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ARTICLE

# Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage?

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**Abstract** Thyroid disorders have been associated with recurrent miscarriage. Little evidence is available on the influence of subclinical hypothyroidism on live birth rates. In this cohort study, women who had experienced miscarriage and subclinical hypothyroidism (defined as thyroid-stimulating hormone >97.5th percentile mU/l with a normal thyroxine level) were investigated; the control group included women who had experienced recurrent miscarriage and normal thyroid function. Multivariable logistic regression was used to investigate the association of subclinical hypothyroidism. Data were available for 848 women; 20 (2.4%) had subclinical hypothyroidism; 818 women (96%) had euthyroidism; and 10 (1.2%) had overt hypothyroidism. The live birth rate was 45% in women with subclinical hypothyroidism and 52% in euthyroid women (OR 0.69, 95% CI 0.28 to 1.71). The ongoing pregnancy rate was 65% versus 69% (OR 0.82, 95% CI 0.32 to 2.10) and the miscarriage rate was 35% versus 28% (OR 1.43, 95% CI 0.56 to 3.68), respectively. No differences were found when thyroid stimulating hormone 2.5 mU/l was used as cut-off level to define subclinical hypothyroidism. In women with unexplained miscarriage, no differences were found in live birth, ongoing pregnancy and miscarriage rates between women with subclinical hypothyroidism and euthyroid women.



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**KEYWORDS:** live birth rate, miscarriage rate, ongoing pregnancy rate, recurrent miscarriage, recurrent pregnancy loss, subclinical hypothyroidism

## Introduction

A miscarriage occurs in about 15% of all clinically recognized pregnancies in the general population. Recurrent miscarriage (RM) has a prevalence of 1–3% of all couples trying to conceive (van den Boogaard et al., 2011). Couples with parental chromosome abnormalities and women with uterine anomalies, endocrine disturbances, hyperhomocysteinemia and antiphospholipid syndrome have a higher risk for RM. Despite comprehensive investigations, an underlying risk factor for RM is identified in less than 50% of couples (Alijotas-Reig and Garrido-Gimenez, 2013). At present, no effective treatment has been established to improve the live birth rates for women with unexplained RM. For couples who experience RM, a reliable prognosis for the chance of a live birth is of utmost importance in their decision whether or not to conceive again, as RM has often distressing physical and emotional consequences (Kolte et al., 2015b).

Thyroid disorders, especially hypothyroidism, have been associated with miscarriage. Overt hypothyroidism is associated with an increased risk for miscarriage (OR 5.78, 95% CI 2.4 to 14), but also with other pregnancy complications, such as low birth weight, premature delivery, placental abruption and pregnancy-induced hypertension (Abalovich et al., 2002; Kabadi, 1993; Negro et al., 2010; Stagnaro-Green, 2011; van den Boogaard et al., 2011). It often presents with clinical symptoms and, therefore, most women already receive treatment before conception.

Subclinical hypothyroidism is a more common thyroid disorder among women of fertile age. It is defined as a raised serum thyroid-stimulating hormone (TSH) level above the upper limit of normal with a normal level of serum free thyroxine (T4). The prevalence of subclinical hypothyroidism has been estimated to be between 4.0% and 8.5% in the normal population and between 1.5% and 4% in pregnancy (Abalovich et al., 2002; Fatourechi, 2009; Negro, 2011). To date, studies investigating an association between subclinical hypothyroidism and RM have been conflicting. Also, the effect of subclinical hypothyroidism on live birth rates in women who experience RM is unclear and limited to one published study. In this observational cohort study that compared 55 patients with RM and subclinical hypothyroidism (TSH ≥2.5 mU/l) (19% of the total cohort) with euthyroid women who experienced RM, no significant difference in the subsequent live birth rates was found (Bernardi et al., 2013).

Evidence of an association between subclinical hypothyroidism and a single miscarriage is conflicting. Two cohort studies found an increased risk of miscarriage in women with subclinical hypothyroidism compared with euthyroid women (Benhadi et al., 2009; Liu et al., 2014). The largest cohort study found no evidence of a difference in miscarriage rate between women subclinical hypothyroid or euthyroid women (Cleary-Goldman et al., 2008).

Interpreting the data on studies of subclinical hypothyroidism is complicated by the use of differential cut-off levels for TSH and by inter-laboratory differences using various different analysers.

No consensus has been reached on the optimal TSH cut-off level to define subclinical hypothyroidism. The American Thyroid Association recommends TSH levels to be trimester specific, with 2.5 mU/l as upper limit, and the Endocrine Society advises a TSH level of 0.1–2.5 mU/l in the first trimester (Lazarus et al., 2014; Stagnaro-Green et al., 2011). The British Thyroid Association recommends a TSH reference range in pregnancy of 0.4–2.5 mU/l in the first trimester or trimester-specific reference ranges for the population if available (Okosieme et al., 2016). Recommendations on cut-off levels for diagnosing subclinical hypothyroidism at preconception are not available. Data cannot automatically be extrapolated to all ethnicities as TSH levels are known to be population specific with intrinsic ethnic variation (Korevaar et al., 2013).

Although subclinical hypothyroidism is associated with pregnancy complications, its association with RM remains unclear. Therefore, we evaluated the effect of subclinical hypothyroidism on live birth rates in a cohort of women with unexplained RM.

## Materials and methods

### Study population

The study population consisted of women 18–40 years of age with RM who presented to the Recurrent Miscarriage Clinic at the Liverpool Women's Hospital, Liverpool, UK, between 2004 and 2011. In accordance with the Special Interest Group for Early Pregnancy (European Society of Human Reproduction and Endocrinology) consensus statement, RM was defined as two or more, not necessarily consecutive, miscarriages before 20 weeks of gestation, verified by a pregnancy test, ultrasonography, or both (Kolte et al., 2015a).

Biochemical pregnancies were not included as pregnancy losses, and were categorized as 'other pregnancies'. Unexplained RM was defined when an underlying risk factor for RM was not present. Diagnostic workup for RM included testing for antiphospholipid syndrome (lupus anticoagulant, immunoglobulin G and immunoglobulin M anti-cardiolipin antibodies (according to the Sapporo Classification Criteria 1999 for the antiphospholipid antibody syndrome (Wilson, 2001), uterine abnormalities, thrombophilia (Factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, antithrombin deficiency) and hyperhomocysteinaemia.

Women with pre-existent thyroid disease or women who were using thyroid drugs were excluded. Women were not included for analysis if their evaluation did not include thyroid function tests (TSH, T4, or both) and when no data for the outcome measure were available. The diagnostic workup of RM did not include testing for the presence of TPO-Ab according to recent guidelines, where TPO-Ab screening is not advised in routine RM workup (Jauniaux et al., 2006; NVOG, 2007; De Groot et al., 2012). During the study period, women who had experienced RM were given no other intervention than

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