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Editorial

Maternal Stress Across the Maternal–Fetal Interface.

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Abstract

Maternal psychological stress during pregnancy is increasingly recognized as an important component of the maternal–fetal environment, interacting with neuroendocrine, inflammatory, metabolic, oxidative, genetic, and placental pathways. Rather than representing a direct cause of adverse pregnancy outcomes, maternal distress should be understood within a multidimensional framework of biological vulnerability and physiological adaptation. Emerging evidence supports moving beyond isolated biomarkers toward integrated assessment and, importantly, translating research into action. This editorial highlights a continuum from maternal-stress research and early identification to workforce education, screening and referral, and accessible, culturally appropriate interventions. Integrating maternal mental health into routine antenatal care may provide an important opportunity to move from documenting risk toward prevention, resilience, and better long-term health for mothers and their children.

Keywords:
Maternal Psychological Stress, Maternal–Fetal Interface, Perinatal Mental Health, Multimodal Biological Framework, Low- And Middle-Income Countries

The Problem Begins Before Birth

Pregnancy is one of the most biologically dynamic periods of a woman's life. The maternal cardiovascular, metabolic, immune, endocrine and nervous systems adapt simultaneously while the placenta supports a rapidly developing fetus. Yet in routine antenatal practice, the psychological component of this adaptation remains comparatively easy to overlook. We measure blood pressure because hypertension can harm mother and child; we test blood glucose because hyperglycaemia matters; we monitor fetal growth because altered growth can signal risk. Psychological distress, by contrast, may be documented only when it becomes severe enough to meet criteria for anxiety, depression or another mental-health disorder. WHO's guidance on perinatal mental health explicitly argues for integrating identification and response into maternal and child health services rather than treating mental health as a separate concern. We argue that this division between the "emotional" mother and the "physical" pregnancy is increasingly difficult to defend. Maternal stress is first experienced psychologically, but the stress response is expressed through physiology. At the same time, we must resist a second error: replacing neglect with overstatement. Stress is neither a universal explanation for obstetric disease nor a reason to blame a woman for complications during pregnancy. The emerging evidence instead supports a more nuanced proposition: maternal psychological state is one component of the intrauterine environment, interacting with biological vulnerability, disease, nutrition, social conditions and placental function [1,2]. This matter because fetal development, and especially brain development, is extraordinarily time-sensitive. The phrase two brains under stress should therefore be understood as a translational metaphor, not as a claim that mother and fetus experience stress identically. One brain perceives and regulates the maternal environment; the other is developing within the biological consequences of that environment. Recent neuroimaging reviews find associations between prenatal maternal distress and differences in fetal and infant brain structure and function, particularly in circuits involving the limbic system, prefrontal cortex, hippocampus and amygdala. These findings are important, but heterogeneous and predominantly observational; they indicate altered developmental trajectories and probabilities, not predetermined outcomes [2].

Biological Embedding and What Our Studies Add

The hypothalamic–pituitary–adrenal axis is an intuitive starting point. Psychological challenges can alter glucocorticoid physiology, and cortisol is frequently proposed as a mediator connecting maternal experience to pregnancy biology. Yet cortisol should not be treated as a simple biochemical equivalent of "how stressed a woman is." A 2023 scoping review of 48 studies found that associations between stress exposures and prenatal cortisol varied according to timing, type of stress and methodological factors, with earlier-life stress showing more consistent relationships than proximal pregnancy stress [1]. This is exactly why maternal stress research benefits from a multimarker rather than single-marker model.

Other candidate pathways include inflammatory signaling, autonomic and metabolic regulation, oxidative balance and placental communication. Maternal distress has been associated in the wider literature with changes in inflammatory markers including C-reactive protein and cytokine signaling, while placental pathways can influence fetal exposure to hormones, nutrients and inflammatory signals. Recent reviews therefore conceptualize the placenta not as a passive barrier but as a central mediator of maternal–fetal communication [2]. Blood pressure, heart rate and glucose add clinically accessible information about cardiovascular and metabolic state, although none is specific enough to be labelled a "stress biomarker" in isolation.

