"OVIDIUS" UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
DOCTORAL FIELD OF RESEARCH: MEDICINE
UNIVERSITY YEAR 2020-2021

Abstract of PhD Thesis

PhD Coordinator:

Prof.Univ.Dr. Circo Eduard

PhD Student :

Scutaru (Scrinic) Olesea

CONSTANȚA 2021

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Iodine and thyroid status in a group of pregnant women from the perimarine area of Romania - pathological implications

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CONTENT

The structure of the doctoral thesis:

• General Part - Current state of knowledge - distributed in 4 chapters

• Special part - Personal contribution - distributed in 5 chapters

• The thesis contains: 235 tables and 261 figures

• Bibliographic references: 219

Keywords: pregnancy, thyroid, urinary iodine concentration, indicators, chronic autoimmune thyroiditis, perimarina area.

Note: The content of the abstract is identical to the original one in the thesis.

INTRODUCTION

Iodine and thyroid status in pregnant women is a basic element in the early detection, monitoring and specific treatment of possible thyroid dysfunction and the information in this paper being a new and recent source in terms of thyroid disease in pregnant women in the perimarine area of Romania.

Adequate iodine intake is essential in maintaining normal thyroid function during pregnancy, as thyroid hormones play an important role in the neurocognitive development of the conception product. Maternal thyroid morphofunctional balance begins in the pre-pregnancy period, continues during it and is reflected in the postpartum stage and the whole life of the child.

Thus, Dobrogea, the perimarine area of Romania, is considered a territory with sufficient iodine intake. However, certain population categories such as: pregnant women, children, breastfeeding women have increased needs for iodine intake in different and variable amounts, requiring adaptation according to international and national regulations.

Universal salt iodization (USI) for human consumption, animal feed and use in the food industry, regulated nationally in Romania by government decision in 2002, is the most effective measure to eradicate iodine deficiency disorders (IDD).

A large number of national studies have been conducted on the thyroid and iodine nutritional status of pregnant women, but most have been conducted in endemic areas, and extensive studies in the perimarine region are missing.

In this context we tried to develop and conduct a prospective study of pregnant women on iodine status assessed by urinary iodine dosage, thyroid morpho-functional status and assessment of the incidence and prevalence of thyroid dysfunction in the first months of pregnancy and their influence on materno-fetal complications in the antepartum and postpartum period, as well as the assessment of the association of insufficient or excess iodine intake or thyropathy on neonatal parameters. An indicator of congenital hypothyroidism determined by neonatal TSH was also monitored.

GENERAL PART

CHAPTER 1
Thyroid pathophysiology in pregnancy

Pregnancy defines a complex functional unit - *feto-placental unit* - which has its own endocrine activity with a series of maternal adaptive changes necessary for embryo-fetal development. The factors involved in the genesis of thyroid-functional changes are: endogenous - autoimmunity, placental hormones; exogenous or environmental - iodine intake, contact with guitrogenic substances, drugs.

The main events that occur during pregnancy are [1]: marked increase in serum thyroxine binding globulin (TBG) concentrations, moderate decrease in free hormone levels (under sufficient iodine conditions), which is significantly amplified when there are restrictions on iodine or obvious iodine deficiency, a frequent tendency towards a slight increase in basal thyrotropin or thyroid stimulating hormone (TSH) levels between the first trimester and until term, direct stimulation of the maternal thyroid gland by high levels of human chorionic gonadotropin (hCG), which occurs mainly near the end of the first trimester and may be associated with a transient decrease in serum TSH and changes in the metabolism of maternal thyroid hormones. The placenta is permeable to TPOAb, TGAb, anti-TSH receptor antibodies and antithyroid drugs.

Thyroid pathology in pregnancy

The prevalence of clinically manifest thyroid dysfunction in pregnancy is estimated to be around 1% [2]. Hyperthyroidism in pregnancy has a prevalence between 0.1 - 0.4%, clinically manifest hypothyroidism (CMH) between 0.3% - 0.5%, and subclinical hypothyroidism (SCH) between 2 - 3% [3].

Hypothyroidism in pregnancy

• **Maternal risks** of hypothyroidism are miscarriage and recurrence, anemia, gestational hypertension, placental abruption, postpartum hemorrhage [4,5].

- The study of Abalovich et al. have shown that women with inadequately treated clinical manifest hypothyroidism have an estimated 60% risk of miscarriage [4].

• **Fetal risks** of hypothyroidism: premature birth, low birth weight, neonatal respiratory distress, intrauterine growth restriction with suffering at birth, perinatal mortality, neurocognitive deficit affecting the neuropsychic development of the child [5].

Hyperthyroidism in pregnancy

• **Maternal risks** of hyperthyroidism are: miscarriage, premature birth, placenta praevia, pregnancy induced hypertension, congestive heart failure, thyrotoxic crisis [5, 6].

• **Fetal risks** of hyperthyroidism are: neonatal fetal thyrotoxicosis, low birth weight, intrauterine growth restriction, prematurity, perinatal death [5,7].

Transient gestational thyrotoxicosis is a transient clinical hyperthyroidism, frequently limited to the first half of pregnancy, diagnosed between 1-3% of pregnancies [5].

