolski *et al* (12) pioneered the first matched cohort analysis of corresponding maternal-neonatal pairs in pregnancies complicated by GDM. Utilizing multiple regression models and 2:1 propensity score matching (adjusting for gestational age, infant sex, and mode of delivery), they established that neonatal cord blood log-BDNF is significantly suppressed in GDM pregnancies, with the most profound deficit observed

in insulin-dependent patients. Their findings demonstrated that GDM is associated with a marked reduction in neonatal neurotrophic support, which occurs independently of maternal systemic BDNF levels and highlights the vulnerability of the foetus to maternal metabolic dysregulation. While maternal log-BDNF levels in GDM exhibited a downward trend (mean reduction of 79.6 pg/ml), this difference did not reach statistical significance after adjustment. This indicates that the foetal-placental compartment undergoes more severe and immediate BDNF suppression under conditions of maternal hyperglycaemia than the maternal system, posing a direct threat to intrauterine foetal brain development (12).

An Israeli research group [Chermon and Birk (58)] carried out a large genetic cohort study by analysing data from 4,025 women to investigate the association of common *BDNF* SNPs with GDM susceptibility. They identified a significant association between the *BDNF* rs925946 Tag-SNP and GDM risk. Additionally, their study associated the *BDNF* rs6265 (Val66Met) polymorphism with pre-pregnancy obesity in patients with GDM, linking genetic neuroendocrine disruption to clinical metabolic phenotypes (58).

Briana *et al* (59) prospectively evaluated cord blood neurotrophic factors (BDNF, NGF and NT-4) in 80 term gestations categorized by foetal growth patterns, including large for gestational age (LGA), IUGR and appropriate-for-gestational-age (AGA) infants born to GDM and control mothers. They also established that IUGR infants of mothers with GDM suffer from a concurrent deficiency in NGF, further compounding their risk for long-term neurological sequelae (59).

Su *et al* (60) conducted a longitudinal and prospective study that tracked infants of mothers with GDM (IMGD) at birth, 6 months and 12 months of age, and correlated serial serum BDNF levels with neurodevelopmental outcomes using the Bayley Scales of Infant Development III (BSID-III). They demonstrated that by 12 months of age, IMGD demonstrated significantly lower systemic BDNF concentrations than healthy control infants. Crucially, this postnatal BDNF deficiency was accompanied by significantly lower language composite scores on the BSID-III in GDM offspring. This longitudinal research was the first to establish a direct clinical link between gestational BDNF downregulation and functional neurodevelopmental deficits, specifically delayed language acquisition, in human infants (60). Complementing these clinical findings, experimental research by Valle *et al* (61) demonstrated that early metabolic stress during gestation induces severe central and peripheral BDNF deficiency, leading to programmed insulin resistance and metabolic dysfunction in adult offspring.

Huang *et al* (62) analysed the clinical intersection of peripheral BDNF, pancreatic islet function and cognitive decline. They concluded that, as pancreatic  $\beta$ -cell function declines, a compensatory increase in peripheral BDNF occurs. However, in patients carrying the Met allele of the *BDNF* Val66Met polymorphism, this compensatory loop is insufficient, which leads to accelerated cognitive decline and impaired verbal logical memory compared to Val/Val homozygotes. These findings established peripheral BDNF and its genetic variants as key predictive biomarkers for diabetic cognitive impairment (62). In Russian perinatal medicine, Evsyukova established GDM as a major pathogenetic risk factor for neurological and psychiatric disorders in offspring. That study demonstrated

that GDM-associated maternal insulin resistance, hyperleptinemia, hyperinsulinemia and placental insufficiency combine to cause chronic foetal hypoxia (63).

The reduction in neonatal BDNF in GDM is particularly noteworthy, as it remains significantly lower even after adjusting for factors such as maternal BMI and mode of delivery. This deficiency in the foetal circulation may have long-term implications for the neurodevelopment of children born to diabetic mothers, potentially predisposing them to metabolic and psychiatric disorders later in life (65).

*Foetal development issues: BDNF in neonates who are small for gestational age (SGA) and FGR.* FGR or IUGR, represents a pathological state in which the foetus fails to achieve its genetically predetermined growth potential (66). According to Pascual-Mancho *et al* (42), cord blood BDNF levels are consistently found to be lower in neonates with FGR who are SGA compared to those with weight AGA.

Under chronic hypoxic conditions and nutrient deprivation, the foetus initiates a highly conserved circulatory adaptation known as the 'brain-sparing' effect. Briana *et al* (59) further explained these mechanisms by demonstrating that BDNF concentrations in the cord blood of foetuses with FGR are significantly lower than those observed in appropriately grown foetuses. This finding was attributed to the 'brain-sparing effect', a compensatory adaptive response in which chronic foetal hypoxia leads to preferential redistribution of blood flow toward the central nervous system. However, despite this circulatory centralisation, the absolute deficiency of BDNF appears to limit the effectiveness of neuroprotective mechanisms, thereby contributing to microstructural injury of the developing white matter (59,67). This phenomenon is characterised by the selective vasodilation of the foetal middle cerebral artery (MCA) in response to a drop in cerebral oxygen tension, ensuring a redistribution of cardiac output to vital organs-primarily the brain, myocardium and adrenal glands-at the expense of mesenteric, renal and peripheral perfusion.