Oxidative biology adds another layer. In our multicentre case-control study of 240 pregnant women, serum glutathione progressively decreased across normotensive pregnancy, pregnancy-induced hypertension, pre-eclampsia and eclampsia, with the lowest concentrations in the eclampsia group; fetal biparietal diameter and femur length also differed across groups [3]. Our related work examining selenium in hypertensive pregnancy similarly treated antioxidant status as part of the maternal–fetal biological environment [9]. These findings support the importance of oxidative and antioxidant pathways in complicated pregnancy. They do not demonstrate that psychological stress caused glutathione depletion, pre-eclampsia or altered fetal growth. Their value to a maternal-stress framework is that they identify redox physiology as one dimension that can be studied alongside psychological, endocrine, inflammatory and metabolic measures rather than interpreted in isolation.

Our subsequent work in GDM extends this multidimensional thinking into neurohormonal genetics. Abid et al. studied 140 pregnant women, 50 with GDM and 90 healthy pregnant controls and examined OXTR rs53576 and MTNR1B rs1387153 together with perceived stress and diabetes-related distress [4]. Among women with GDM, MTNR1B genotype was associated with perceived stress and several dimensions of diabetes-related distress, while OXTR genotype was associated with regimen-related distress [4]. These are associations from a relatively small case-control study. They should not be translated into claims of a "stress gene," nor do they show that these variants cause GDM. Rather, they illustrate a more useful question for precision maternal health: why do women exposed to apparently similar psychosocial and metabolic demands differ in their psychological and physiological responses?

The research model that emerges is therefore layered: validated questionnaires for stress, anxiety and depression; neuroendocrine measures such as cortisol; inflammatory measures such as CRP and interleukins; cardiovascular and metabolic parameters including blood pressure, heart rate and glucose; antioxidant measures such as glutathione and selenium; and candidate neurohormonal or metabolic genetic pathways such as OXTR and MTNR1B. These domains should not be considered isolated or necessarily sequential mechanisms; rather, they represent potentially interacting dimensions of maternal biology that may converge at the maternal–fetal interface and be associated with maternal, fetal, and longer-term child outcomes.

This multimodal conceptual framework, extending from maternal psychosocial assessment through biological pathways to the maternal–fetal interface and subsequent maternal and child outcomes, is summarized in Figure 1. Importantly, these biological pathways function as parallel, interacting networks rather than direct linear causes. The purpose is not to create an expensive laboratory panel for every pregnant woman. It is to understand, through research, which combinations eventually yield simple, clinically actionable risk information.

