

Endocrine Disorders and Preterm Labor

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Abstract

Preterm labor remains one of the most important problems in obstetrics and common public health problem.

It should be noted, that a large group of diseases associated with the development of prematurity are endocrine disorders and the share of various forms of endocrine disorders in pregnancy is increasing.

Research objective: to study the structure and frequency of endocrine disorders in women with preterm labor.

Materials and methods. A retrospective study was conducted to study the structure and frequency of endocrine disorders in 2,426 women with preterm labor. Frequency of endocrine disorders were assessed, such as: hyperandrogenism (polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia (CAH), Cushing's syndrome), thyroid disorders (hypothyroidism, autoimmune thyroid disease, hyperthyroidism), hyperprolactinaemia, diabetes mellitus, including gestational diabetes mellitus; hyperparathyroidism.

Results. The study showed that endocrine disorders were observed in 37% of women with preterm labor (898 women out of 2,426 women with preterm labor).

In particular, 364 (15%) women with preterm labor had diabetes mellitus, including gestational diabetes mellitus, 339 (13,8%) - PCOS, 170 (7%) - non-classic congenital adrenal hyperplasia (CAH), 3 (0.12%) - Cushing's syndrome. Hyperprolactinaemia was observed in 267 (11%) women with preterm labor, hyperparathyroidism - in 2 (0.08%) women with preterm labor. Thyroid disorders occurred in 582 (23,9%) women with preterm labor.

Among women with preterm labor and thyroid disorders, the largest group was women with mild thyroid dysfunction, such as subclinical hypothyroidism, isolated hypothyroxinemia or TPOAb positivity - 379 (65%) women out of 582 women with thyroid disorders.

It is significant, that women with preterm labor most often had uncontrolled endocrine disorders, whether poorly controlled pre-conception or first diagnosed during pregnancy

- 503 (56%) women out of 898 women with ED.

Conclusions. The high frequency of endocrine disorders among women with preterm labor (37%), revealed in our study, indicates that today endocrine disorders remains an important factor of preterm labor.

In addition, results of our study showed, that among women with preterm labor and thyroid disorders, the largest group was women with mild thyroid dysfunction. It also implies that it is important to actively plan to assess early gestational thyroid function tests in women known to be thyroid disorders pre-conception.

It is significant, that women with preterm labor most often had uncontrolled endocrine disorders, whether poorly controlled pre-conception or first diagnosed during pregnancy. This should be considered when developing a strategy for the prevention of preterm labor and planning a pregnancy in women with endocrine disorders.

Keywords: preterm labor; endocrine disorders; hormonal imbalance

Introduction

Preterm labor remains one of the most important problems in obstetrics and common public health problem.

Despite numerous studies on the etiology and pathogenesis of preterm labor, the development and implementation of new medicines and ways to treat for this pathology, the frequency of preterm labor is not decreasing, occurring in 5 to 18 percent of births worldwide [1, 2, 3, 4].

Approximately 15 million children are born prematurely every year [1].

Preterm labor is a leading cause of infant mortality, morbidity, and long-term disability, and these risks increase with decreasing gestational age [3, 5]. Approximately 1 million children die each year due to complications of preterm birth [6].

Many survivors face a lifetime of disability, including reduced renal function [7], neurodevelopmental impairments [8], cerebral palsy [9], visual, hearing problems and reduced myocardial function [10].

Globally, prematurity is the leading cause of death in children under the age of 5 years [1].

Prematurity is also a major socio-economic problem. In addition to intensive neonatal care, most premature infants require long-term medical care at high financial cost.

Despite being a common public health problem, the causes of preterm labor are largely unknown.

Recently, many authors attach particular importance to the concept of heterogeneity of causes of prematurity, pointing out that preterm labor can be caused by a large number of direct and indirect factors [11]. We support this statement, given our recent research, including our analysis of women with preterm labor.

However, it should be noted, that a large group of diseases associated with the development of prematurity are endocrine disorders (ED).

As our experience shows, in obstetric practice recently among the diseases that complicate the course of pregnancy and delivery, the share of various forms of ED is increasing.

It is known that the endocrine system plays an important role in the gestational process [12, 13]. During pregnancy, there are close hormonal relationships between the mother

and fetus. The development of a new endocrine complex of mother-placenta-fetus provides the physiological course of pregnancy. ED in a pregnant woman has an adverse effect on her health, is a cause of complications during pregnancy and childbirth, and is a high-risk factor for preterm labor [13]. Therefore, understanding the impact of hormonal disorders on the prolongation of pregnancy and the condition of the fetus, the role of ED in the development of prematurity could shed light on the mechanisms associated with preterm labor and reduce their frequency.

Hormones of special interest during pregnancy should be conditionally divided into two categories: reproductive hormones (estriol, progesterone, testosterone and sex hormone binding globulin (SHBG)) and thyroid hormones.

