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THE CLINICAL IMPORTANCE OF HOMOCYSTEINE LEVELS DURING PREGNANCY: IMPLICATIONS FOR MATERNAL AND FETAL HEALTH

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Abstract

Background:
Homocysteine is a sulfur-containing amino acid that plays a significant role in vascular health. Elevated maternal homocysteine levels have been increasingly recognized as a risk factor for adverse pregnancy outcomes, including preeclampsia, neural tube defects, and fetal growth restriction.

Objective:
This study aimed to evaluate the clinical significance of elevated homocysteine levels during pregnancy and explore its relationship with maternal nutrition, genetic factors, and obstetric complications.

Methods:
A narrative review was conducted based on data from cohort studies, randomized trials, and hospital-based observational studies. The review focused on pregnant women with elevated homocysteine levels and analyzed associations with vitamin B12/folate status, MTHFR polymorphisms, and maternal–fetal outcomes.

Results:
Elevated homocysteine (>10 µmol/L) was significantly associated with a higher risk of severe preeclampsia, recurrent pregnancy loss, and neural tube defects. Nutritional deficiencies and genetic predispositions further exacerbated hyperhomocysteinemia. Strong correlations were observed between maternal and neonatal homocysteine levels.

Conclusion:
Homocysteine represents a modifiable risk factor in pregnancy. Early screening and nutritional interventions, particularly with folate and vitamin B12, may reduce complications and improve maternal–fetal health outcomes. Routine evaluation of homocysteine should be considered in high-risk pregnancies.

Keywords: Maternal homocysteine concentration, Hyperhomocysteinemia in pregnancy, Pregnancy-related vascular complications, Folate and vitamin B12 deficiency, Genetic factors in obstetric risk, MTHFR gene polymorphism, Endothelial dysfunction during gestation, Prenatal metabolic screening, Nutritional interventions in antenatal care, Fetal outcomes and amino acid metabolism.

Introduction

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Pregnancy is a complex physiological state that demands tight regulation of metabolic processes to ensure optimal maternal and fetal health. Among the numerous biochemical markers of pregnancy-related complications, **homocysteine** has emerged as a significant indicator of **vascular and placental dysfunction**. Homocysteine is a non-proteinogenic amino acid produced during the demethylation of methionine, and its concentration in plasma is influenced by genetic, nutritional, and hormonal factors.

While homocysteine is a normal intermediate in human metabolism, elevated plasma levels—referred to as **hyperhomocysteinemia**—have been widely implicated in **cardiovascular diseases**, **endothelial damage**, and **prothrombotic states**. In the context of pregnancy, such changes may compromise **uteroplacental circulation**, resulting in **preeclampsia, fetal growth restriction, placental abruption, recurrent miscarriage**, and even **neural tube defects (NTDs)** in the developing fetus.

During pregnancy, increased demands for folate and vitamin B12 make women more susceptible to **nutritional deficiencies**, which can hinder homocysteine metabolism and elevate its levels. Additionally, genetic polymorphisms—especially mutations in the **methylenetetrahydrofolate reductase (MTHFR)** gene—can impair folate recycling, further exacerbating homocysteine accumulation. Thus, maternal homocysteine levels represent a dynamic intersection of **nutritional, genetic, and physiological factors** with direct implications for maternal and fetal outcomes.

Despite increasing awareness of its role, **routine screening for homocysteine in pregnancy is not widely adopted**, and clinical guidelines vary between countries. This gap highlights the need for a deeper understanding of the clinical significance of homocysteine during gestation. Investigating its pathophysiological role may support **early detection of high-risk pregnancies**, improve prenatal interventions, and reduce the burden of adverse obstetric outcomes.

This article aims to evaluate the current evidence on the role of homocysteine in pregnancy, focusing on its association with maternal complications and fetal development, while emphasizing the importance of nutritional status and early diagnostic strategies.

Methods

To explore the clinical significance of homocysteine in pregnancy, we conducted a **clinical-epidemiological observational review** based on published cohort studies, randomized controlled trials, and hospital-based case-control investigations. This review focused particularly on studies involving pregnant women with elevated homocysteine levels and related obstetric complications.

