International Journal of Gynecology and Obstetrics 123 (2013) 196–199

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Optimal treatment of hypothyroidism associated with live birth in cases of previous recurrent placental abruption and stillbirth

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ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form 20 May 2013
Accepted 23 August 2013

Keywords:
Hypothyroidism
Obstetrics
Placental abruption
Pregnancy outcome
Stillbirth

ABSTRACT

Objective: To examine the clinical management of and placentas from pregnant women with hypothyroidism and obstetric history of recurrent stillbirth in order to identify possible etiologic mechanisms. *Methods:* Two cases involving 26-year-old women with hypothyroidism and history of recurrent stillbirth are reported. Placentas from all of the women's pregnancies were compared in order to identify histologic similarities. *Results:* In both cases, multifocal hemorrhagic infarctions and abruptions were seen, indicating progressive uteroplacental ischemic damage leading to stillbirth. Thrombophilia, infection, and diabetes tests were all negative. With meticulous monitoring and normalization of thyroid function by end of first/early second trimester in subsequent pregnancies, there were live births and no evidence of infarction on placental histology. *Conclusion:* The 2 reported cases raise the possibility of uteroplacental ischemia and placental abruption being mechanisms by which hypothyroidism can lead to stillbirth; they also highlight the potential of minimizing this risk via adequate levothyroxine treatment from early pregnancy.

1. Introduction

Hypothyroidism—including overt hypothyroidism, hypothyroidism adequately or partially treated with levothyroxine, and subclinical hypothyroidism (elevated circulating thyroid-stimulating hormone [TSH] concentration with normal free thyroxine [FT4] concentration)—complicates approximately 3.5% of pregnancies [1]. Untreated overt hypothyroidism is associated with adverse obstetric outcomes, including pregnancy-induced hypertension, placental abruption, prematurity, low birth weight, and offspring with low IQ [2]. The risk of stillbirth is 9 times higher among women with untreated hypothyroidism compared with controls [3]. Even subclinical hypothyroidism is associated with an increased risk of pregnancy loss and pre-eclampsia: odds ratios of 2.7 and 1.7, respectively [4,5]. Subclinical hypothyroidism has also been associated with placental abruption and preterm birth [6].

Retrospective studies have found that obstetric risks are correlated to the extent of an individual's thyroid dysfunction and the gestational age by which euthyroidism is achieved [7,8]. The 2 cases reported in the present article highlight the potential role of hypothyroidism in stillbirth associated with placental abruption, as well as the potential importance of adequate levothyroxine treatment.

2. Materials and methods

Two cases involving women with hypothyroidism and history of recurrent stillbirth are reported. The women attended Birmingham Women's NHS Foundation Trust, Birmingham, UK, between 2007 and 2010. Both women gave consent for their cases to be reported. Placental histopathology was reviewed, in addition to thyroid status and obstetric outcome, in order to shed light on possible mechanisms mediating the adverse outcomes in hypothyroidism.

3. Results

The first case involved a 26-year-old smoker with a normal body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of 24 and autoimmune hypothyroidism with elevated thyroid peroxidase (TPO) antibody titers (718 IU/mL in index pregnancy). She was in her third pregnancy, having previously experienced 2 stillbirths at 33 and 24 weeks of pregnancy. Overt hypothyroidism was diagnosed several months after the first stillbirth, when she was investigated for lethargy. Her thyroid status during the first pregnancy was unknown. When the woman booked her second pregnancy at 17 weeks, her hypothyroidism was found to have been only partially treated (50 μg of levothyroxine daily), as she had elevated TSH levels (6.89 mU/L) and FT4 levels toward the lower end of the normal range (11.9 pmol/L; normal range, 10.0–22.0 pmol/L). Levothyroxine was increased to 75 μg; however, intrauterine death was diagnosed before a repeat thyroid function test could be performed.

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http://dx.doi.org/10.1016/j.ijgo.2013.05.025

Both fetuses were small for gestational age according to the customized growth chart (corrected for ethnicity, BMI, parity, gestational age, and sex) [9], with birth weights at the 9th and 1st percentiles, respectively.

In the index pregnancy, thyroid function tests just before conception had shown suppressed TSH levels, which prompted a reduction of levothyroxine from 100 μg to 75 μg. At 6 weeks of pregnancy, the patient's TSH levels were elevated (7.54 mU/L), with normal FT4 levels of 10.7 pmol/L (first-trimester normal range, 8.3–14.6 pmol/L). Levothyroxine was increased to 150 μg and aspirin (75 mg) was administered daily. Euthyroidism was achieved by 16 weeks (TSH 0.29 mU/L). Levothyroxine was gradually reduced to 100 μg by 32 weeks in order to maintain TSH levels between 0.1 and 2 mU/L. A mid-trimester fetal anomaly scan was normal. Uterine artery Doppler velocities at 24 weeks demonstrated an elevated pulsatility index with a unilateral left-sided notched waveform. Fortnightly growth scans revealed a gradual decline in estimated fetal weight (EFW), from the 50th percentile (customized) at 26 weeks to the 8th percentile by 32 weeks. Liquor volume and umbilical artery Doppler studies conducted weekly (between 26 and 30 weeks) then thrice weekly (from 30 weeks) were all normal. In view of the patient's history and these findings, she was delivered via cesarean at 32 weeks, having received a course of betamethasone at 30 weeks to promote fetal lung maturity. A live male (1600 g; 12th percentile) was delivered, with 1- and 5-minute Apgar scores of 9. He was observed in the neonatal unit for 5 weeks and required 6 days of continuous positive airway pressure (CPAP). The infant developed jaundice and was diagnosed with eventration of the diaphragm and moderate patent ductus arteriosus but he made an uneventful recovery.