Based on current data, the following mechanisms of adverse effects of hormonal disorders on the prolongation of pregnancy should be considered.

1. Increasing levels of testosterone

- May reduce levels of endometrial secretory proteins which are positively associated with length of gestation [14].

- May act antagonistically with estrogens [15].
- Testosterone circulates through the body bound to SHBG, so changing SHBG concentrations could affect the concentration of bioavailable testosterone.

2. Estriol and progesterone imbalance

- It's critically important for the timing of labor, as estriol primes the uterus for contractions [16] and progesterone promotes quiescence of the uterus until the time of labor [17].

- Progesterone concentrations increase during pregnancy, contributing to uterine quiescence, downregulation of prostaglandin production, and immune tolerance of the fetus [17]. At the beginning of labor, the concentration of progesterone is not significantly reduced; rather, the body's response to progesterone is suppressed. It is unclear exactly how this occurs, but possibly include decreasing in progesterone receptor expression, changes in receptor isoforms, and local progesterone metabolism [18].

- As term approaches, the ratio of progesterone to estriol changes in favor of estrogen, and a functional decrease in progesterone stimulates the onset of labor. The new dominance of estrogen increases prostaglandin and oxytocin receptors and enzymes responsible for muscle contraction, which together promote delivery [19].

- Progesterone keeps the effects of estriol under control during pregnancy, but the untimely transition of dominance from progesterone to estriol can lead to preterm labor [20].

3. Thyroid hormones.

Numerous clinical studies have convincingly demonstrated that thyroid hormones, synthesized in sufficient quantities, support optimal prolactin production, monoamine synthesis, corpus luteum activity and, thus, ensure the normal functioning of the gonads, the possibility of pregnancy and its physiological course to term of labor, play an important role in the normal development of the fetus [21].

There is a close relationship between the reproductive and thyroid systems [22, 23, 24].

- First, they have
- common central regulatory mechanisms - thyrotropin-releasing hormone (TRH) stimulates not only the secretion of thyroid-stimulating hormone (TSH), but also prolactin.

- Secondly, there is a structural homology of luteinizing hormone (LH), follicle-stimulating (FSH) hormone, human chorionic gonadotropin (hCG) and TSH. The structural α -unit is common to all these hormones and only the β -subunit is specific to each of them. This allows, in particular, hCG to bind to TSH receptors. Increased production of hCG causes an increase in free thyroxine (fT4) and, consequently, suppression of TSH.

- In addition, estrogens stimulate the synthesis in the liver of not only sex steroid-binding, but also thyroid-binding globulins. Changes in the levels of these proteins are important in the pathogenesis of reproductive dysfunction.

- Also, experimental studies revealed the presence of receptors for TSH and triiodothyronine (T3) in the ovaries (oocytes and granulosa cells). This means, that thyroid hormones act unidirectionally with FSH

at the cellular level. And thyroid dysfunction has a direct impact on steroidogenesis, ovulation and corpus luteum function, quality and viability of embryos.

4. Corticotropin releasing hormone (CRH)

Corticotropin releasing hormone, which is secreted from the hypothalamus and normally involved in stress response, may also be key in understanding the endocrine role in preterm labor. CRH concentrations are low in the first half of pregnancy and then begin to exponentially increase around the 20th week of gestation to peak at birth [25]. An earlier and more rapid increase of CRH concentrations has been observed in women who experience preterm labor [26, 27], suggesting that CRH may be involved in a «placental clock» [28]. CRH receptors are present in the myometrium and in the fetal zone of the fetal adrenal gland, so CRH could exert its effects on labor by interacting with these receptors [25].

Research objective: to study the structure and frequency of endocrine disorders in women with preterm labor.

Materials and methods

We conducted a retrospective study to research the structure and frequency of endocrine disorders in 2,426 women with preterm labor. The study group included women who gave birth prematurely in the period from January 2018 to November 2021 in the Perinatal Center of Kyiv (Ukraine).

We evaluated spontaneous preterm labor, defined as labor that starts before 37 weeks of pregnancy, presenting with premature rupture of membranes, spontaneous preterm labor, or both [29].

Gestational age was calculated on the basis of recommendations from the American College of Obstetricians and Gynecologists, self-reported date of the last menstrual period (LMP) was collected at the first study

visit and used in combination with early ultrasound measurements to determine gestational age at birth [30]. Briefly, the LMP was used as the gold standard and was compared to ultrasound measurements taken primarily before 14 weeks gestation. Gestational age was changed from the LMP estimate to the ultrasound estimate if the difference between the two methods was greater than a certain number of days, depending on which week the ultrasound was performed.

All women agreed to participate in the study.