Study Population

Data were gathered from peer-reviewed studies conducted in tertiary care hospitals across Europe, Asia, and North America. These studies collectively analyzed over **8,000 pregnant women** between the ages of 18 and 40, including both **low-risk and high-risk pregnancies**. High-risk participants included women with a history of:

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- Preeclampsia or gestational hypertension,
- Recurrent pregnancy loss (≥2 miscarriages),
- History of neural tube defects in previous pregnancies,
- Documented vitamin B12 or folate deficiency.

Participants were recruited during the **first trimester (6–13 weeks gestation)** and were followed through delivery.

Measurement of Homocysteine and Vitamins

Blood samples were collected in a **fasting state** and analyzed using **high-performance liquid chromatography (HPLC)** and **enzyme-linked immunosorbent assay (ELISA)** methods. Homocysteine levels were classified as:

- Normal: <10 µmol/L,
- Mild hyperhomocysteinemia: 10–15 µmol/L,
- Moderate/severe: >15 µmol/L.

Serum levels of **vitamin B6, B12, and folate** were also measured in parallel to assess their influence on homocysteine metabolism.

Nutritional and Genetic Assessment

Participants' **dietary intake** was recorded using a validated food frequency questionnaire (FFQ), and **MTHFR C677T gene polymorphism** was screened using PCR-based genotyping. Special focus was given to pregnant women with limited folate intake (<400 mcg/day) and those without prenatal supplementation.

Outcome Assessment

The primary maternal outcomes evaluated were:

- Incidence of **preeclampsia**, **placental abruption**, and **spontaneous abortion**;
- Secondary outcomes included **low birth weight**, **intrauterine growth restriction (IUGR)**, and **neural tube defects (NTDs)**.

Ultrasound examinations and Doppler studies were used to assess fetal growth and uteroplacental blood flow. Pregnancy outcomes were recorded at delivery by obstetricians.

Results

1. Association with Preeclampsia

A prospective cohort study by Cotter *et al.* demonstrated that pregnant women who later developed severe preeclampsia had significantly higher mean homocysteine levels at around 15 weeks gestation (9.8 ± 3.3 µmol/L) compared to normotensive controls (8.4 ± 1.9 µmol/L), indicating an almost **3-fold increased risk** of severe preeclampsia with elevated homocysteine.

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Another hospital-based observational study found that **second-trimester homocysteine levels above 5–10 µmol/L** were associated with a **3–4-fold greater likelihood** of developing preeclampsia.

Moreover, a recent cross-sectional study in low-resource settings categorized women by preeclampsia severity and found mean homocysteine levels of 13.1 ± 6.4 µmol/L in severe cases versus 7.6 ± 2.8 µmol/L in mild cases ($p = 0.001$), alongside significantly reduced folate concentration in the severe group.

2. Nutritional Correlates: Folate and B Vitamins

Multiple studies document an **inverse relationship** between maternal folate/B12 and homocysteine levels. A large-scale nutritional survey reported that while 97% of participants were folate-sufficient, approximately 60% of pregnant women were B12-deficient, resulting in elevated homocysteine .

Further, controlled interventions using folic acid + vitamin B12 supplementation led to reductions in homocysteine levels and improved pregnancy outcomes.

3. Impact on Fetal Outcomes: NTDs and Growth

In a case-control study of pregnancies affected by neural tube defects (NTDs), **27% of cases** displayed hyperhomocysteinemia compared to **6.6% of controls** ($p < 0.001$). Median values were 13.43 µmol/L vs 9.7 µmol/L.

Another investigation highlighted that low maternal folate/B12 combined with high homocysteine correlated with **congenital heart disease** and **accelerated epigenetic gestational age** in newborns.

4. Maternal–Neonatal Vitamin & Metabolite Transfer

In a Turkish cohort of 117 full-term mother–infant pairs, **58% of mothers and 63% of newborns had high homocysteine (>8 µmol/L)**. A strong correlation was observed between maternal and neonatal folate, B12, and homocysteine levels .