At the tissue level, placental hypoperfusion stimulates a compensatory angiogenic response driven by the synergistic action of BDNF and MMP-9. BDNF functions as a direct angiogenic factor within the placental vasculature, promoting endothelial cell migration and capillary tubulogenesis. Concurrently, MMP-9 degrades extracellular matrix components, facilitating the sprouting of new capillary networks and maternal trophoblast invasion (68).

According to the comparative clinical trial conducted by Ardiani *et al* (68) in their Padang-based cohort, healthy and symmetrically growing neonates (appropriate for gestational age, n=31) demonstrated baseline cord blood concentrations of mBDNF of 1.58 ng/ml (standard deviation of 0.23), coupled with physiological MMP-9 levels of 1.09 ng/ml (standard deviation of 0.20). According to their interpretation, this biochemically balanced state reflects stable physiological angiogenesis, adequate trophoblastic invasion, and controlled extracellular matrix degradation. Conversely, as shown in their results, in moderately mature neonates diagnosed with intrauterine growth restriction (n=31), a statistically significant depletion of cord blood BDNF to 1.25 ng/ml (standard deviation of 0.35) was observed (P=0.001). According to the researchers, this neurotrophic deficiency was accompanied by a significant

compensatory upregulation of MMP-9 to 1.25 ng/ml (standard deviation of 0.35) (P=0.03), which demonstrates the systemic impact of chronic hypoxia and ischemic stress on placental architecture and tissue remodelling (68). Mechanistically, they proposed that BDNF deficiency directly impairs placental angiogenesis, while the elevated MMP-9 levels reflect a compensatory but ultimately pathological tissue remodelling response. As stated by Ardiani *et al* (68), inadequate trophoblast invasion is met with a compensatory release of MMP-9 to degrade the extracellular matrix, attempting to facilitate placental expansion, though it fails to overcome the primary neurotrophic and foeto-placental deficit (68).

Similarly, as documented in the amniotic fluid study by Flöck *et al* (14), the biochemical composition of the amniotic fluid compartment reveals a separate and highly sensitive adaptational response along the spectrum of foetal growth (14). According to Malamitsi-Puchner *et al* (67), this elevated concentration serves as an endogenous adaptive response, wherein the foetus mobilises its neurotrophic reserves to accelerate cerebral development and counter the hostile and nutrient-deprived intrauterine environment (67).

The 2025 study by Kan *et al* (69) (n=45) explained that a significant decrease in the expression of both pro-BDNF and pro-NGF within maternal foetal neuronal exosomes (FNEs) occurs in the early-onset FGR cohort. Crucially, mature neurotrophin proteins were not detected in the FNE cargo, confirming that the vesicle cargo primarily reflects the non-processed precursor forms. Furthermore, Kan *et al* (69) established a direct clinical correlation: Downregulations in pro-BDNF levels within maternal-blood FNEs were specifically linked to the subsequent occurrence of neonatal intraventricular haemorrhage in late-onset FGR newborns. As stated by the authors, this discovery introduced a diagnostic 'liquid biopsy' of the foetal brain, permitting the early prenatal identification of foetuses at risk of severe cerebral ischemic injury (69).

*Maternal obesity, sexual dimorphism and placental dysfunction.* Pre-pregnancy maternal obesity (defined as a pre-pregnancy) acts as a state of chronic low-grade inflammation, oxidative stress and hypoxia, which profoundly impairs the molecular machinery of the BDNF/TRKB pathway within the placenta (70). Circulating maternal blood BDNF levels are known to be significantly and negatively correlated with pre-pregnancy BMI. Flöck *et al* (14) analysed mother-foetus trios and demonstrated that maternal obesity restricts the availability of BDNF in the amniotic fluid. In pregnancies where amniotic fluid BDNF fell below the lower limit of quantitation (<1.19 pg/ml), patients had a significantly higher pre-pregnancy BMI (26.3±6.7 kg/m<sup>2</sup> compared to 23.8±4.5 kg/m<sup>2</sup> in the detectable group) and significantly lower maternal circulating blood BDNF concentrations (510.6±554.7 pg/ml compared to 910.1±690.1 pg/ml in the detectable group; P<0.0001), suggesting that maternal adiposity impairs the transplacental transfer of neurotrophic support (14).

The placental molecular response to maternal obesity and high-fat diet exposure is characterised by a striking sexual dimorphism (71). The capacity of the placenta to adapt to an adverse intrauterine environment and compensate for maternal metabolic perturbations varies significantly depending on

foetal sex, with male fetuses exhibiting a pronounced vulnerability to prenatal insults. In their investigation of maternal obesity, Muralimanoharan *et al* (72) identified sex-specific mitochondrial dysfunction in the placenta mediated by miR-210. They discovered that the inflammatory intrauterine environment of maternal obesity selectively upregulates miR-210 in female placentas, but not in male placentas. TNF drives this female-specific upregulation by stimulating NF- $\kappa$ B binding to the placental miR-210 promoter (72).

