



Original article

Physiological Changes in Thyroid Function Tests in Women with Silent Miscarriage

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Abstract

Silent miscarriage is a type of miscarriage where the fetus has died but has not been naturally expelled from the uterus, and it can result in maternal morbidity. This study was conducted to determine the physiological changes in thyroid function tests and progesterone in women with silent miscarriage; to evaluate the role of these parameters in the diagnosis of silent miscarriage; and to assess the impact of maternal and gestational age as well as family history. The study involved 96 women: 46 healthy pregnant women as controls and 50 women with silent miscarriage. We evaluated thyroid function tests (thyroid stimulating hormone TSH, thyroxine T4, triiodothyronine T3) and progesterone P4 levels. Additional analyses were performed between silent miscarriage women subgroups based on gestational age, maternal age, and family history. Women who had miscarried often showed elevated TSH and decreased thyroid hormones (T4, T3) and progesterone levels compared to healthy pregnancies. A subanalysis of the miscarried women group revealed a significant increase in thyroid function profile and progesterone in the 2nd trimester. Miscarried women with a positive family history of miscarriage had significantly lower levels than those without a family history. Lastly, no age-related differences were observed for any of the parameters. Thyroid dysfunction and decreased progesterone levels were significantly associated with silent miscarriage, and gestational age and family history were associated with the severity of these abnormalities.

Keywords: Silent Miscarriage, Thyroid Function Tests, Progesterone.

Introduction

Silent miscarriage (SM), also known as missed abortion, is a unique form of spontaneous miscarriage, defined as embryonic or fetal death with retained intrauterine products of conception that are not naturally expelled [1, 2], which remain in the uterus for days or weeks with a closed cervix. This is a very common complication, occurring in approximately 15% of all clinically recognized pregnancies. The pathogenesis of SM is still not completely clear, and it is generally thought that several factors interact to produce this result [3, 4]. The primary recognized causes of SM are genetic factors, intrauterine environment abnormalities, endocrine disorders, immune dysfunction, heavy smoking, serious systemic infections, environmental chemicals, and trauma [4, 5].

Thyroid hormone influences nearly every organ system in the body, including the heart, CNS, autonomic nervous system, bone, GI, and metabolism. It is famous for regulating metabolism, growth, and plays a key role in body temperature, reproductive health, nervous system development, and bone turnover [6, 7]. The thyroid gland, anterior pituitary gland, and hypothalamus make up a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The two most important hormones made by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3) [6, 8]. The value of the thyroid hormones for the achievement of pregnancy and its

maintenance was owing to the fact that they were involved in many processes of embryonic implantation, placental development, and fetal brain development. Thyroid gland dysfunction during pregnancy, overt or subclinical, has also been associated with pregnancy complications [9, 10] such as spontaneous early pregnancy loss, preterm delivery, and preeclampsia.

P4, "the pregnancy hormone," has a central role in the establishment and maintenance of a successful pregnancy by modulating maternal immune response and thus contributing to immune tolerance against the semi-allogeneic fetus [11, 12]. P4 produced by the ovarian CL is necessary for the priming of the endometrium and to induce an immunological milieu favoring pregnancy, and in this way it conditions the endometrial mucosa to let the early embryo implant in the uterus. P4 is essential to prevent uterine contractions and maternal immune rejection of the fetus [13, 14].

Methods

This was a prospective case-control study of 50 women with silent abortion (embryo without cardiac pulsation before 20 gestational weeks) and 46 age-matched healthy pregnant women as controls. All women were in reproductive age, and gestational age for silent miscarriage and healthy pregnancy was < 20 weeks of gestation. The silent miscarriage group was further subdivided to complete certain objectives: gestational



age (GA) [32] miscarriage women in the 1st trimester vs. All the information was saved. Data of each participant were saved, including the woman's name, age, occupation, smoking habits, alcohol consumption, family history, co-medication, and any drug intake. Women with a history of medical diseases such as diabetes mellitus, renal, cardiovascular or any chronic diseases, smoking, alcohol consumption, and drug abuse were excluded from this study. The diagnosis of silent miscarriage is based on clinical history, clinical examination by a gynecologist specialist and obstetric ultrasonography.