Thyroid autoimmunity in pregnancy

The risk of intranatal and perinatal maternal-fetal complications associated with thyroid autoimmunity is supported by numerous studies.

The most common gestational pathology associated with chronic autoimmune thyroid (CAT) is spontanous or recurrent miscarriage (double risk [8]) and the risk of premature birth. Other complications associated with thyroid autoimmunity were perinatal mortality, placental abruption, postpartum depression or neonatal respiratory distress syndrome [9], child outsourcing problems, namely attention deficit hyperactivity disorder [10].

Possible incriminating mechanisms were: autoimmune process that increases fetal resorption, antibody-mediated hypothyroidism, cross-reactivity of antithyroid antibody with hCG receptors in the pellucid area, the presence of a competing nonorgan-specific autoimmunity and the increased level of endometrial cytokines in women with thyroid autoimmunity [5,11].

The prevalence of thyroid nodules in pregnancy varies between 3% and 21% and increases with parity and age [5].

CHAPTER 2
Iodine status in pregnancy

During pregnancy, the iodine intake undergoes a series of changes in concentration due to the increased need for maintaining the state of euthyroidism by the mother, the transfer of iodine to the fetus and the increase in maternal iodine renal clearance, thus increasing the need for iodine in pregnant women [12].

Due to increased thyroid hormone production, increased renal iodine loss, and fetal iodine requirements during pregnancy, dietary iodine requirements are higher in pregnant women than in non-pregnant women. The daily iodine requirement recommended by the World Health Organisation (WHO), together with The International Council for the Control of Iodine Deficiency Disorders (ICCIDD) and UNICEF for pregnant women is 250 mcg / day.

Indicators of iodine status are determined by *clinical methods*: thyroid volume by objective examination (inspection and palpation) or thyroid ultrasound with appreciation of the degree of goiter or *paraclinical methods*: neonatal TSH, serum thyroglobulin, concentration of peripheral thyroid hormones (T3, T4), urinary iodine concentration (UIC) [13].

The prevalence of goiter in school-age children according to the WHO is an epidemiological criterion for determining the severity of iodine deficiency based on a value of > 5% characteristic of a mild iodine deficiency, > 20% moderate deficiency and > 30% severe deficiency. But the prevalence of goiter is of limited utility because it does not reflect the impact of iodine fortification, and goiter can persist for months or years in endemic areas where iodine deficiency has been corrected, so this indicator better reflects the history of long-term iodine status of a population [13].

Neonatal TSH is used in screening for congenital hypothyroidism and can be useful in assessing the iodine status of the population, but also the degrees of iodine deficiency that can be established depending on the prevalence of the neonatal population with TSH over 5 mIU/L. The prevalence of newborns with TSH > 5 mIU / L in over 3% of the studied population is characteristic of mild iodine deficiency, over 20% reflect a moderate iodine deficiency, and over 40% reflect a severe iodine deficiency. Neonatal TSH may be influenced by maternal nutritional status, type of birth, blood sample collection time, maternal or neonatal exposure to iodinated antiseptics and testing method. Due to this intraindividual variability in the thyroid ability to compensate for inadequate iodine intake, TSH is not a sensitive indicator of iodine status of the population, except for neonatal assessment [14,15].

Urinary iodine concentration (UIC) - is the most useful indicator that reflects the recent iodine intake. The epidemiological criteria for determining the iodine nutritional status based on the median UIC for pregnant women are: inadequate iodine intake below 150 mcg/l, adequate between 150 - 249 mcg/l, more than adequate between 250 - 499 mcg/l and excessive at over 500 mcg/l [15].

The appreciation of UIC in spontaneous urine in pregnant women may underestimate the true value of urinary iodine levels, because during pregnancy the glomerular filtration rate increases by approx. 40–50%, being the reason for the increase in urine volume/24 h and thus causing a dilution of urine, consequently increasing the renal clearance of iodine and renal excretion of iodine. Thus, adaptation to pregnancy conditions, by excluding a variation of urine volume and dilution, can be achieved by correcting the concentration of urinary iodine to creatinine, providing a more accurate index of iodine status by assessing the ratio of urinary iodine concentration adjusted to urinary creatinine (UIC / UCr ratio) [16].

Efficiency indicators of iodine deficiency prevention programs

The latest monitoring data (national or regional) must be collected in the last five years. In support of the sustainable elimination of iodine deficiency as a public health problem, the WHO recommends meeting the following criteria [13]:

1. Salt iodization: The availability and use of properly iodized salt (> 15 ppm iodine and < 40 ppm household) must be guaranteed and demonstrated by the use of **> 90%** of households.

2. Iodized nutritional status of the population: median UIC in the general population = 100-199 mcg/l, and median UIC in pregnant women = 150–249 mcg / l.

Global iodine status

Statistical data provided by IGN (Iodine Global Network) in 2017 on the global iodine status among school-age children and pregnant women obtained from cross-sectional population studies conducted between 2002 and 2017 through a systemic online search based on PubMed and ISI Web of Science data showed [17]: - a significant reduction in the number of countries with insufficient iodine intake from *54 in 2003* to *19 in 2017* out of a total of 194 WHO countries, and in 2017 <10%

of the world's population lived in countries classified as iodine deficient based on iodine intake in the general population [17].

