



Subclinical Hypothyroidism as An Unexpected Etiology of Recurrent Miscarriages

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WebLog Open Access Publications
Article ID : wjed.2026.b1407
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Abstract

Recurrent miscarriages are a rare occurrence in routine medical practice (1-3% of pregnancies) and represent a significant diagnostic challenge.

Subclinical hypothyroidism (SCH) is the most common thyroid disorder during pregnancy (3-5% of pregnant women) and can be responsible for several obstetric complications such as miscarriage, preterm birth, gestational hypertension, preeclampsia, and increased perinatal mortality. SCH remains an exceptional and still controversial cause of recurrent miscarriages.

We report an original observation of isolated SCH as unexpected etiology of four consecutive spontaneous miscarriages at 10, 14, and 16 weeks of amenorrhea in a 28-year-old Tunisian woman.

Keywords: Subclinical Hypothyroidism; Hypothyroidism; Miscarriage; Pregnancy Loss; Recurrent Miscarriages

Introduction

Subclinical hypothyroidism (SCH), also known as mild or asymptomatic hypothyroidism, is the most common thyroid dysfunction but is often underdiagnosed and overlooked by healthcare professionals [1]. It is defined by a slightly elevated thyroid-stimulating hormone (TSH), normal free thyroxine (fT4), and the absence of clinical signs [1-3]. Recently, it has been shown to be associated with various clinical (neuropsychiatric, cardiovascular, hepatobiliary, renal, hematopoietic, and metabolic) and biological repercussions, raising questions about its classification as "asymptomatic" [1-7]. These repercussions are inconsistent, nonspecific, and nondiscriminatory [1], with a frequently troubling clinico-biological dissociation between thyroid hormone levels and the severity of clinical expression [1, 8, 9], making the true clinical significance of SCH highly controversial [1, 10].

In women, this thyroid dysfunction is associated with a high risk of hypofertility/infertility, menstrual cycle disorders, maternal and fetal complications, as well as a poor prognosis during pregnancy and childbirth [1-3, 10]. Miscarriages, while particularly recurrent, remain exceptional in the context of SCH [11].

This case illustrates this original obstetrical aspect of SCH as the unexpected etiology of recurrent miscarriages in a young woman.

Case Presentation

A 28-year-old woman with no significant past medical history was referred to our Internal Medicine clinic by her gynecologist for further investigation of recurrent miscarriages (suspicion of antiphospholipid syndrome).

Married for two years, she had experienced four consecutive miscarriages at 10, 14, and 16 weeks of amenorrhea, with no apparent cause (negative infectious disease investigations, normal baseline blood tests, normal levels of gonadotropins and female sex hormones, and uterine morphology without anomalies).

Immunological tests ruled out antiphospholipid syndrome or underlying systemic lupus erythematosus (antinuclear, anti-native DNA, anti-soluble antigens, anticardiolipin, anti-beta-2-glycoprotein-1, anti-annexin V antibodies, and lupus anticoagulant were negative). Screening for inherited thrombophilia was negative (normal levels of protein C and S, antithrombin III, and

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Received Date: 15 Jan 2026

Accepted Date: 12 Feb 2026

Published Date: 14 Feb 2026

Citation:

Bouomrani S, Letaïef W, Ben Teber S, Mahdhaoui W. Subclinical Hypothyroidism as An Unexpected Etiology of Recurrent Miscarriages. *WebLog J Endocrinol Diabetes*. wjed.2026.b1407. <https://doi.org/10.5281/zenodo.18811489>

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homocysteine, and no activated protein C resistance or coagulation factor II mutation). Hormonal screening revealed a TSH at 6.94 $\mu\text{IU/mL}$ and a normal free T4 at 14 pmol/L . Cervical ultrasound was normal, and thyroid antibodies were negative (anti-thyroglobulin, anti-thyropoxidase, and blocking type anti-TSH receptor antibodies).

The patient was started on hormone replacement therapy, which normalized her TSH to 2.5 $\mu\text{IU/mL}$ with 50 $\mu\text{g/day}$ of levothyroxine. Two months after normalization of thyroid function, the patient became pregnant again, and the pregnancy was carried to term, resulting in the delivery of a healthy male newborn weighing 3200g. No new miscarriages have been recorded for four years now, and there have been two new successful pregnancies.

Discussion

Subclinical hypothyroidism is the most common thyroid disorder during pregnancy [1, 11]. It can be observed in up to 3-5% of pregnant women, particularly during the second and third trimesters [1, 12, 13]. It can be responsible for several obstetric complications such as miscarriage, preterm birth, gestational hypertension, preeclampsia, and increased perinatal mortality [1, 11-14].

Recurrent miscarriages, defined as two or more consecutive spontaneous pregnancy losses [15], are a rare occurrence in routine medical practice and represent a significant diagnostic challenge. Indeed, their prevalence is estimated at 1-3% of pregnancies, and their etiology remains unexplained in more than 50% of cases [15, 16].

Subclinical hypothyroidism is an exceptional and still controversial cause of recurrent miscarriages [15, 16]. Indeed, SCH was found in 8.39% of women with recurrent and late miscarriage in the study by Khalid AS et al [17], and in 19% of women with recurrent early pregnancy loss in the Bernardi LA et al cohort [18]. This prevalence is slightly higher than that in euthyroid women, although the difference is not statistically significant: the miscarriage rate was 35% in women who had experienced recurrent miscarriage with SCH versus 28% in women with normal thyroid function in the van Dijk MM et al study [19]. Similarly, the live birth rate was lower in women with SCH compared to that of euthyroid women (45% versus 52%) [19]. These results, although still debated by some authors [14, 18], suggest a direct causal link between SCH and pregnancy loss [15, 16, 19].

As already demonstrated for the cardiovascular and neuropsychiatric complications of SCH [1-4], TSH-normalizing hormone replacement therapy appears to have a positive effect on pregnancy outcomes, and particularly on reducing the prevalence of miscarriages [18, 20]. Indeed, the meta-analysis by Velkeniers B et al showed a significant reduction in the risk of miscarriage in pregnant women with SCH receiving TSH-normalizing hormone replacement therapy: thyroxine treatment significantly lowered miscarriage rate with a pooled Relative Risk of 0.45 ($P=0.010$) [20]. However, these results also remain controversial, and to date there is no consensus on the systematic use of hormone replacement therapy in these situations [14].

Conclusion

Our observation confirms once again the direct causal link between subclinical hypothyroidism and recurrent miscarriages. However exceptional and unusual it may be, SCH should be considered as a

possible cause of recurrent and unexplained miscarriages. Therefore, a TSH test is justified as part of the etiological investigations of recurrent miscarriages or female infertility, even in the absence of clinical and biological signs of thyroid dysfunction.

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