The second case involved a 26-year-old non-smoker with a raised BMI of 35 and long-standing autoimmune hypothyroidism with elevated TPO antibody titers (4667 IU/mL in index pregnancy). The patient was in her fifth pregnancy, having experienced a stillbirth at 24 weeks, 2 early spontaneous abortions, and a stillbirth at 30 weeks.

Gestational diabetes was excluded by normal oral glucose tolerance tests at 26 weeks in previous pregnancies and the index pregnancy, and by normal HbA1C measurements following each stillbirth. The first stillborn was small for gestational age (below the 1st percentile) but the second was appropriately grown at 1570 g (50th percentile). The woman admitted poor compliance with levothyroxine treatment during these 2 pregnancies, and TSH concentrations remained elevated. During the second pregnancy that culminated in stillbirth, there were elevated TSH levels (11.6 mU/L) at 18 weeks. Despite an increase in levothyroxine from 50 to 100 μg, TSH levels remained elevated (4.6 mU/L) at 28 weeks. During this second pregnancy, the patient also received low-dose aspirin (75 mg) and low molecular weight heparin (40 mg) once daily from early gestation. Two days before the diagnosis of the second intrauterine death, ultrasound scans showed normal liquor volume and umbilical artery Doppler studies accompanied by normal cardiotocography. Reduced fetal movements were reported only on the day fetal death was diagnosed.

A month before conception in the index pregnancy, the patient was found to have overt hypothyroidism (TSH > 100 mU/L, FT4 1.2 pmol/L), again admitting poor compliance with levothyroxine. Levothyroxine was increased from 50 μg to 200 μg daily, and by 6 weeks the patient's thyroid function had improved markedly (elevated TSH of 8.29 mU/L, normal FT4 of 10.5 pmol/L). By 12 weeks, euthyroidism had been

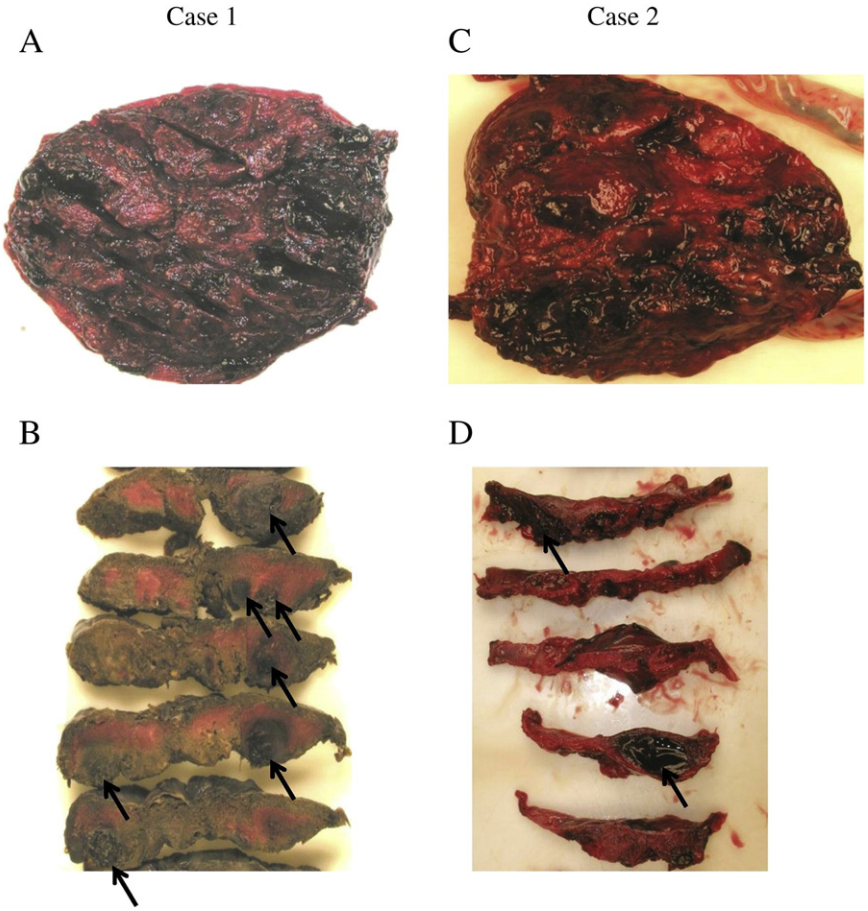

Fig. 1. Gross placental pathology of cases. (A) Placenta of the second stillbirth of case 1, viewed from the maternal surface. The surface is irregular and shows multiple small craters reflecting small abruptions. On cut section (B), there are multiple areas of centrally hemorrhagic infarction (arrows). The infarcts are of differing ages. (C) Placenta of the first stillbirth of case 2, viewed from the maternal surface. No abruption is evident. On cut section (D), the placenta is very thin and shows multiple fresh hemorrhagic infarcts (arrows).