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Cobalamin Disorders in Gynecology and Obstetrics: Implications for Fertility, Pregnancy, and Offspring Health

Emmanuel Andrès[1,2*], Xavier Jannot[1,2], Jean-Edouard Terrade[1,2] & Noel Lorenzo Villalba[1,2]

[1]*Department of Internal Medicine, University Hospitals of Strasbourg, Strasbourg, France*
[2]*CARE B12 Network, Clinical and Academic Research on Cobalamin Deficiency (CARE B12), Strasbourg, France*

[*]**Corresponding author:** Emmanuel Andrès, Department of Internal Medicine, University Hospitals of Strasbourg, Strasbourg, France.

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Abstract
Cobalamin (vitamin B_{12}) plays a fundamental role in DNA synthesis, cellular division, and neurological development. Disorders of cobalamin metabolism are increasingly recognized as contributors to gynecological and obstetric complications. This review examines the pathophysiological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic implications of cobalamin deficiency in women of reproductive age, during pregnancy, and in the postpartum period. Gynecological manifestations include infertility, menstrual disorders, recurrent pregnancy loss, and cervical dysplasia. Obstetric consequences range from neural tube defects and fetal growth restriction to preeclampsia and adverse neurodevelopmental outcomes. Early detection and adequate supplementation are essential to improve maternal and fetal outcomes.

Keywords: Cobalamin. Vitamin B_{12}. Infertility. Menstrual Disorders. Pregnancy Loss. Cervical Dysplasia. Neural Tube Defect. Fetal Growth Restriction. Neurodevelopmental Outcomes.

Key Points

- Cobalamin deficiency is common in women of reproductive age and often underdiagnosed.
- Disorders of cobalamin metabolism impair DNA synthesis and placental function.
- Deficiency is associated with infertility, recurrent miscarriage, and adverse pregnancy outcomes.
- Neurological sequelae may affect both mother and offspring.
- Systematic screening should be considered in high-risk pregnancies.

Introduction

Cobalamin (vitamin B12) is an indispensable water-soluble micronutrient required for DNA synthesis, cellular replication, and epigenetic regulation. Its biological importance is particularly evident in gynecology and obstetrics, where reproductive success depends on tightly coordinated processes of cell proliferation, differentiation, angiogenesis, and immune tolerance. These processes are critically dependent on one-carbon metabolism, a biochemical network in which cobalamin plays a central role. Despite this, disorders of cobalamin metabolism remain under recognized in women of reproductive age and during pregnancy, even in high-income countries [1]. Pregnancy represents a state of increased metabolic demand, during which maternal micronutrient reserves must support both maternal physiology and fetal growth [1, 2]. While folate deficiency has long been recognized as a major determinant of adverse pregnancy outcomes, accumulating evidence indicates that cobalamin deficiency independently contributes to infertility, recurrent pregnancy loss, placental dysfunction, fetal growth restriction, neural tube defects, and long-term neurodevelopmental impairment in offspring. Importantly, biochemical cobalamin deficiency may occur in the absence of overt hematological manifestations, rendering diagnosis challenging in routine clinical practice.

Dietary transitions, including increasing adherence to vegetarian and vegan diets, rising prevalence of gastrointestinal disorders, and population ageing, have further amplified the public-health relevance of cobalamin deficiency among women of reproductive age [1, 3]. In parallel, physiological changes of pregnancy—including hemodilution and active placental transport of cobalamin—complicate interpretation of serum concentrations, leading to potential under diagnosis. This Review synthesizes current evidence on the physiological role of cobalamin in female reproduction, epidemiology and risk factors, gynecological and obstetric manifestations, diagnostic strategies, and management considerations, with a focus on clinical relevance for internists, obstetricians, and gynecologists.

Physiological Role of Cobalamin in Reproduction

Cobalamin acts as a cofactor for two essential enzymatic reactions in humans. First, it is required for methionine synthase, which catalyses the remethylation of homocysteine to methionine. This reaction sustains intracellular pools of methionine and S-adenosylmethionine, the universal methyl donor for DNA, RNA, protein, and lipid methylation. Second, cobalamin functions as a cofactor for methylmalonyl-CoA mutase, an enzyme involved in mitochondrial energy metabolism through the conversion of methylmalonyl-CoA to succinyl-CoA.

In reproductive tissues, these pathways are indispensable. Oocyte maturation requires precise regulation of meiotic division and chromatin remodeling, both of which are sensitive to disruptions in methylation capacity. Similarly, endometrial receptivity depends on cyclic changes in gene expression and stromal cell differentiation, processes that are tightly regulated by epigenetic mechanisms. During early pregnancy, trophoblast proliferation, invasion, and spiral artery remodeling are highly dependent on nucleotide synthesis, mitochondrial function, and endothelial integrity. Impairment of cobalamin-dependent reactions therefore has far-reaching consequences for fertility and placental development [1, 2].