In 2020, globally, according to IGN, following the data from the last 15 years, there are only 23 countries with insufficient iodine intake, 14 countries with excess iodine intake and 115 countries with adequate iodine nutritional status and including the data before 2004, the number countries with adequate input increases to 131 [18].

In 2003, according to the "Iodine status worldwide - WHO Global Database on Iodine Deficiency", the number of people with insufficient iodine intake worldwide, estimated on the median urinary iodine concentration (urinary iodine <100 mcg/l) was 1988 million, of which 285 mln. (36.5%) being children of school age [19]. Following the USI programs applied in as many countries as possible globally, the statistical data provided by the World Health Organization in 2012 showed a number of 1924.9 million people with iodine deficiency, of which 246.2 mln. (29.8%) school-age children, data wich decrease from 2003 reports [20].

Iodized salt consumption in households assessed by national surveys, being an indicator of the effectiveness of programs to combat iodine deficiency, indicated in 2012 that approximately 70% of households worldwide had access to iodized salt [20]. In 2018 UNICEF published the map overall iodine consumption in households, a percentage that increased to 88% compared to 70% in 2012 [21].

Iodized status in Romania in the general population and pregnant women

In 2002, the introduction of Universal Salt Iodization in Romania took place, being approved by Government Decision (GD) no.568/2002, republished in 2004, 2006 with last update being in 2009 [22,23,24.]

The largest study carried out approximately 2 years after the introduction by law of universal salt iodization throughout Romania, on the population of pregnant women conducted by National Institute for Mother and Child Health together with UNICEF Romania on a 1595 cases in 2005, has a median UIC of 73 µg / l corresponding to insufficient intake and moderate iodate deficiency [25].

One of the most recent studies of National Institute for Mother and Child Health Bucharest and National Institute of Endocrinology "IC Parhon", UMF "Carol Davila" was performed in 2016 - 2017 from 15 endemic counties of Romania, regarding the evaluation of iodine status in pregnancy continues to reveal a persistence of suboptimal iodide values in pregnant women in endemic areas of Romania. The conclusions of this study were: median UIC - 116 mcg/l demonstrating an insufficient iodine intake [26].

Thus, 15 years after the implementation of universal salt iodization in Romania, pregnant women still have a slight iodine deficiency, probably due to the reduction salt intake of pregnant women or insufficient iodization of salt.

But there are also data obtained nationally for pregnant women from non-endemic and endemic areas conducted in 2015 by Ursu et al. on a group of 118 pregnant women who presented a median CIU of 200.3 mcg / l corresponding to an adequate iodine intake [27].

However, according to the latest data from 2020 from the global iodine network - IGN the general population of Romania is characterized by an adequate iodine intake based on the median UIC in school-age children of (255 mcg/l) [28.29].

Although the mountainous and perimountainous regions on the Romanian have been considered endemic in the past regarding iodine deficiency, according to recent studies from 2005 and 2014 conducted after the introduction of USI since 2002, we find an iodine deficiency, although mild, throughout Romania [25,30].

Iodine status in the Dobrogea region

The perimarine area of Romania is considered to be the region with sufficient iodine intake. The first data on the iodine status of the population in this region can be found in the studies of Prof.Univ. Dr. Circo Eduard since 1986 when the prevalence of goiter in a number of 1133 school-age children from Mangalia was 8.0%, in 1991 another study on 1095 children from 3 localities of Constanța County shows a prevalence of goiter of 10.7%. The last survey conducted in the Dobrogea region took place in 1995, on a number of 1010 children, with an increase in goiter prevalence of up to 12.8% compared to previous surveys, all these data certify a mild iodine deficiency, results that were published in 1996 in the Romanian Journal of Endocrinology [31] and found in the WHO global database on iodine deficiency for Romania [32].

Studies on the perimarine goiter among the adult population carried out in Dobrogea between 1998 and 2001 show an increased prevalence of up to 64.6% revealing the involvement of a number of environmental factors with potential goitrogenic effect in this region [33]. Pollution with nitrites, nitrates and organic substances in the groundwater of Constanta and Danube county. Also, the biochemical composition of the Dobrogean soil in which limestone rocks and alkaline salts predominate will determine that the phreatic water is characterized as intensely mineralized water due to the calcium salts with an alkaline reaction. A characteristic of the soil in which limestone rocks predominate is the low amount of iodine, a phenomenon that is balanced by the geographical location of Dobrogea where the marine source of iodine is provided to the soil by rainwater. However, the occurrence of particular conditions of interference of calcium salts with intestinal absorption of iodine, as well as individual reactivity or zonal quantitative variations of iodine may be involved in differences in iodine intake and increased prevalence of goiter in a geographical area considered sufficient in iodine [33].

Attestations prior to the introduction of USI of the iodine nutritional status of the Dobrogean population by determining urinary iodine were carried out among school-age children and communicated in 1991 by Simescu M et al.with a median UIC of 107 mcg / l characteristic to an adequate iodine intake and in Tulcea county a median of 34 mcg / l characteristic of an insufficient iodine intake [34].