A striking feature of neonatal BDNF biology is the presence of significant sex-specific differences. At birth, male infants naturally possess serum BDNF levels that are ~10 to 20% lower than those of female infants. This disparity has led researchers to propose the ‘male vulnerability’ hypothesis, which suggests that boys may be at an increased risk of developing neurodevelopmental disorders as they have a lower baseline of neurotrophic protection. The ‘Grown in Wales Study’ provided empirical support for this hypothesis by correlating cord serum BDNF levels with neurodevelopmental outcomes at 1 year of age (73). While no association was found between BDNF levels and general cognitive or language scores across the entire group, a significant sex-specific association emerged for attention. In boys specifically, higher cord serum BDNF was linked to a greater intensity of facial interest during a sustained attention task at 12 to 14 months (73).

These findings suggest that male and female fetuses may utilize different molecular strategies to adapt to maternal metabolic stress, which may contribute to the observed sex differences in the prevalence of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (65).

*Mental health and neurodevelopment: The perinatal connection.* In alignment with the neurotrophin hypothesis of depression, which links depleted BDNF to altered hippocampal neurogenesis and subsequent affective pathology, reductions in circulating maternal BDNF are directly implicated in the pathogenesis of perinatal mood disorders. During early pregnancy, depleted maternal serum BDNF functions as a sensitive biomarker for the development of antepartum depression (27).

At the clinical and epidemiological level, the understanding of the longitudinal behaviour of maternal circulating BDNF across gestation was greatly advanced by Christian *et al* (11), who mapped serum neurotrophin levels across all three trimesters and postpartum, revealing a physiological decline in BDNF concentrations toward late pregnancy and its association with prenatal depression and risk for low birth weight. As gestation progresses, maternal BDNF levels in the second trimester continue to show a strong, predictive and negative association with late-pregnancy depressive symptoms (11). Reduced maternal serum BDNF concentrations around the time of childbirth have emerged as a promising biomarker for the prediction of postpartum depression (PPD). A growing evidence indicates that women who subsequently develop PPD exhibit significantly lower circulating BDNF levels both at delivery and during the early postpartum period, typically between 6 and 11 weeks after birth. The clinical study by Gao *et al* (74) further demonstrated the prognostic value of BDNF measurements at parturition. In particular, a maternal serum BDNF concentration  $\leq 12.0$  ng/ml has been proposed

as a clinically relevant threshold for identifying women at elevated risk of postpartum depression. Using this cut-off value, individuals with BDNF levels below the threshold were found to have more than a sevenfold increased likelihood of developing PPD within the first 3 months following delivery (OR, 7.243; 95% CI, 3.883-12.746;  $P < 0.0001$ ) (74). Collectively, these findings suggest that peripartum BDNF assessment may offer valuable opportunities for the early identification of vulnerable women and the implementation of targeted preventive interventions.

The association between BDNF and mood is further complicated by the influence of the hypothalamic-pituitary-adrenal (HPA) axis. High levels of cortisol, the primary stress hormone, are concurrently associated with lower serum BDNF levels, particularly during the second trimester. This cortisol-BDNF interplay suggests that chronic maternal stress may suppress neurotrophic support for the brain of the mother, contributing to depressive phenotypes and potentially affecting foetal brain development through altered placental transfer or paracrine effects (11,75). High maternal distress is associated with reduced hippocampal and cerebellar volumes and altered functional connectivity in the offspring. Chronic variations in glucocorticoids affect BDNF-TrkB function in the prefrontal cortex, contributing to stress-induced cognitive alterations. Conventional antidepressants have been shown to restore BDNF levels, highlighting the role of this factor as both a biomarker and a therapeutic target (76).

Maternal mental health and sleep quality also significantly influence the neurotrophic milieu. In migrant pregnancies, poor sleep quality has been associated with significantly lower maternal BDNF levels. By contrast, women with mild to moderate depression in the first trimester had higher BDNF levels, suggesting a possible early compensatory response that may later fail as stress becomes chronic (77).

*Preterm birth and developmental domains.* Preterm birth is associated with a profound disruption of neurotrophic support during a critical period of foetal development. The molecular analyses conducted by Dhobale *et al* (78) demonstrated that the placental mRNA expression of both BDNF and NGF was reduced by ~2.5-fold in cases of spontaneous preterm delivery, potentially depriving the immature foetal brain of essential trophic signals required for neuronal survival and maturation (78). The clinical research by Rao *et al* (79) established a positive association between gestational age and umbilical cord blood BDNF concentrations; preterm infants are born with significantly lower BDNF concentrations compared to term infants, and both groups have lower levels than adults (79). A rigorous systematic meta-analysis confirmed that preterm birth was associated with a significant decrease in baseline BDNF [standardized mean difference (SMD), -0.32;  $P = 0.014$ ] and NT-3 (SMD, -0.31;  $P = 0.004$ ) compared to term infants, although NGF and NT-4 did not exhibit no significant variations (80). Heterogeneity within these meta-analytical findings is primarily moderated by the type of biospecimen analysed, such as placental tissue, cerebrospinal fluid, peripheral blood, or umbilical cord blood (80).