Cobalamin deficiency leads to accumulation of homocysteine and methylmalonic acid, both of which exert direct cellular toxicity. Hyperhomocysteinaemia promotes oxidative stress, endothelial dysfunction, and a prothrombotic state, while elevated methylmalonic acid disrupts mitochondrial metabolism. These biochemical disturbances provide a mechanistic link between cobalamin deficiency and adverse gynecological and obstetric outcomes.

Epidemiology in Women of Reproductive Age

Population-based studies suggest that cobalamin deficiency affects approximately 10–20% of women of reproductive age in high-income countries, with considerably higher prevalence reported in low- and middle-income settings [3]. Subclinical deficiency, defined by low or borderline biochemical markers in the absence of anemia, is particularly common and clinically relevant.

Dietary intake is a major determinant of cobalamin status, as the vitamin is found almost exclusively in animal-derived foods. Women adhering to vegetarian or vegan diets are therefore at increased risk, particularly if supplementation is inconsistent. Gastrointestinal disorders, including coeliac disease, inflammatory bowel disease, and prior bariatric surgery, impair absorption and further increase vulnerability. Autoimmune conditions such as pernicious anemia, characterized by intrinsic factor deficiency, represent an important but often overlooked cause in younger women.

Pregnancy introduces additional complexity. Maternal serum cobalamin concentrations decline progressively across gestation, reflecting hemodilution, hormonal influences, and active placental transport to the fetus [4]. As a result, biochemical deficiency may be misclassified as a physiological change, leading to missed opportunities for intervention. Several cohort studies have demonstrated that low maternal cobalamin status during pregnancy is common and associated with adverse outcomes, even when serum concentrations remain within conventionally defined reference ranges [5].

Gynecological Manifestations

Infertility and Subfertility

Female infertility is a multifactorial condition, and nutritional status represents a potentially modifiable contributor. Cobalamin deficiency has been associated with impaired fertility through several mechanisms, including defective DNA synthesis, altered methylation patterns, and accumulation of homocysteine. Elevated homocysteine concentrations have been shown to exert cytotoxic effects on ovarian granulosa cells and may impair follicular development.

Observational studies in women undergoing assisted reproductive technologies have reported associations between low cobalamin status, hyperhomocysteinaemia, and reduced implantation and pregnancy rates [6]. Although causality cannot be conclusively established, case reports and small interventional studies suggest that correction of cobalamin deficiency may restore ovulatory function and improve fertility outcomes in selected patients.

Menstrual Disorders

Menstrual irregularities, including oligomenorrhea and amenorrhea, have been described in women with prolonged or severe cobalamin deficiency. These disturbances are likely mediated by a combination of anemia-related hypothalamic dysfunction, impaired steroid hormone synthesis, and reduced proliferative capacity of the endometrium. Although data are limited, these manifestations underscore the importance of considering micronutrient deficiency in the differential diagnosis of unexplained menstrual disorders.

Recurrent Pregnancy Loss

Recurrent pregnancy loss has been linked to disturbances in one-carbon metabolism, particularly hyperhomocysteinaemia. Cobalamin deficiency contributes to elevated homocysteine concentrations, which promote endothelial dysfunction, platelet activation, and microthrombus formation within placental vessels. A landmark study by Nelen and colleagues demonstrated a significantly higher prevalence of hyperhomocysteinaemia among women with recurrent early pregnancy loss compared with controls [7]. Subsequent studies have supported a role for B-vitamin deficiencies, including cobalamin, in this context.

Cervical Dysplasia

Epidemiological studies have identified associations between low cobalamin status and increased risk of cervical intraepithelial neoplasia. Impaired DNA repair, altered methylation of oncogenes and tumor suppressor genes, and increased susceptibility to persistent human papillomavirus infection have been proposed as underlying mechanisms [8]. Although causality remains uncertain, these findings suggest that adequate cobalamin status may contribute to cervical epithelial integrity and genomic stability.

Obstetric Manifestations

Neural Tube Defects

Neural tube defects (NTDs) are among the most severe congenital anomalies and remain a major cause of perinatal morbidity and mortality worldwide. While folate deficiency is the primary nutritional determinant, cobalamin deficiency independently increases NTD risk. Maternal cobalamin deficiency impairs folate metabolism and reduces methylation capacity, thereby exacerbating defects in neural tube closure.