The need for regular population-level assessment, especially in vulnerable groups, is needed in the context of national efforts to prevent and eliminate iodine deficiency disorders.

Disorders of iodine intake in pregnancy

Iodine deficiency disorders

According to the WHO, the classification of iodine deficiency by determining the median of UIC by degrees of severity for pregnant women is as follows: below 50 mcg/l = severe deficiency, between 50 - 149 mcg/l = moderate deficiency [27]. Both moderate and severe Iodine deficiency in pregnancy are associated with a number of complications such as maternal clinical and subclinical hypothyroidism, endemic cretinism, sporadic or repetitive miscarriage, premature birth, perinatal mortality, low birth weight, intrauterine growth restriction (IUGR) [5.35]. Globally deficient iodine nutritional status is the most important cause of preventable mental deficiency and universal salt iodization being the most effective measure that can prevent and ameliorate this iodine deficiency[36].

Excess iodine disorders

In the the fetal period, full maturation to escape the Wolff-Chaikoff effect occurs at approx. 36 weeks of pregnancy, thus the fetus is prone to iodine-induced hypothyroidism [37].

An indicator of excess iodine may be the determination of thyroglobulin in women at risk of exposure to excessive doses of iodine [38]. Another risk of excess iodine is even a low dose of iodine that may be a trigger for the onset of thyroid autoimmunity [39]. Iodine-induced hypothyroidism has also been reported in children exposed to iodinated radiocontrast agents [40].

CHAPTER 3

Fetal and neonatal implications of inadequate iodine intake

Neonatal thyroid screening

Universal screening for thyroid dysfunction is a unanimously accepted intervention to be useful and benefic for the early and rapid detection of thyroid pathology. Thyroid function tests have been included in newborn screening programs since the mid-1970s and have facilitated the early detection and treatment of newborns with clinical hypothyroidism, largely eliminating the impairment of neurodevelopment in hypothyroidism [41,42].

Thyroid screening in Romania is addressed to all newborns. The incidence of neonatal hypothyroidism in Romania is between 1/3,000 - 1/4,000 newborns [43]. In 2016 an incidence of 1/ 3,285 and in 2017 - 1/4.131 were reported by National Institute for Mother and Child Health [44].

Studies describing a number of specific biomarkers of neuronal proliferation and migration have emerged in the last 10 years. BDNF (brain-derived neurotrophic factor), LPA (lysophosphatidic acid) and GDNF (growth-derived neurotrophic factor) are considered to be useful parameters in the evaluation of infant neurodevelopment [45]. A number of studies sustain that BDNF in umbilical cord blood has significant variations in special conditions such as prematurity or preeclampsia [46,47]. And experimental data have identified the association between BDNF and hypothyroidism, even in models with subclinical hypothyroidism [48,49]. There are also studies showing an inversely proportional relationship between BDNF and TSH as well as between BDNF and oxidative stress during pregnancy, suggesting a decrease in the hippocampus and cerebellum of BDNF concentration and increased oxidative stress during early neurodevelopment which may contributes to the development of adverse effects of hypothyroidism during pregnancy on the neurodevelopment of the product of conception [50].

Alteration of the mechanism of LPA-dependent intracellular signal during pregnancy may be etiologically involved in the occurrence of obstetric complications, such as implantation failure, preeclampsia and preterm birth. Thus, the level of LPA and neurotrophins can be used for biomarkers of neurodevelopment in the early stages of life, but also as potential predictors of nervous system disorders [51.52].

The ministery of health guide from Romania recommends CH screening by neonatal TSH dosage during 2 - 4 day of life, using dry - spot method, the established pathological value (cut-off) over 20 mIU/ml being considered to indicate a possible congenital hypothyroidism [43].

Congenital hyperthyroidism

There is an increased risk for the development of hyperthyroidism in newborns from mothers diagnosed with Graves' disease, due to the transplacental passage of TSH receptor stimulating antibodies. The incidence of neonatal hyperthyroidism varies between 2-20% in different studies. The clinical picture is different and may include goiter that can even cause compression of the trachea, tachycardia, low birth weight, hypertension, diarrhea, irritability and low weight gain [53].

CHAPTER 4

The particularities of thyroid screening in pregnancy

The most common thyroid disorders: hypothyroidism, hyperthyroidism and thyroid autoimmunity have a number of maternal-fetal complications during pregnancy, childbirth and postpartum. Although the incidence of overt clinical hypothyroidism is much lower compared to subclinical hypothyroidism, the main goal in supporting universal screening is to detect early subclinical hypothyroidism and prevent possible overt hypothyroidism.