Following delivery, there is a sharp and abrupt withdrawal of maternal and placental neurotrophic support, causing a rapid decline in postnatal BDNF levels. In term infants, this

drop is transient, recovering by the fourth postnatal day. However, preterm infants experience a prolonged neurotrophic deficiency, with BDNF concentrations remaining depressed through the first weeks of life before gradually rising by discharge (79). Preterm birth remains a primary risk factor for adverse neurological outcomes, with complications, such as periventricular leukomalacia, diffuse white matter injury and cerebral palsy (CP) occurring at rates inversely proportional to gestational age (79,81). In extremely preterm neonates born before 28 weeks of gestation, circulating BDNF concentrations are markedly reduced due to the interruption of the critical period of neurotrophin transfer and endogenous synthesis that normally peaks during the third trimester of pregnancy. Additional clinical evidence highlights the broader implications of BDNF deficiency in preterm infants. In a retrospective cohort study involving 400 preterm neonates, Sahay *et al* (13) identified a significant association between BDNF concentrations measured within the first 24 h of life and the subsequent development of severe retinopathy of prematurity (13).

Moreover, D'Souza *et al* (46) proposed that a substantial decline in maternal systemic BDNF levels may contribute to the pathogenesis of preterm premature rupture of membranes through the activation of pro-inflammatory cytokine pathways, including TNF- $\alpha$  and IL-1 $\beta$  (46). Integrating biochemically non-invasive markers into clinical care remains a key research priority. In a prospective study conducted in Brazil, 40 preterm neonates (GA 28 to 32 weeks) were evaluated across four time points (83). Preterm infants with below-expected motor development (evaluated using the Test of Infant Motor Performance) had significantly elevated urinary concentrations of BDNF and glial cell line-derived neurotrophic factor compared to those with typical development (83).

Analysing long-term neurodevelopmental outcomes is further complicated by changes in standardized assessment tools. While early editions such as the BSID-II relied on combined developmental indices (the Mental Developmental Index and Psychomotor Developmental Index), the Bayley-III separated these into distinct Cognitive, Language and Motor scales (84,85). This structural separation helps identify specific language deficits independently of overall cognitive performance, but comparative studies have identified a systematic overestimation of scores (a Flynn-like effect) when transitioning to the Bayley-III.

*Inconsistencies in autism research.* According to a previous meta-analysis, peripheral blood BDNF levels are moderately, yet significantly elevated in children with ASD compared to typically developing controls (86). In that study, the researchers compared this consistently elevated neurotrophic state with the biomarkers of classic psychotic-affective disorders (86). According to that study, this pattern is highly concordant with the 'diametric model of the social brain' proposed by Crespi and Badcock (87). In their study, they present an evolutionary and developmental framework which posits that autism and psychotic-affective disorders represent opposite extremes of human social-cognitive development (87).

As previously demonstrated, the elevated BDNF levels observed in ASD represent a primary growth-signalling driver that aligns with the macrocephaly and cortical overgrowth frequently documented in young autistic cohorts, whereas

depleted BDNF levels in schizophrenia correspond directly to progressive cortical thinning and volume loss (86-90). The association between neonatal BDNF and ASD remains controversial and inconsistent (17).

*Clinical utility in acute obstetric management.* Observational clinical studies demonstrate that maternal circulating plasma BDNF concentrations are significantly lower in women with PE than in gestational age-matched normotensive controls. Depressed plasma BDNF is negatively associated with anti-inflammatory mediators, such as Annexin A1 and positively with clinical severity indicators, including diastolic blood pressure and pre-pregnancy BMI. The reduction in maternal circulating plasma BDNF during early and mid-gestation reflects an underlying impairment in placental synthesis alongside progressive endothelial cell injury (47,107).

During parturition, acute clinical events can cause sudden placental and foetal hypoxia, initiating cellular depolarization, metabolic acidosis and excitotoxic cascades in the developing brain (91). MSAF is a common clinical sign of acute or chronic foetal stress, complicating up to 27.1% of post-term deliveries and placing the neonate at risk for meconium aspiration syndrome and subsequent cerebral palsy (92). According to a recent clinical evaluation by Jihad and Mohammed (93), maternal and umbilical vein BDNF concentrations were significantly lower in pregnancies complicated by MSAF compared to healthy controls ( $P < 0.001$ ), reflecting a state of acute neurotrophic exhaustion under hypoxic stress. This diagnostic performance suggests that maternal BDNF can distinguish between benign meconium passage and severe, progressive intrauterine asphyxia, offering clinicians an objective biochemically based screening tool to guide the timing of operative delivery (93).

