Preventing subclinical hypothyroidism during pregnancy: promising data from a singular case

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ABSTRACT — Physiologic changes during pregnancy have a profound impact on the thyroid gland and thyroid function. Subclinical hypothyroidism (SCH) is a common pregnancy-related thyroid disorder. The ATA/AACE Guidelines recommend to maintain the thyroid hormones levels within the normal range during pregnancy, to avoid the risk of arising mother and fetal complications. This paper draws attention to the importance of prevention of these events during the gestation period. Here the author describes a recent case report of a 31-year-old pregnant woman with borderline thyroid hormones levels, who was administered with myo-inositol plus selenium throughout all pregnancy to prevent SCH and associated adverse maternal/neonatal outcomes. A trimester-specific screening revealed that serum TSH, fT_4 and fT_3 remained stable during 9 months of pregnancy. Our experience may open a new scenario in the prevention of SCH in pregnant women at risk of developing this disorder.

KEYWORDS
Subclinical hypothyroidism, Myo-inositol, Inositol, Selenium, TSH, Thyroid hormones, Pregnancy.

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as an elevated thyroid-stimulating hormone (TSH) concentration with normal serum levels of thyroxine (T_4). It is a common pregnancy-related thyroid disorder that affects 3-5% of pregnant women worldwide. Physiologic changes during the gestation period give rise to considerable alterations in maternal thyroid activity. High concentrations of human chorionic gonadotrophin activate the TSH receptor altering circulating TSH levels[1,2]. This triggers in the first trimester of pregnancy a higher synthesis and release of T_4 from the thyroid. Indeed, during pregnancy the total T_4 and triiodothyronine (T_3) increase by 50%[3]. Hypothyroidism and SCH are mostly caused by environmental iodine deficiency[4]; furthermore, during pregnancy the iodine renal clearance increases along with the glomerular filtration rate[5-7]. This may gravely impact on the thyroid responsiveness to TSH. Clinicians recommend setting trimester-specific screening of serum TSH and fT_4 levels from the 12-16th weeks of gestation[8]. Serum TSH is the most accurate indication of thyroid status and, following guidelines recommendations, it is good clinical practice to maintain TSH values below 2.5 mIU/L in women planning pregnancy[9]. It should not exceed 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester and 3.5 mIU/L in the third trimester of gestation[3]. SCH during pregnancy is associated with numerous adverse maternal and neonatal outcomes like preterm delivery, pregnancy loss, premature rupture of membranes, gestational diabetes and hypertension, placental abruption, preeclampsia, intrauterine growth restriction, low birth weight, neurocognitive deficits in the offspring and neonatal death[10,11]. Levothyroxine is the most used treatment for SCH; however, its efficacy in preventing these adverse outcomes remains still uncertain[11].

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Therefore, taking in consideration either the experts' recommendations and the negative-multifaceted impact of SCH on pregnancy outcomes we introduced an interesting approach in preventing this disorder.

CASE REPORT

A 31-year-old Caucasian woman, in her first pregnancy attended to our Outpatient Unit for prenatal care at the 8th week of gestation. As standard protocol, she filled an informed consent and the ATA/AACE Guidelines[3] were followed. Patient body mass index (BMI) at first trimester was 21.8 kg/m^2. Her personal history was unremarkable. The patient did not smoke and there was neither past nor family history of diabetes mellitus or risk factors for developing gestational diabetes mellitus. The first examination of TSH, fT_3 and fT_4 was performed by the 12th week of pregnancy. In the first trimester, her TSH levels were 2.41 mIU/L, showing a borderline limit. FT_4 and fT_3 were 1.89 ng/dl and 2.45 pg/ml, respectively (Table 1). Patient was asked to take tablets containing 600 mg myo-inositol (myo-ins) plus 16.6 mg L-selenomethionine (= 83 µg selenium, -Se), until delivery. Patient started taking the dietary supplement (myo-ins-Se) at 10 week of gestation by daily oral route with water about 2 hours before or after meal, until the end of pregnancy. In addition, she was asked to take folic acid throughout the first trimester of pregnancy, omega 3 from the 20th weeks and iron from the 24th weeks up to delivery, as recommended to pregnant women. She received no instructions regarding diet and lifestyle. In the second trimester, levels of thyroid hormones were slightly decreased but maintained the normal value range: TSH was 2.05 mIU/L, fT_4 was 1.78 ng/dl and fT_3 was 2.21 pg/ml. In the third trimester, TSH levels were stable (2.25 mIU/L), as well as fT_4 (1.91 ng/dl) and fT_3 (2.89 pg/ml) (Table 1). The oral glucose tolerance test (OGTT) at the 26th week was negative. The ultrasound exams were performed during routine visits of second and third trimesters. The ultrasound examination at the 20-22nd weeks reflected normal fetal morphology and fetal biometry corresponding to the period of amenorrhea. Ultrasound on the 30th-32nd weeks indicated fetal biometry corresponding to 50th percentile for gestational age, normal emodynamic umbilical artery and regular amniotic fluid. An ultrasound examination at 36-weeks revealed the fetus to be growing normally. Patient had spontaneous vaginal delivery at 40-weeks gestational age. No medical complications in mother and neonate were recorded. The weight and length of the newborn baby were 3170 g and 52 cm, respectively. Apgar score was 9/10.

Table I. Trimester-specific screening of serum TSH, fT_4 and fT_3 levels.

Parameters	1° Trimester	2° Trimester	3° Trimester
TSH (mIU/L)	2.41	2.05	2.25
fT_4 (ng/dl)	1.89	1.78	1.91
fT_3 (pg/ml)	2.45	2.21	2.89

1° Trimester: ≤12 weeks of pregnancy; 2° Trimester: ≤26 weeks of pregnancy; 3° Trimester: ≤36 weeks of pregnancy.