Many endocrinology societies and associations have not reached a consensus on supporting or rejecting universal thyroid screening during pregnancy. Clinical guides for Management of Thyroid Disease During Pregnancy and the Postpartum of ATA[5] and Endocrine Society[3] recommends identifying pregnant women at high risk for the development of thyroid disease during pregnancy, this category includes pregnant women with a history of hypothyroidism or hyperthyroidism, the presence of goiter or thyroid autoimmunity. Other risk factors include age over 30 years [54], history of abortion, premature birth or infertility [55], diabetes or other autoimmune diseases [56], history of thyroid surgery or previous cervical irradiation [57.58], family history of thyroid autoimmunity [59], use of amiodarone[60], morbid obesity [61], recent use of iodinated contrast agents, multiparity [62] and origin from an area with moderate or severe iodine deficiency [63].

Thyroid status can be determined quickly with available serum hormone tests, such as TSH, FT4 and ATPO dosing. The main focus on the effectiveness of thyroid screening in pregnancy is focused on identifying the effectiveness of treatment especially in the population of pregnant women with subclinical hypothyroidism. The identification and treatment with LT4 of subclinical hypothyroidism or thyroid autoimmunity in order to reduce obstetric and perinatal complications, also in order to prevent and reduce the impairment of neurocognitive development of children is one of the most investigated aspects related to the usefulness of thyroid screening in pregnancy.

Universal screening versus screening for high-risk cases

An important aspect presented by the guidelines for diagnosis and treatment of thyroid diseases during pregnancy and postpartum in 2011 by ATA [5] and in 2012 by Endocrine Society [3] that expand the definition of high-risk pregnant women including women over 30 years. Consequently, this broad definition of high-risk pregnant women has increased the number of cases in the populations of pregnant women with high maternal age.

There are quite controversial data regarding the adoption of a universal screening or high-risk case for pregnant women. No consensus has been reached between the largest specialized forums. Thus, supporters of universal screening are 74% of ATA members, and in the latest 2014 guide of ETA (European Thyroid Assocation) members of this society advocate for universal screening citing the benefits of early therapy in overt clinical hypothyroidism, but also the risk of underdiagnosis an increased number of pregnant women with subclinical hypothyroidism [64,65,66]. Interpretation of functional thyroid status using only risk-case screening can underdiagnose up to approx. 30 - 40% of thyroid dysfunctions support a series of studies [67,68].

PERSONAL CONTRIBUTION

CHAPTER 1
Motivation and objectives of the research

Thyroid dysfunction in a specific category of the population, *pregnant women*, is an interdisciplinary priority for the obstetrician, the family doctor and the endocrinologist. Untreated these diseases are associated with significant maternal and fetal risks. Early identification of thyroid disorders in pregnancy is essential in the prevention and treatment of these disorders, which can be achieved by screening all pregnant women in the first trimester of pregnancy.

Although the Dobrogea area, a sufficient marine and perimarine area in iodine, it is considered to have a sufficient iodine intake to prevent the development of cretinism and mental retardation secondary to iodine deficiency, there are a number of other factors that can influence the mother's health, pregnancy and fetus development: goitrogenic factors, smoking, clinically manifest or subclinical maternal hypothyroidism, maternal hypothyroxinemia and of course the presence of maternal antithyroid autoantibodies.

Published studies on the indicators of iodine nutritional status in the perimarine region of Romania are prior to the introduction by law of universal iodization of salt, so in 1991 the median

iodine among school-age children was 107 mcg/l characteristic of an adequate iodized intake, and in 1996 the prevalence of goiter in Dobrogea was 12.8% value indicating a mild iodine deficiency (an indicator that predominantly reflects the history of iodized intake of a region and not the current iodinated nutritional status) [69.70].

Currently, there are no statistical data from the marine and perimarine area of Romania on iodine status in pregnant women, but also on functional and autoimmune thyroid status, these being the reasons for the elaboration of this doctoral thesis on " Iodine and thyroid status in a group of pregnant women from the perimarine area of Romania - pathological implications ".

The main objectives of the research are:

1. Assessment of maternal iodine status in the perimarine area by determination of maternal urinary iodine with identification of iodine deficiency or the presence of excess iodine
2. Analysis of the maternal thyroid functional and ecostructural status
3. Identification and monitoring of maternal thyroid dysfunction during pregnancy
4. Assessment of maternal thyroid autoimmune status and correlation with maternal-fetal pathology
5. Determining the incidence of maternal and fetal peripartum complications in pregnant women with thyroid dysfunction
6. Analysis of the association between maternal iodine nutritional status and maternal-fetal pathology during pregnancy or neonatal pathology
7. Analysis of the association between maternal functional and morphological thyroid status and maternal-fetal pathology during pregnancy or neonatal pathology
8. Analysis of possible risk factors: smoking, parity.
9. The influence of specific thyroxine replacement therapy in thyroid dysfunction on the evolution of pregnancy.

CHAPTER 2
Materials and method

Used materials :

• The study was carried out in the location of the specialized outpatient clinic within the Gastromond-Regina Maria Clinic, Constanţa and consultation offices of the Endocrinology department of the Constanţa County Emergency Clinical Hospital.

• Regina Maria analysis laboratories with the appropriate analyzers for hormonal determinations and the iodine laboratory within the "Alessandrescu-Rusescu" National Institute for Mother and Child Health - Bucuresti, Romania with the appropriate equipment for determining urine iodine.