Five milliliters of venous blood were drawn from all the subjects and were immediately placed into non-heated gel serum separator tubes (SST) and then incubated at 37 °C in a water bath for approximately 10 min to coagulate the sample prior to centrifugation for 15 min at 3000 rpm to obtain the blood serum. The separated blood sera were aspirated and used for the assay of Thyroid function profile (TSH, total thyroxine TT4, and total triiodothyronine TT3), and progesterone P4. 4 Thyroid hormones profile; sera TSH, TT4 and TT3 were determined by an enzyme linked immunoassay sandwich method (DRG, Germany).

Serum P4 human estimation was performed using the ELISA kit based on the manufacturer's instructions (DiaPlus Inc., Canada) (REF: DP4816).

The results were statistically analyzed using the t-test. The results were expressed as means $\pm$ SD. A significance level was set at $p \leq 0.05$ [15].

Results

A significant difference was observed in the thyroid function profile and progesterone levels between silent miscarriage women and the well-health pregnant control group. Women who have miscarried frequently show elevated TSH and reduced thyroid hormones (T4, T3) and progesterone levels, in comparison with healthy pregnancies that continue to term. As shown in Table 1, the levels of TSH were significantly higher in the miscarriage group (36.34 ± 7.94 vs. 1.92 ± 0.55) than in the control group. Conversely, thyroid hormone (T4: 114.1 ± 21.8 vs. 127.3 ± 27.2), (T3: 1.55 ± 0.18 vs. 2.04 ± 0.38) and progesterone (P4: 18.4 ± 13.7 vs. 49.4 ± 23.5) levels were notably lower in the miscarriage group.

The gestational age-based comparison within silent miscarriage women was done by focusing on a comparison between the 1st and 2nd trimester of gestation as presented in Table 2. The 2nd trimester showed a pointedly elevation levels of thyroid function profile and progesterone (TSH: 2.35 ± 0.47 vs. 2.22 ± 0.35), (T4: 131.0 ± 16.4 vs. 127.3 ± 27.2), (T3: 1.64 ± 0.18 vs. 1.50 ± 0.16) and (P4: 30.2 ± 16.1 vs. 11.76 ± 5.26) than the 1st trimester.

Table (1): Thyroid function tests and progesterone in women with silent miscarriage and control group

Parameters	Mean $\pm$ SD		T-value	P-value
	Control group (No.=46)	Silent miscarriage group (No.=50)		
TSH (mIU/L)	1.92 ± 0.55	2.35 ± 0.47	-4.12	≤ 0.001
T4 (nmol/L)	127.3 ± 27.2	114.1 ± 21.8	2.63	≤ 0.01
T3 (nmol/L)	2.04 ± 0.38	1.55 ± 0.18	8.10	≤ 0.001
P4 (ng/ml)	49.4 ± 23.5	18.4 ± 13.7	7.79	≤ 0.001

Table (2): Effect of gestational age on thyroid function tests and progesterone among silent miscarriage group

Parameters	Mean± SD		T- value	P- value
	Gestational age			
	1 st trimester (No.=32)	2 nd trimester (No.=18)		
TSH (mIU/L)	2.22±0.35	2.58±0.570	-2.71	≤0.01
T4 (nmol/L)	104.6±18.7	131.0±16.4	-4.99	≤0.001
T3 (nmol/L)	1.50±0.16	1.64±0.18	-2.68	≤0.01
P4 (ng/ml)	11.76±5.26	30.2±16.1	-6.00	≤0.001

Biochemical parameters were significantly worse in women with a positive family history of spontaneous miscarriage than in miscarriage women with no family history for all parameters, as shown in Table 3. The familial group had significantly lower thyroid function profile (TSH: 2.23 ± 0.36 vs. 2.53 ± 0.56), (T4: 109.1 ± 19.2 vs. 121.6 ± 23.9), (T3: 1.51 ± 0.17 vs. 1.61 ± 0.19), and similar trend of progesterone (P4: 15.0 ± 12.7 vs. 23.5 ± 13.8) than non-familial group.