A large population-based study demonstrated that women with the lowest quartile of serum cobalamin concentrations had a significantly increased risk of NTD-affected pregnancies, independent of folate status [9]. These findings have important implications for preconception care, particularly in populations with adequate folate intake but unrecognized cobalamin deficiency.

Fetal Growth Restriction and Low Birth Weight

Low maternal cobalamin concentrations have been consistently associated with fetal growth restriction and low birth weight. Proposed mechanisms include impaired placental angiogenesis, endothelial dysfunction, and reduced transplacental nutrient transport. In a large cohort study, Rogne and colleagues reported that low maternal cobalamin status was associated with reduced birth weight and increased risk of small-for-gestational-age infants [10].

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy, including pre-eclampsia, are major contributors to maternal and perinatal morbidity. Hyperhomocysteinaemia related to cobalamin deficiency promotes oxidative stress and endothelial dysfunction, key pathophysiological features of pre-eclampsia. Observational studies have reported higher homocysteine concentrations and lower cobalamin levels in women with pre-eclampsia compared with normotensive controls [11].

Preterm Birth

Preterm birth remains a leading cause of neonatal morbidity and mortality. Several cohort studies have demonstrated associations between low maternal cobalamin concentrations and increased risk of preterm delivery [12]. Inflammatory activation, impaired placental function, and altered immune tolerance have been proposed as mediating pathways.

Neonatal and Long-Term offspring Outcomes

Infants born to cobalamin-deficient mothers are at risk of low hepatic cobalamin stores at birth, particularly if maternal deficiency is severe or prolonged. Exclusive breastfeeding by a cobalamin-deficient mother may further exacerbate deficiency in the infant. Clinical manifestations include failure to thrive, hypotonia, developmental delay, and, in severe cases, neurodevelopmental regression. Longitudinal studies suggest that early-life cobalamin deficiency may have lasting effects on cognitive function and metabolic health [13]. Emerging evidence from epigenetic studies indicates that maternal cobalamin status may influence gene expression patterns in offspring, with potential implications for long-term disease risk.

Diagnostic Approach in Gynecology and Obstetrics

Serum vitamin B12 measurement remains the most commonly used screening test but has limited sensitivity, particularly during pregnancy. Functional biomarkers such as methylmalonic acid and homocysteine provide greater diagnostic accuracy, although their interpretation may be influenced by renal function and folate status. Holotranscobalamin, which reflects the biologically active fraction of circulating cobalamin, has emerged as a promising marker, including in pregnancy [14].

Targeted screening should be considered in women with infertility, recurrent pregnancy loss, restrictive diets, gastrointestinal disease, autoimmune conditions, or unexplained anemia. Development of pregnancy-specific reference ranges remains an important research priority.

Table 1: Gynecological and Obstetric Manifestations of Cobalamin Deficiency

Clinical Domain	Manifestation	Mechanism
Gynecology	Infertility	Impaired DNA synthesis
Gynecology	Recurrent miscarriage	Hyperhomocysteinemia
Obstetrics	Neural tube defects	Defective methylation
Obstetrics	Fetal growth restriction	Placental dysfunction
Neonatal	Neurodevelopmental delay	Low fetal stores

Management and Prevention Strategies

Cobalamin supplementation is safe, inexpensive, and highly effective. Oral supplementation at doses of 250–1000 µg daily is sufficient for most women, including during pregnancy. Parenteral therapy is reserved for severe deficiency or malabsorption syndromes. Combined supplementation with folate and cobalamin is recommended in high-risk populations to optimize one-carbon metabolism and reduce adverse outcomes [3].

Public-health strategies should emphasize preconception nutritional assessment, particularly in women adhering to plant-based diets or with known risk factors for malabsorption.

Table 2: Supplementation Strategies

Population	Dose	Route
Preconception	250–500 µg/day	Oral
Pregnancy	250–1,000 µg/day	Oral
Severe deficiency	1,000 µg/week	IM
Malabsorption	1,000 µg/month	IM

Challenges and Future Perspectives

The absence of standardized screening guidelines, reliance on serum cobalamin alone and limited awareness among clinicians contribute to under diagnosis. Future research should focus on defining optimal biomarkers, establishing pregnancy-specific thresholds, and evaluating the impact of routine supplementation on reproductive and long-term offspring outcomes.

Conclusion

Cobalamin deficiency represents a common, under recognized and modifiable risk factor for adverse gynecological and obstetric outcomes. Its effects span the reproductive lifespan, influencing fertility, pregnancy success, and offspring health. Greater clinical awareness, targeted screening, and timely supplementation have the potential to substantially improve maternal and child health outcomes.

Conflicts of Interest

The author declares no conflicts of interest related to this work.

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