• blood samples collected for hormonal dosing by laboratory staff according to the collection recommendations of Regina Maria laboratories and spontaneous emission urine samples for iodine dosing, disposable glasses, universal harvesters, pipette, refrigerator.

• LOGIQ P7 ultrasound - General Electric with linear probe L6-12 for thyroid imaging examination

Methodology:

The present scientific paper represents a prospective clinical study on a number of 82 pregnant women in the first or second trimester of pregnancy, originating from the Dobrogea area: Constanța and Tulcea counties. The study took place between 10.2018 and 12.2020. Clinical and paraclinical data were collected by the endocrinologist Scrinic Olesea, under the guidance of the coordinator of the doctoral thesis Prof.Univ.Dr. Circus Eduard. The studied group of pregnant women was made following the application of inclusion and exclusion criteria.

Inclusion criteria: confirmed pregnancy, origin and residence in Constanța or Tulcea counties and pregnant in the first or second trimester of pregnancy, signed informed consent.

Exclusion criteria: pregnant women who did not give birth in Romania, pregnant women with extreme iodine values above 800 mcg / ml and absence of informed consent.

The number of pregnant women included at the beginning of the study was 82, of which 2 pregnant women were excluded after the results of iodide because they showed extreme values > 800 mcg/ml (samples suggesting iodine contamination), also 6 more pregnant women after postpartum re-evaluation they were excluded because they did not give birth on Romanian territory. At the end of the study, 74 pregnant women were eligible according to the inclusion and exclusion criteria.

The study received the approval of the Bioethics Commission of the "Ovidius" University of Constanța, as well as the approval of the Ethics Commission for the approval of clinical studies and research works within the Emergency County Clinical Hospital "St. Apostol Andrei" Constanta.

1. Inclusion in the study - the first visit included the following:

¬ description of the study, obtaining the agreement and signing the informed consent

¬ anamnesis, endocrine clinical examination (presence of goiter); paraclinical examination : thyroid hormone dosage: TSH, FT4, ATPO, ATG

¬ the dosage of urinary iodine from the spontaneous sample, urinary creatinine and the ratio between the 2 analyzes

¬ imaging evaluation of the thyroid

2. Prenatal reassessment of pregnant women in the last trimester included:

¬ the presence of prenatal gestational and mateno-fetal pathology

¬ monitoring pregnant women with thyroid diseases diagnosed before pregnancy or during pregnancy, adjusting thyroxine replacement therapy

3. Postpartum reassessment:

¬ the presence of perinatal and neonatal pathology, birth peculiarities, neonatal parameters

¬ determining the thyroid functional status of newborns by determining neonatal TSH

The research data were entered into an Excel MS 2010 database and then analyzed using the IBM SPSS Statistics statistical processing program 23.

CHAPTER 3
Research results
3.1. General characteristics of the study group

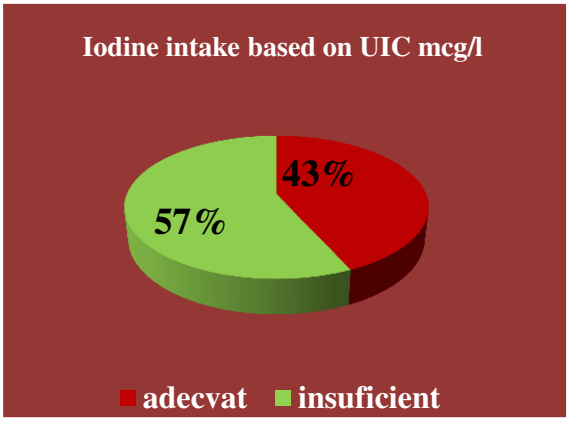
Basic characteristics of the study	
Nr. cases	74
Mean age (years), SD	29,9 (+/- 4,54)
Median gestational age, (weeks), IQR	**11 (8, 13)**
Multiple pregnancy, n (%)	42 (56,7 %)
Area of living: -urban **- rural**	56 (75,6) 18 (24,3)
BMI (kg/m2) (IQR)	23,21 (20,44 - 27,11)
Smoker, n (%)	30 (**40,5**)
Family history of thyroid disease, n (%)	29 (**39,1**)
Personal history of thyroid disease, n (%)	21 (**30,4**)
Iodized salt consumption, n (%)	61 (**82, 43**)
Iodine suppliments use (> 150 mcg/day) , n (%)	25 (**33,7**)
Completed pregnancies, n (%)	69 (93,2)

3.2. Determination of maternal iodine status indicators

1. Analysis of median urinary iodine concentration (UIC) and adjusted iodine ratio to urinary creatinine (UIC / UCr ratio)

	UIC, median (IQR)	UCr, median (IQR)	UIC/UCr ratio , median (IQR)
Total , n=74	**133.03** (69.1, 204.6)	**0.98** (0.516, 1.430	**152.83** (102.55, 211.21)