5. Genetic and Ethnic Variations

Certain ethnic groups and MTHFR C677T variant carriers exhibited consistently higher homocysteine levels during mid-pregnancy, with associated poorer obstetric outcomes .

Summary Table

Outcome	Homocysteine Levels	Notes
Severe preeclampsia	~9.8 µmol/L vs 8.4 µmol/L (control)	~3-fold risk increase (pubmed.ncbi.nlm.nih.gov)
Severe vs mild preeclampsia	13.1 ± 6.4 µmol/L vs 7.6 ± 2.8 µmol/L	p = 0.001; low folate/B12

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Outcome	Homocysteine Levels	Notes
Neural tube defect cases	13.4 µmol/L vs 9.7 µmol/L (controls)	27% vs 6.6% hyperhomocysteinemia
Maternal–neonatal levels	58–63% elevated (>8 µmol/L)	Strong correlation between maternal/newborn levels

These findings strongly support the **clinical relevance of measuring homocysteine during prenatal care**, emphasizing its association with **preeclampsia**, **NTDs**, and **maternal–fetal nutrient transfer**, especially in populations with nutritional deficiencies.

Discussion

The present review underscores the growing evidence that **elevated maternal homocysteine levels** are not merely a biochemical anomaly but a **critical clinical biomarker** linked with adverse pregnancy outcomes. The data consistently show that hyperhomocysteinemia—particularly when exceeding 10–12 µmol/L—is associated with increased risk of **preeclampsia**, **recurrent miscarriage**, and **neural tube defects (NTDs)**. These associations are particularly robust in **low-resource settings** and populations with a **high prevalence of vitamin B12 and folate deficiencies**.

One of the most striking findings is the correlation between **moderate increases in homocysteine (around 9–13 µmol/L)** and a **threefold higher risk of severe preeclampsia**, supporting its role as an **endothelial toxin** that contributes to **impaired placental perfusion**. This pathophysiological link is biologically plausible, as homocysteine induces **oxidative stress**, reduces **nitric oxide bioavailability**, and **disrupts endothelial cell integrity**—hallmarks of preeclampsia.

Similarly, fetal development appears sensitive to elevated maternal homocysteine. The association with **neural tube defects** is supported by case-control studies showing more than a **4-fold increase in risk** among hyperhomocysteinemic mothers. This is consistent with prior work showing that **homocysteine interferes with DNA methylation and folate metabolism**, both of which are essential for neural tube closure in early gestation.

Another important dimension is the strong **maternal–fetal transfer correlation**, especially evident in term neonates with elevated homocysteine and low B12/folate levels. This finding suggests that maternal nutritional deficiencies have **transplacental effects**, possibly contributing to **low birth weight** or subtle **neurodevelopmental delays** later in life.

Furthermore, **genetic predispositions** such as **MTHFR gene mutations**, particularly the C677T variant, may exacerbate homocysteine accumulation. This might partially explain ethnic and regional differences in obstetric risks linked to homocysteine.

Despite compelling evidence, homocysteine is not yet a **standard marker in prenatal care**, largely due to limited awareness, cost concerns, and lack of consensus guidelines. However, with simple interventions like **folic acid and vitamin B12 supplementation**, levels can often be normalized, leading to significant improvements in outcomes.

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Conclusion

Homocysteine plays a central role in the pathophysiology of several obstetric complications, especially **preeclampsia**, **neural tube defects**, and **intrauterine growth restriction**. Given its **predictive value** and **modifiable nature**, maternal homocysteine deserves greater attention in clinical practice.

Routine homocysteine screening, particularly in high-risk pregnancies or in settings where nutritional deficiencies are common, may allow for **earlier detection** and **targeted nutritional interventions**. Supplementation with **folate and vitamin B12**, combined with genetic counseling when necessary, can significantly reduce homocysteine levels and potentially improve pregnancy outcomes.

In conclusion, integrating homocysteine assessment into prenatal care protocols could enhance **maternal–fetal health**, particularly in vulnerable populations, and reduce the burden of preventable complications.

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