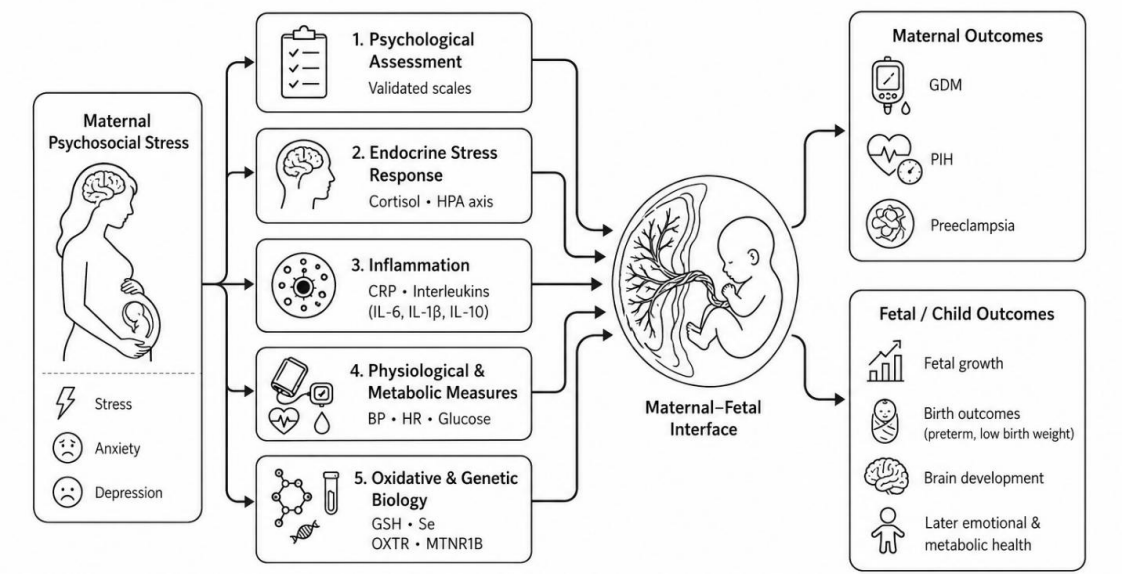

Figure 1: Multimodal framework linking maternal psychosocial stress, biological pathways, and maternal–fetal outcomes during pregnancy. Abbreviations: BP, blood pressure; CRP, C-reactive protein; GDM, gestational diabetes mellitus; GSH, glutathione; HPA, hypothalamic–pituitary–adrenal; HR, heart rate; MTNR1B, melatonin receptor 1B; OXTR, oxytocin receptor; PIH, pregnancy-induced hypertension; Se, selenium.

The framework illustrates a multimodal approach to studying maternal psychosocial distress, including stress, anxiety, and depression, through validated psychological assessment and potentially interacting biological domains. These include endocrine stress responses involving cortisol and the hypothalamic–pituitary–adrenal (HPA) axis; inflammatory signaling involving C-reactive protein (CRP) and interleukins; physiological and metabolic measures including blood pressure (BP), heart rate (HR), and glucose; and oxidative and genetic factors including glutathione (GSH), selenium (Se), OXTR, and MTNR1B. These domains may interact at the maternal–fetal interface and are relevant to the investigation of maternal outcomes, including gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), and pre-eclampsia, and fetal/child outcomes including fetal growth, preterm birth, low birth weight, brain development, and later emotional and metabolic health.

The Developing Brain and the Child Beyond Birth

The fetal brain is especially relevant because its architecture is being established during a period when maternal endocrine, immune, metabolic and placental signals continuously shape the intrauterine environment. A 2024 systematic review of 71 neuroimaging studies reported that prenatal maternal anxiety, stress or depression was associated across studies with structural and functional differences involving the limbic system, prefrontal cortex and insula during fetal life and the first year after birth [8]. A complementary Molecular Psychiatry review described reported differences in fetal and childhood cerebral and cerebellar volumes, cortical folding, microstructure and functional connectivity, including findings involving the hippocampus and amygdala [2].

These observations offer a plausible biological foundation for associations reported between prenatal maternal distress and later cognitive, emotional and behavioural outcomes, but they should be communicated with care. Neurodevelopment is influenced by genetics, postnatal caregiving, nutrition, illness, socioeconomic conditions, education and countless subsequent experiences. Maternal stress is therefore a modifiable risk exposure, not a developmental destiny. That distinction is scientifically important and ethically essential: knowledge about prenatal stress must empower mothers, never burden them with guilt [2,8].

From Evidence to Solution

The central question for the next phase of this field is no longer only, Can we measure maternal stress? It is, What can we realistically do when we identify it? WHO recommends embedding perinatal mental-health capacity within maternal and child health services, including workforce education, appropriate identification, culturally responsive care, referral pathways, supervision and implementation monitoring [5]. In LMIC settings, this means obstetricians alone cannot carry the responsibility. Midwives, nurses, family physicians, psychologists and appropriately trained community health workers need basic competency in recognising psychological distress, asking about social adversity, responding without stigma and escalating women who require specialist care. Screening without a pathway to assistance is not sufficient.