DISCUSSION

We believe this case report illustrates how a pregnant woman can potentially benefit from the supplementation of myo-ins-Se in preventing SCH. The ability of myo-ins-Se administration in restoring the euthyroid state in patients diagnosed with autoimmune thyroiditis has been shown in different clinical trials[12,13]. Myo-ins belongs to the inositol family, naturally found in cell membranes. It is a carbocyclic polyol precursor of phosphoinositide synthesis involved in cell signaling and, as second messenger, regulates TSH, follicle-stimulating hormone (FSH) and insulin activities[14]. Myo-ins, is involved in cell cytogenesis and morphogenesis, cell growth and lipid synthesis. In follicular cells, TSH activates the cAMP cascade and the Ca^{2+} phosphatidyl-inositol phosphate cascade (PIP2)[15] and it seems that increment of myo-ins availability at cellular level improves TSH sensitivity of the thyroid follicular cell. Therefore, this might explain the effect of myo-ins in maintaining the TSH levels at normal values throughout patient's pregnancy. Furthermore, myo-ins plays a therapeutic role in a number of clinical disorders and its safety and effectiveness have been confirmed extensively[16].

Se is a very important trace element for the human health as it is involved in many antioxidant, oxidation-reduction, and thyroid hormone deiodination pathways[17]. Se has been shown to be effective, either in treating and preventing hypothyroidism and thyroid autoimmunity including Graves' orbitopathy[18,19]. However, the only Se administration reduces the thyroid antibodies but does not affect TSH or fT_4 levels[20]. This emphasizes the marked importance of combining myo-ins and Se to obtain the best clinical approach for thyroid dysfunction and related-complications. This singular case opens a new scenario in the prevention during pregnancy of SCH and the adverse-outcomes correlated. Indeed, it was seen how a pregnant woman, administered daily with myo-ins-Se maintained normal the hormones levels throughout all gestation period. This is the desirable endpoint recommended by all guidelines stating that TSH values, as the most reliable therapeutic parameter, should not exceed 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester and 3.5 mIU/L

in the third trimester[3]. Pregnancy is a delicate time physically and emotionally for a woman, and smartest choices need to be taken since the first trimester to avoid late complications for mother and/or fetus. Therefore, prevention seems to be a very critical option that would raise undoubtedly great advantages and health benefit. Our experience would suggest to gynecologists to check TSH levels at the first visit and to consider the supplementation of myo-ins-Se in case of borderline high TSH levels. Patient education is also important, to enhance awareness of SCH-related symptoms and complications. However, further studies on a larger cohort are required to confirm these preliminary but interesting data.

Conflicts of interest:
The Authors declare that there are no conflicts of interest

References

1. Glinoer D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest 1993; 16: 881-888.
2. Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990; 71: 276-287.
3. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W. Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum. Thyroid 2011; 21: 1081-1125.
4. Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the technical consultation. Public Health Nutr 2007; 10: 1606-1611.
5. Aboul-Khair SA, Crooks J, Turnbull AC, Hytten FE. The physiological changes in thyroid function during pregnancy. Clin Sci 1964; 27: 195-207.
6. Davison JM, Hytten FE. Glomerular filtration during and after pregnancy. J Obstet Gynaecol Br Commonw 1974; 81: 588-595.
7. Córdoba Ramírez N, García Botina HD, Builes Barrera CA. Physiological changes in thyroid function during pregnancy: an approach to the interpretation of thyroid tests. Iatreia 2013; 26: 185-196.
8. Allahabadia A, Razvi S, Abraham P, Franklyn J. Diagnosis and treatment of primary hypothyroidism. BMJ 2009; 338: b725.
9. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012; 18: 988-1028.
10. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999; 341: 549-555.
11. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, Coddington CC 3rd, Stan MN, Murad MH, Montori VM. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid 2016; 26: 580-590.
12. Nordio M, Basciani S. Myo-inositol plus selenium restore euthyroid state in Hashimoto's patients with subclinical hypothyroidism. Eur Rev Med Pharmacol Sci 2017; 21(2 Suppl): 51-59.
13. Nordio M, Pajalich R. Combined treatment with myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. J Thyroid Res 2013; 2013: 424163.
14. Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opin Drug Metab Toxicol 2016; 12: 1181-1196.
15. Corvilain B, Laurent E, Lecomte M, Vansande J, Dumont JE. Role of the cyclic adenosine 3′,5′-monophosphate and the phosphatidylinositol-Ca2+ cascades in mediating the effects of thyrotropin and iodide on hormone synthesis and secretion in human thyroid slices. J Clin Endocrinol Metab 1994; 79: 152-159.
16. Unfer V, Orrù B, Monastra G. Inositols: from physiology to rational therapy in gynecological clinical practice. Expert Opin Drug Metab Toxicol 2016; 12: 1129-1131.
17. Rayman MP. The importance of selenium to human health. Lancet 2000; 356: 233-241.
18. Negro R. Selenium and thyroid autoimmunity. Biologics 2008; 2: 265-273.
19. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, M Nardi, Pitz S, Boboridis K, Sivelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W. Selenium and the Course of Mild Graves' Orbitopathy. N Engl J Med 2011; 364: 1920-1931.
20. Nacamulli D, Mian C, Petricca D, Lazzarotto F, Barollo S, Pozza D, Masiero S, Faggian D, Plebani M, Girelli ME, Mantero F, Betterle C. Influence of physiological dietary selenium supplementation on the natural course of autoimmune thyroiditis. Clin Endocrinol 2010; 73: 535-539.