According to the study by Lorain *et al* (94), the development of moderate-to-severe hypoxic-ischemic encephalopathy (HIE) in infants with severe intrapartum acidosis (pH  $\leq 7.0$  at birth) is independently associated with specific acute obstetric factors. Within this clinical cohort, multi-variable analyses confirm that the occurrence of an acute intrapartum event (aOR, 6.4; 95% CI, 1.8-22.5), maternal fever (aOR, 3.5; 95% CI, 1.0-11.9) and thick meconium during labour (aOR, 2.9; 95% CI, 1.0-8.6) are the primary independent risk factors for HIE. Elevated maternal and foetal BDNF levels, along with high 25-hydroxyvitamin D [25(OH)D] concentrations, act as significant protective factors against such brain injury (95).

Gusar *et al* (96) demonstrated that isolation of foetal neuronal vesicles (FNVs) from maternal blood, effectively serving as a 'foetal brain liquid biopsy'. These vesicles allow for the early and non-invasive detection of neuronal dysfunction in pregnancies complicated by FGR. In FGR cohorts, distinct protein expression patterns have been identified within FNVs, including significant alterations in pro-BDNF and presynaptic proteins such as synaptophysin. These changes often precede clinical manifestations and are associated with a higher risk of intraventricular haemorrhage in newborns (96).

The primary question asked by this team was whether FNEs isolated from maternal blood could serve as a clinical surrogate to detect early and substructural signs of foetal brain damage in utero before permanent neurological deficits manifest postnatally. They questioned the safety of the classic

'brain-sparing effect' observed during Doppler ultrasonography. While macrovascular Doppler studies reveal blood flow redistribution to preserve the foetal brain during placental insufficiency, Gusar *et al* (97) investigated whether these hemodynamic shifts provide true neuroprotection or paradoxically aggravate neuronal damage through oxidative stress and reperfusion injury.

*Explanatory hypotheses for discrepant and paradoxical BDNF dynamics.* A major challenge in perinatal neuroendocrinology is explaining compartmental BDNF paradoxes, most notably the finding where AF-BDNF concentrations are elevated or sustained in growth-restricted pregnancies, while corresponding umbilical cord blood BDNF levels are severely depleted. Similarly, maternal peripheral serum BDNF increases in severe PE despite marked downregulation within preeclamptic placental tissue (1,11,42). To account for these compartmental divergences, four explanatory hypotheses are systematically evaluated below:

**Hypothesis 1: The compensatory brain-sparing mechanism and central neuroprotective transudation.** Under chronic placental insufficiency and intrauterine hypoxia, the foetus triggers an adaptive cardiovascular mechanism known as the 'brain-sparing effect' (97). This response redistributes cardiac output to prioritize blood flow to the brain, myocardium and adrenal glands, mediated by MCA vasodilation and increased systemic vascular resistance (41). Amniotic fluid functions as an integrative reservoir, capturing cumulative foetal excretory products and resulting in elevated AF-BDNF levels. By contrast, umbilical cord blood BDNF reflects immediate and real-time output from the placental factory and foetal peripheral endothelial beds. Cord blood BDNF concentrations fall because the hypoxic placenta suffers structural damage and downregulation of local BDNF expression. The elevated AF-BDNF serves as a marker of central neuronal stress and compensatory brain-sparing, whereas the low cord blood BDNF signals peripheral placental vascular exhaustion (1,42).

**Hypothesis 2: Impaired proteolytic cleavage, pro-BDNF accumulation and receptor switching.** A second explanation focuses on post-translational processing impairments induced by local tissue inflammation and oxidative stress. In pathological states, such as in severe PE, FGR and maternal immune activation, elevated levels of ROS and pro-inflammatory cytokines (such as IL-6 and TNF- $\alpha$ ) suppress the enzymatic activity of intracellular furin and extracellular convertases, including plasmin, MMP-2 and MMP-9. This enzymatic inhibition blocks the cleavage of pro-BDNF into mBDNF, altering the pro-BDNF/mBDNF ratio (3,11,41).

**Hypothesis 3: Compartmental sequestration, exosomal trafficking and blood-brain barrier trapping.** A third mechanism involves vesicular packaging and exosomal transport across the maternal-foetal-placental unit. Central foetal neurons package neuroprotective factors, post-translational modifiers (such as sumoylation proteins SUMO2/3/4 and neddylation proteins NAE1/UBC12), and neurotrophic precursors into FNEs or FNVs. Assays that analyse un-fractionated serum or plasma record low free BDNF levels in cord blood, even as FNE-packaged neurotrophic cargo surges as an endogenous protective response to cerebral hypoperfusion (42,96).

**Hypothesis 4: Vitamin D depletion, epigenetic vitamin D receptor (VDR) deregulation and attenuated BDNF transcription.** An additional mechanistically distinct hypothesis links maternal and foetal BDNF deficits to systemic vitamin D deficiency (VDD) and disrupted VDR signalling. Active 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] functions as a potent steroid hormone that readily crosses the placenta and blood-brain barrier (109). Maternal VDD, combined with placenta-derived oxidative stress, downregulates placental VDR and CYP27B1 [the enzyme synthesizing active 1,25(OH)2D3], blunting local autocrine and paracrine vitamin D signalling, where the absence of sufficient active VDR-RXR complex binding leads to the epigenetic silencing at the *BDNF* locus. Consequently, tissues fail to mount an adequate transcriptional BDNF response, compromising trophoblast invasion, foetal vascular endothelial repair and hippocampal neurogenesis. Supplementation with vitamin D has been shown to restore VDR-mediated BDNF gene transcription, mitigate HPA axis hyperactivation, and attenuate hypoxia-induced neurodevelopmental deficits (17,110).