3.2.1. Determination of iodine intake based on UIC and UIC/UCr ratio



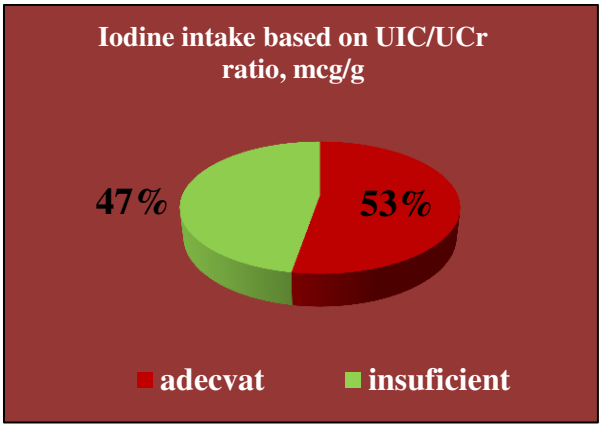
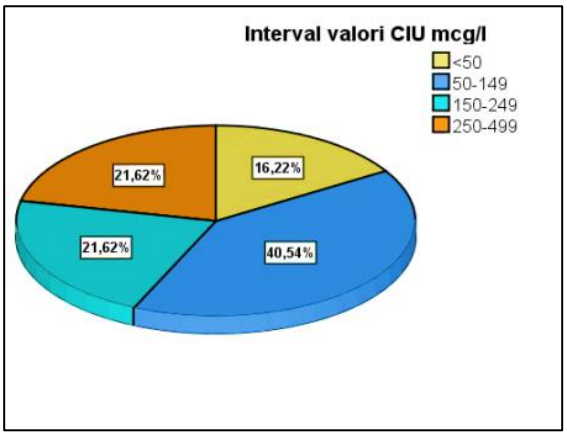


Figure no. 58 and 60 - Pie type representation for the variable iodine intake based on the value of urinary iodine concentration and the ratio of urinary iodine concentration to urinary creatinine.

Adequate iodine intake is characterized by urinary iodine value> 150 mcg / l and insufficient iodine <150 mcg / l.

3.2.2. Distribution of the study group by UIC value ranges and UIC / UCr ratio with determination of iodine deficiency levels



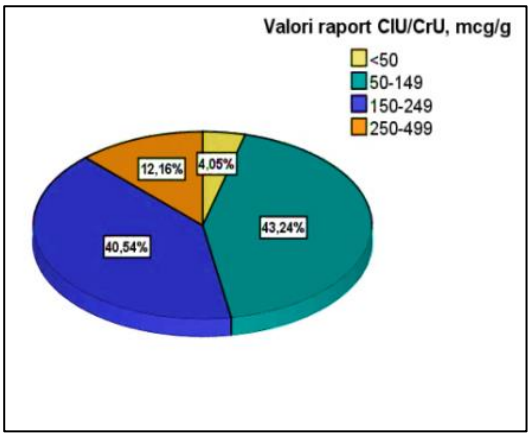


Figure no. 64, 66 - Pie type representation for the CIU value range (mcg / l) and CIU / CrU ratio (mcg / g)

3.2.3. Prevalence of maternal goiter - clinical indicator of iodine status

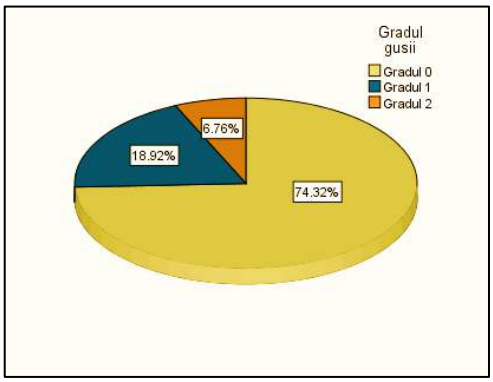


Figure no. 130 - Standard representation for the variable presence of goiter at inclusion in the study