Table (3): Effect of family history on thyroid function tests and progesterone among silent miscarriage group

Group

Parameters	Family history Mean± SD		T- value	P- value
	Silent miscarriage without family history (No.=20)	Silent miscarriage with family history (No.=30)		
TSH (mIU/L)	2.53±0.56	2.23±0.36	-2.35	0.023
T4 (nmol/L)	121.6±23.9	109.1±19.2	-2.04	0.047
T3 (nmol/L)	1.61±0.19	1.51±0.17	-2.44	0.018
P4 (ng/ml)	23.5±13.8	15.0±12.7	-2.24	0.03

Table 4 shows the age-related comparison within the silent miscarriage group; there were no statistically significant differences between the two age groups for any of the parameters studied.

Table (4): Effect of maternal age on thyroid function tests and progesterone among silent miscarriage group



Parameters	Mean± SD Maternal age		T- value	P- value
	(20-30) yr. (No.=29)	(31-40) yr. (No.=21)		
TSH (mIU/L)	2.30±0.36	2.42±0.59	-0.89	0.38
T4 (nmol/L)	111.3±19.8	118.0±24.3	-1.08	0.29
T3 (nmol/L)	1.51±0.17	1.61±0.18	-1.98	0.054
P4 (ng/ml)	17.9±14.3	19.2±13.1	-0.32	0.75

Significant at ($p \leq 0.05$)

Discussion

The research revealed a close relation between hypothyroidism, hypoprogesteronemia, and silent abortion. Increased TSH and Decreased T3 and T4 Levels: Compared with the control group, the TSH level was increased, and the T3 and T4 levels were decreased, in accordance with studies stating that subclinical hypothyroidism increases the risk of abortion before 20 weeks of gestation [16-18]. Possible Mechanism(s): Deficiency of thyroid hormone impairs embryo implantation and placenta formation, and alters corpus luteum function and progesterone synthesis. High TSH is also associated with high inflammatory cytokines and increased activation of natural killer (NK) cells in the uterine lining [19, 20].

The levels of progesterone were significantly lower in silent miscarriage 18.4 ± 13.7 ng/mL as compared to the control group of pregnant women 49.4 ± 23.5 ng/mL. This is consistent with the critical role of progesterone in pregnancy maintenance, and its withdrawal results in regression of the corpus luteum and induction of uterine contractions leading to pregnancy loss [21, 22].

The first-trimester women had higher TSH levels and lower T4 and progesterone levels than the second-trimester women. These changes reflect physiological alterations in thyroid function and the progressive increase in placental progesterone after the tenth week [23, 24].

Women with a positive family history of miscarriage had high TSH, low levels of T4, T3, and progesterone. These observations are consistent with the hypothesis that there is a genetic component to the risk of thyroid dysfunction and development (or re-development) of miscarriage. Clinical Relevance: These results highlight the need for prompt evaluation of thyroid function and progesterone levels, especially in women with prior miscarriage, because early intervention for subclinical hypothyroidism decreases the likelihood of spontaneous miscarriage [25, 26].

Conclusion

This study confirmed that low progesterone and thyroid hormone levels and high TSH levels have a significant link with the occurrence of silent miscarriage. The severity of these hormonal perturbations was reported to be influenced by gestational age and family history of

miscarriage. The study recommends that it is necessary to examine thyroid function and progesterone levels routinely for all pregnant women at the beginning of the pregnancy, mainly in women with a history of miscarriage, so as to identify risk very early and give therapeutic intervention that may reduce the incidence of this obstetrical disorder.

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Conflict of interest

The author confirms there is no conflict of interest

Adherence to Ethical Standards

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