The foetal programming hypothesis suggests that prenatal exposure to maternal psychological distress can 'reprogram' foetal development, leading to an increased risk of behavioural and psychiatric disorders later in life. BDNF is a central player in this process, as its levels in both maternal and foetal serum are directly influenced by the stress hormone cortisol (8). When a pregnant woman experiences chronic stress or acute trauma, the activation of her HPA axis results in elevated circulating glucocorticoids. These hormones can cross the placental barrier and interfere with BDNF signalling through several pathways, including the downregulation of BDNF mRNA and the induction of epigenetic modifications (23,34). According to Christian *et al* (11), the optimal cut-off for serum BDNF as an indicator of postpartum depression was estimated to be 12.0 ng/ml, yielding a sensitivity of 82.8% and a specificity of 72.6% (11). This reduction in foetal circulating BDNF may serve as a biological marker for the negative effects of maternal emotional stress on the developing brain (75,98,99). According to Fung *et al* (100), women whose early-pregnancy serum BDNF levels fall in the lowest three quartiles (<17.32 ng/ml) exhibit a 1.61-fold increased odds of developing antepartum depression compared to those in the highest quartile (>25.31 ng/ml; 95% CI, 1.13-2.30). Furthermore, serum BDNF measured at parturition serves as a potent predictive biomarker for PPD (100).

One of the most compelling mechanisms by which maternal experience is biologically embedded in the offspring is through DNA methylation of the BDNF gene. DNA methylation typically involves the addition of a methyl group to CpG sites within promoter regions, which often leads to transcriptional silencing (34). Studies of mothers exposed to extreme trauma, such as war stress in the Democratic Republic of Congo, have identified specific BDNF methylation patterns in maternal blood, placental tissue and umbilical cord blood (23). The tissue-specificity of these effects is high; for example, trauma may be associated with hypomethylation in maternal blood; however, hypermethylation at different sites in the placenta or cord blood. This suggests that the epigenetic response to stress is highly nuanced and tailored to the specific functional requirements of each tissue during development (23,101).

*Genetic and environmental modulators of BDNF in pregnancy.* Maternal exposure to environmental contaminants, such as per- and polyfluoroalkyl substances (PFAS) and heavy metals [lead (Pb), mercury (Hg), cadmium (Cd) and arsenic (As)], has also been linked to alterations in the BDNF signalling pathway. Research PFAS has shown that certain compounds, specifically perfluorononanoic acid, can disrupt BDNF signalling in placental trophoblast cells. These environmental endocrine disruptors readily cross the placental barrier and are associated with adverse neurobehavioral outcomes in children, likely through the suppression of neurotrophic support during critical periods of brain development (20). Exposure to heavy metals during the first trimester has been significantly associated with lower circulating BDNF levels, highlighting the vulnerability of this neurotrophic system to industrial pollutants. Blood As concentrations have been positively associated with a 2.6-fold increased risk of low plasma BDNF levels in early pregnancy. Pb exposure has been inversely correlated with placental and umbilical cord levels of kisspeptin-1 and BDNF, while Cd has been shown to increase the levels of the pro-apoptotic pro-BDNF isoform in trophoblast cells. These environmental stressors disrupt the 'internal exposome', potentially leading to long-term neurodevelopmental vulnerabilities in the offspring (3,27,32). Zaw *et al* (32) thoroughly investigated the toxicological control aspect of neurotrophin levels. Studying a cohort of pregnant migrant women exposed to industrial pollutants, they revealed the mechanisms of BDNF suppression under the influence of heavy metals, specifically arsenic (32). Their study confirmed that toxic environmental pressure can completely disrupt the natural trajectory of BDNF as early as the first trimester of pregnancy, creating conditions for aberrant development of the foetal cerebral cortex (33).

BDNF has been investigated as a biomarker for several major gestational complications, with varying levels of clinical utility and predictive performance. In PE, BDNF appears to be a potential predictor of disease severity; however, its diagnostic accuracy is currently considered moderate and requires further validation. For GDM, BDNF levels exhibit an inverse association with maternal glucose concentrations. Studies have reported a strong association between altered BDNF levels and GDM, indicating that BDNF may be particularly useful for identifying more severe cases of the disorder (53-60). BDNF has also shown relevance in FGR and SGA pregnancies. Measurements in cord blood have been proposed as indicators of foetal growth impairment, and significant associations have been observed in Doppler-based assessments. These findings suggest that BDNF may possess considerable prognostic value in monitoring foetal growth outcomes (66,67).

Given the associations between BDNF and major gestational complications, there is a clear impetus for evaluating BDNF as a clinical biomarker and as a target for therapeutic intervention. Integrating biochemical markers like BDNF with biophysical parameters (such as uterine artery Doppler) and maternal characteristics using artificial intelligence and machine learning models has shown promise in achieving detection accuracies as high as 93.4% (43,102).