Pakistan provides particularly encouraging evidence for task-sharing. In the phase III Happy Mother–Healthy Baby randomized trial, pregnant women with at least mild anxiety but without clinical depression received six individual CBT-based sessions delivered by non-specialist providers. At six weeks postpartum, women assigned to the intervention had 81% lower adjusted odds of the joint outcome of major depression or moderate-to-severe anxiety than those receiving enhanced usual care; major depressive episodes occurred in 12% versus 41%, respectively [6]. This is powerful evidence that sophisticated maternal mental-health benefit does not always require specialist-led, high-cost delivery.

There is also scope for lower-intensity supportive approaches. A 2024 systematic review and meta-analysis of 32 studies involving 3,979 pregnant women found that relaxation interventions, including breathing and progressive muscle relaxation, mindfulness, yoga, music and related approaches, reduced maternal stress, anxiety and depressive symptoms overall, although heterogeneity between trials was very high and effects on obstetric or newborn outcomes were less consistent [7]. Thus, the strongest immediate claim is improvement in maternal psychological well-being; not yet prevention of pre-eclampsia, GDM or neurodevelopmental disorders.

Other low-cost strategies deserve a similar evidence-sensitive approach. Nature exposure is promising: an experimental study of pregnant women found acute physiological and affective responses to simulated green-space exposure, but this is not yet equivalent to evidence that nature therapy prevents pregnancy complications [10]. Appropriate physical activity, mindfulness/meditation, sleep support and strengthened partner, family and peer support can be incorporated into multimodal maternal-wellness programs and evaluated pragmatically. HRV biofeedback is also promising but rests on a comparatively small pregnancy evidence base; one randomized study included only 20 pregnant women within a total sample of 50 [11]. Neurofeedback has substantially less pregnancy-specific evidence and should be presented as an intervention requiring clinical trials, not as established antenatal care.

Our research agenda should consequently move from association to intervention through well-designed clinical and implementation trials. Trials should measure not only questionnaire scores but, where feasible, physiological intermediates, cortisol patterns, autonomic indices, inflammatory or oxidative markers, along with clinically meaningful maternal, obstetric, neonatal and longer-term developmental outcomes. Equally important is community translation: awareness sessions, free health camps, professional development, maternal-health education and community engagement can connect published findings with women who might otherwise never encounter them. This translation can be conceptualized as a continuum extending from research and risk identification to workforce education, screening and referral, accessible and scalable interventions, and ultimately improved maternal and child health (Figure 2). The aim is not to turn every community program into a laboratory, but to create a continuum from discovery to prevention, referral and public-health impact, consistent with WHO's integrated-care approach [5].