In the study group of women with preterm labor evaluated the frequency of ED, such as: hyperandrogenism (polycystic ovary syndrome (PCOS), non-classic congenital adrenal hyperplasia (CAH), Cushing's syndrome), thyroid disorders (hypothyroidism, autoimmune thyroid disease, hyperthyroidism), hyperprolactinaemia, diabetes mellitus, including gestational diabetes mellitus; hyperparathyroidism. Research results were adjusted for maternal age, education, parity, marital status, alcohol consumption, smoking and year of delivery.

Results

Our results showed that endocrine disorders were observed in 37% of women with preterm labor (898 women out of 2,426 women with preterm labor).

The structure of ED in women with preterm labor was analyzed (Table 1).

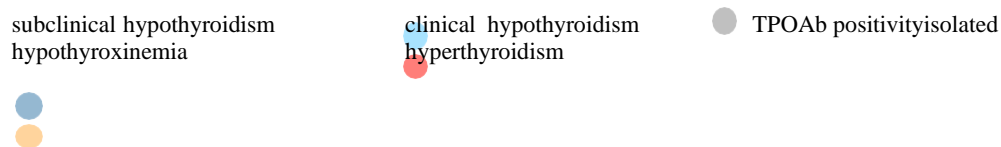
In particular, 364 (15%) women with preterm labor had diabetes mellitus, including gestational diabetes mellitus, 339 (13,8%) - PCOS, 170 (7%) - non-classic congenital adrenal hyperplasia (CAH), 3 (0.12%) - Cushing's syndrome. Hyperprolactinaemia was observed in 267 (11%) women with preterm labor, hyperparathyroidism - in 2 (0.08%) women with preterm labor.

| Endocrine disorders | N (%) |
|---|-------------|
| Thyroid disorders | 582 (23,9%) |
| Diabetes mellitus (including gestational diabetes mellitus) | 364 (15%) |
| PCOS | 339 (13,8%) |
| Non-classic congenital adrenal hyperplasia | 170 (7%) |
| Cushing's syndrome | 3 (0.12%) |
| Hyperprolactinaemia | 267 (11%) |
| Hyperparathyroidism | 2 (0.08%) |

TABLE 1: Structure of endocrine disorders in women with preterm labor (N=2,426)

Thyroid disorders occurred in 582 (23,9%) women with preterm labor (Table 1). Within this cohort, 151 women (26%) had clinical hypothyroidism, 221 women (38%) had subclinical hypothyroidism, 76 women (13%) had isolated hypothyroxinemia and 82 (14%) had thyroid peroxidase antibody (TPOAb) positive (Figure 1). Hyperthyroidism occurred in 52 (9%) women with thyroid disorders (Figure 1).

Thus, among women with preterm labor and thyroid disorders, the largest group was women with mild thyroid dysfunction, such as subclinical hypothyroidism, isolated hypothyroxinemia or TPOAb positivity - 379 (65%) women out of 582 women with thyroid disorders.



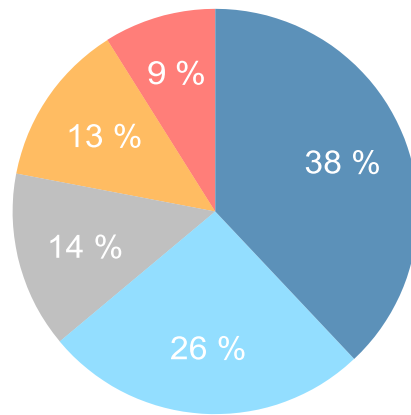


Figure 1. Structure of thyroid disorders in women with preterm labor (n=582)

These findings validate, that mild thyroid dysfunction, such as subclinical hypothyroidism, isolated hypothyroxinemia and TPOAb positivity in pregnant women are also risk factors for preterm labor.

It implies that it is important to actively plan to assess early gestational thyroid function tests in women known to be thyroid disorders preconception.

In addition, it is significant, that women with preterm labor most often had uncontrolled endocrine disorders, whether poorly controlled preconception or first diagnosed during pregnancy - 503 (56%) women out of 898 women with ED.

Conclusions

The high frequency of endocrine disorders among women with preterm labor (37%), revealed in our study, indicates that today ED remains an important factor of preterm labor.

In addition, results of our study showed, that among women with preterm labor and thyroid disorders, the largest group (65%) was women with mild thyroid dysfunction, such as subclinical hypothyroidism, isolated hypothyroxinemia or TPOAb positivity.

It also implies that it is important to actively plan to assess early gestational thyroid function tests in women known to be thyroid disorders preconception.

It is significant, that women with preterm labor most often had uncontrolled endocrine disorders, whether poorly controlled preconception or first diagnosed during pregnancy. This should be considered when developing a strategy for the prevention of preterm labor and planning a pregnancy in women with endocrine disorders.

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