*Mechanisms of correction: Lifestyle and pharmacology.* Maternal lifestyle factors can enhance BDNF bioavailability and improve offspring outcomes. Maternal physical

exercise during pregnancy increases BDNF levels and neuronal cell numbers in the hippocampal formation of the offspring, leading to improved cognitive performance in non-associative and associative memory tasks. According to Gomes da Silva *et al* (104), physical activity during pregnancy has been identified as the most effective lifestyle intervention for increasing BDNF levels and reducing the risk of complications, such as GDM. Structured exercise, specifically combined aerobic and resistance training, leads to favourable changes in metabolic markers and anti-inflammatory cytokines (104). Animal models further demonstrate that maternal exercise increases hippocampal cell numbers and BDNF levels in offspring, directly improving their cognitive performance in spatial learning tasks (104-106). Similarly, nutritional supplementation with omega-3 fatty acids, particularly DHA, can protect against the neurotrophic deficits caused by micronutrient-imbalanced diets. Nutritional strategies, including the optimization of omega-3 fatty acid intake, may also support the BDNF axis, as DHA is known to regulate neurotrophin expression (45,104,107).

Pharmacological strategies are also being explored. Since BDNF has a short half-life and poor blood-brain barrier permeability, small-molecule BDNF mimetics such as 7,8-dihydroxyflavone are being investigated in preclinical models for their ability to activate TrkB signalling and mitigate neurodegenerative and metabolic diseases (16). As reviewed by Escobar *et al* (82) clinical trials are also assessing the use of nutraceutical supplements, such as anthocyanins and alpha-cyclodextrins, to reduce oxidative stress and preserve metabolic health in pregnancies affected by GDM (82). According to the Numakawa *et al* (16), small molecules like coumarin derivatives (LM-031) and flavonoids (7,8-DHF) have exhibited potential in activating the TrkB pathway and protecting neurons from toxicity in preclinical studies (16). These compounds could eventually provide a therapeutic strategy for severe BDNF deficiencies in pregnancy, although their safety profile for human gestation is yet to be established. By monitoring maternal BDNF levels alongside other biomarkers such as sFlt-1/PIGF or Vitamin D, clinicians can better predict the onset of PE, GDM and perinatal depression (27,108).

*Knowledge gaps and future directions.* Several gaps remain in the current understanding of BDNF in pregnancy:

**Longitudinal stability:** The majority of studies focus on specific snapshots. To establish true prognostic value, prospective longitudinal studies with serial sampling starting in early first trimester (weeks 11-13) are urgently required. Evaluating early BDNF trajectory deviations prior to symptom onset is critical to identify early predictive windows for PE and FGR (11,41,68).

**Isoform distinction:** Although the majority of current ELISAs do not differentiate between pro-BDNF and mBDNF, these isoforms have diametrically opposite biological effects. As a result, these assays measure total BDNF rather than distinguishing between precursor and cleaved isoforms. A patient may maintain a stable total BDNF levels, while experiencing a pathological transition toward elevated pro-BDNF and reduced mBDNF, masking early placental ischemia (20,52).

**Biological and patient-level confounding variables:** Peripheral BDNF expression is modulated by several maternal physiological, genetic and environmental factors that must be accounted for to ensure accurate biomarker interpretation: Maternal pre-pregnancy BMI, systemic inflammation and acute-phase reactants [systemic inflammatory states, characterized by elevated levels of C-reactive protein or pro-inflammatory cytokines (IL-6 and TNF- $\alpha$ )], genetic and epigenetic variants (the SNP rs6265 within the *BDNF* gene substitutes methionine for valine at codon 66 within the 5' pro-domain region), metabolic dynamics and glycemic flux, racial disparities (12,20,26,33,60,65).

**Environmental interactions:** The impact of environmental pollutants such as PFAS, maternal smoking, nutritional status and chronic psychological stress induce epigenetic modifications, specifically altering DNA methylation at the BDNF promoter IV region (12,20,26).

**Pre-analytical bottlenecks and methodological standardization:** A major practical obstacle to implementing BDNF in routine clinical diagnostics is its extreme sensitivity to pre-analytical variables (7,14,102). For diagnostic purposes, serum is currently recommended for its higher stability and sensitivity to systemic changes, provided that clotting and centrifugation protocols are standardized (3,19,83).

**The lack of gestational age-specific reference intervals:** From a practical standpoint, a biomarker cannot be utilized at the bedside without clear normative ranges. Developing these baseline gestational trajectories is an essential prerequisite for clinicians to distinguish physiological fluctuations from true pathological deviations in PE or FGR.

**Overcoming these obstacles requires standardized sampling protocols, multi-marker panel integration, liquid biopsy technology and point-of-care testing platforms.** Establishing clinical utility requires standardized pre-analytical handling protocols across research and diagnostic networks: Standardized centrifugation protocols should enforce a primary low-speed separation (for 10 min at 4°C) within 30 min of phlebotomy, followed immediately by a secondary high-speed centrifugation (for 10 min at 4°C) to clear residual platelets (76,102).