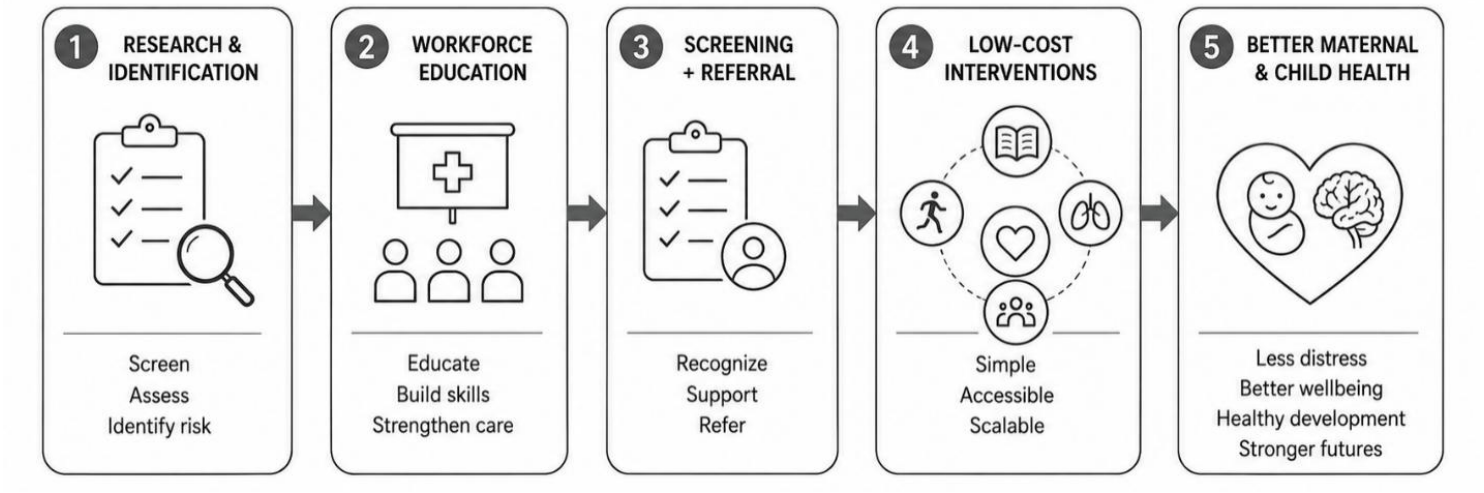

Figure 2: Translational pathway from maternal stress research to preventive maternal and child health interventions.

The figure represents a proposed translational continuum and should not be interpreted as a proven sequential causal pathway. The proposed translational continuum illustrates how research on maternal psychological distress and associated biological and clinical risk factors can progress toward preventive maternal and child health practice. The pathway begins with research, assessment, and identification of potentially modifiable risk factors, followed by workforce education and capacity-building. Integration of appropriate psychosocial screening into maternal healthcare can facilitate early recognition, first-line support, and referral when additional or specialist care is required. Evidence-supported, accessible, and scalable interventions may include psychological and behavioral approaches, appropriate physical activity, relaxation and mindfulness-based strategies, social and family support, and other interventions according to the evidence base and available local resources. The intended public-health goals are reduced psychological distress, improved maternal well-being, healthier child development, and stronger long-term maternal and child health.

A Call to Action for Pakistan and Other LMICs

For Pakistan, the argument is urgent. WHO currently reports a maternal mortality ratio of 155 deaths per 100,000 live births [12]. A 2024 Pakistan-specific systematic review and meta-analysis estimated GDM prevalence at 16.7% approximately one in six pregnancies, although estimates varied substantially according to region and diagnostic criteria [13]. WHO estimates that pre-eclampsia affects 3–8% of women giving birth worldwide; importantly, that 3–8% is a global figure and should not be presented as a Pakistan-specific prevalence estimate [12].

The neonatal figure also requires precision. While 36 deaths per 1,000 live births is frequently cited as a rounded estimate, recent UN Inter-agency Group for Child Mortality Estimation data place Pakistan at approximately 37.6 neonatal deaths per 1,000 live births for 2023 (or approximately 38 per 1,000) [14].

These statistics do not imply that maternal psychological stress accounts for Pakistan's maternal or neonatal mortality in isolation. Obstetric haemorrhage, hypertensive disorders, infection, metabolic disease, prematurity, access to skilled care and broader social determinants remain critical. The policy argument is different: in a health system already carrying a substantial maternal and neonatal burden, overlooking a potentially modifiable dimension of maternal health is a lost opportunity. Antenatal care should progressively include brief culturally validated psychosocial assessment, trained first-line responses, referral for severe illness or safeguarding concerns, and scalable preventive interventions alongside, not instead of blood-pressure monitoring, glucose screening and high-quality obstetric care [5].

The call to action is therefore straightforward. We need to educate the workforce, normalise conversations about maternal mental health, build task-shared interventions, test affordable stress-management strategies through rigorous trials, follow children beyond birth, and evaluate what can actually be implemented at scale. Above all, we must shift from asking whether maternal stress is "psychological or biological." It is experienced psychologically and expressed within biology, while remaining embedded in family and society. The future of maternal-health research lies in understanding these levels together. If science can identify vulnerability before crisis, and convert that knowledge into accessible support, maternal stress research can move from documenting risk to creating resilience, for the mother, the developing child and the next generation.

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