**Overcoming diagnostic non-specificity via multi-marker integration:** To realize the diagnostic potential of BDNFs, future clinical strategies should integrate BDNF (or the pro-BDNF/mBDNF ratio) into composite multi-marker diagnostic algorithms alongside established obstetric parameters, such as the sFlt-1/PIGF ratio, pregnancy-associated plasma protein-A and uterine artery Doppler pulsatility index. Machine learning-driven multi-marker panels represent the most viable pathway toward high sensitivity and specificity in early risk stratification (3,11,104).

**Extracellular vesicle isolation and foetal liquid biopsy:** Isolating cell-specific extracellular vesicles from maternal blood provides a promising approach to bypass maternal systemic noise, such as BMI variations, platelet contamination and acute-phase inflammatory responses. Isolating these vesicles using cell-specific surface markers enables direct analysis of their internal neurotrophic protein cargo (including pro-BDNF and mBDNF). This vesicle-bound pool remains protected from plasma protease degradation and avoids confounding by maternal systemic inflammation or adiposity, delivering a direct 'liquid biopsy' of foetal brain and placental state (97).

**Assay standardization and point-of-care translation:** Current research heavily relies on benchtop ELISA kits, which exhibit high inter-assay variability and lack cross-platform standardization. Furthermore, traditional ELISAs cannot differentiate between neuroprotective mBDNF and pro-apoptotic pro-BDNF. The development of standardized, automated immunoassay platforms and point-of-care microfluidic devices capable of rapidly quantifying BDNF isoforms at the bedside represents a critical technological milestone for future clinical translation. These point-of-care platforms enable near-patient risk stratification during routine prenatal visits, facilitating early intervention for hypertensive or metabolic gestational disorders (102).

In conclusion, the evidence presented in the present scoping review establishes BDNF as a dual-purpose master regulator at the maternal-foetal interface. Its roles span from the microscopic, which means facilitating implantation and trophoblast survival, to the systemic, where it orchestrates vascular remodelling and metabolic homeostasis. The synthesis of high-impact research indicates that BDNF is not merely a bystander in pregnancy but a fundamental determinant of gestational outcome.

The role of BDNF in the development of gestational complications is multifaceted and profound. BDNF is an essential component of the molecular architecture that ensures successful implantation, robust placental growth, and systemic metabolic adaptation during pregnancy. Its dysregulation is a common thread running through PE, GDM and FGR, as well as perinatal mood disorders. The evidence suggests that a deficiency in BDNF early in gestation can set the stage for placental insufficiency and maternal metabolic failure, while the foetal system attempts to compensate through adaptive increases in amniotic fluid neurotrophins.

The mapping of obstetric complications reveals a consistent 'neurotrophic deficit' associated with PE, GDM and FGR. In each of these conditions, the reduction of BDNF bioavailability compromises the ability of the placenta to support the foetus, leading to immediate obstetric risks and long-term neurodevelopmental challenges for the child, specifically an increased risk of ASD and ADHD.

The present scoping review of BDNF in the context of pregnancy and neurodevelopmental programming underscores its role as an indispensable regulator of early human life. The synthesized evidence demonstrates that BDNF serves as a critical proxy for maternal-foetal health, reflecting the cumulative impact of genetic, psychological and environmental factors. However, its successful adoption as a clinical biomarker for gestational complications requires addressing clear methodological and physiological challenges.

To realize the diagnostic potential of BDNF in clinical obstetrics, the field must pursue a structured translational roadmap: First, diagnostic networks must implement standardized serum processing protocols. Second, commercial assay development must transition from non-specific 'total BDNF' measurements to isoform-specific platforms capable of quantifying the proBDNF/mBDNF ratio. Third, clinical trials must validate multi-marker diagnostic panels that combine BDNF with sFlt-1/PIGF, Kisspeptin-1 and maternal clinical covariates (BMI, gestational age, genotype). Finally, research is required to focus on validating non-invasive foetal neuronal and placental extracellular vesicle isolation

to query foetal-placental status while bypassing maternal systemic confounders directly. Future research must prioritize the standardization of longitudinal protocols and investigate the clinical efficacy of lifestyle interventions, such as structured resistance and aerobic exercise, which have shown promise in modulating metabolic and inflammatory biomarkers. Additionally, further research is warranted to investigate the dynamics of BDNF during the very early stages of pregnancy, including the pre-implantation and implantation periods, as these windows may dictate the long-term neurotrophic programming of the offspring. Ultimately, the transition of BDNF from a research target to a formal clinical screening tool offers a transformative opportunity to optimize maternal health and improve neonatal neurodevelopmental trajectories.

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### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

### Authors' contributions

The present scoping review was prepared by all the authors (GS, GT and MS) who conceived and designed the study, wrote the manuscript and contributed to its composition, editing and critical revision. All authors (GS, GT and MS) participated in the revision of the manuscript to ensure that it contained important intellectual content. All authors have read and approved the final manuscript. GT and MS confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

Not applicable.

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Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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