3.2.4. Determination of neonatal TSH and iodine deficiency degrees

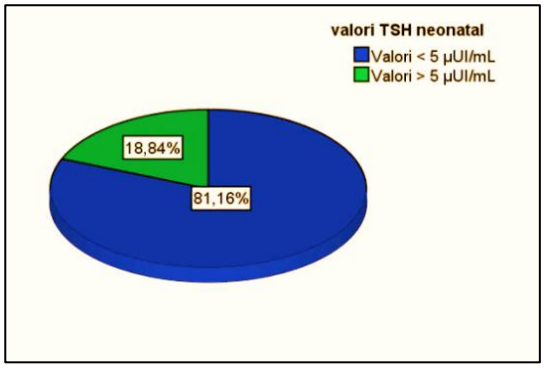


Figure nr. 68 Severity of iodine deficiency based on the value of neonatal TSH

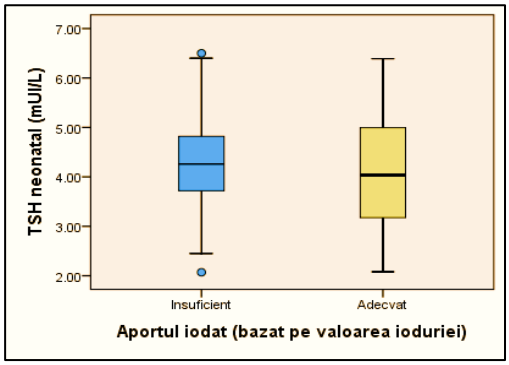
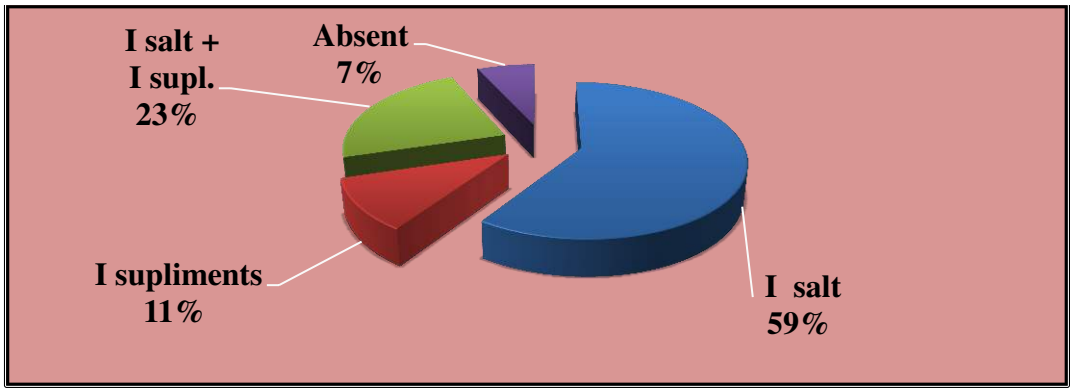


Figure nr. 102 - Box-Plot graphical representation for neonatal TSH variable according to iodized intake based on CIU

The median values of neonatal TSH were 4.17 mIU/L (IQR: 3.54 and 4.84 mIU/L). We identified a difference between the median values of TSH in relation to insufficient maternal iodine intake and adequate : 4.26 mIU / L versus 4.03 mIU/L, although statistically insignificant (p = 0.540).

3.2.5. Distribution of pregnant women according to the type of iodine consumption



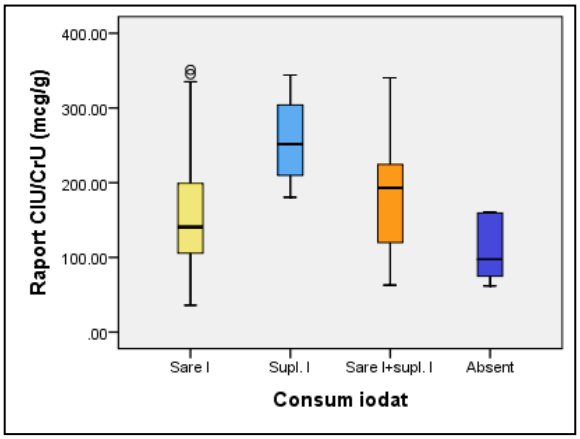
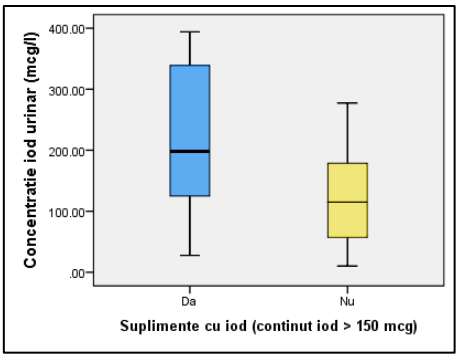


Figure no. 85 - Box-Plot graphical representation for CIU / CrU ratio variable (mcg / l) according to iodine consumption of pregnant women

3.2.6. Iodized status based on UIC and UIC/UCr ratio depending on the consumption of iodinated supplements

	UIC, median (IQR)	UCr, median (IQR)	raport UIC / UCr, median (IQR)
Total , n=74	**133.03** (69.1, 204.6)	0.98 (0.516, 1.430	**152.83** (102.55, 211.21)
Pregnant with iodinated supplements, n = 25	198.100	0,97	206.520
Pregnant without iodinated supplements, n = 49	115.000	0,99	133.020
p	0,014*	0,02*	0,049*



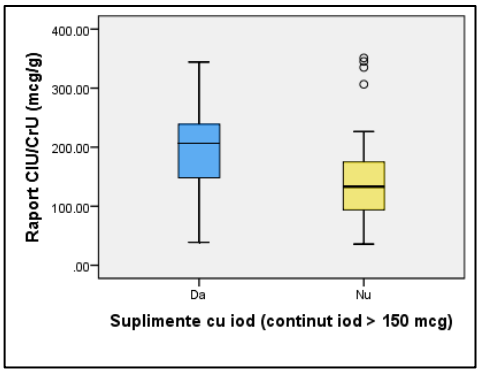


Figure no. 74 and 85 - Box-Plot graphical representation for the variable UIC (mcg / l) and the UIC / UCr ratio depending on the consumption of iodinated supplements

3.3. Analysis of maternal thyroid functional and ecostructural status

3.3.1. Distribution of serum thyroid hormone concentrations for pregnant women

	TSH (mUI/ml)	FT4 (pmol/L)	ATPO (UI/L)	ATG (UI/L)
Mean	3.239	15.075	64.162	58.651
Median	**2.140**	**14.865**	**17.450**	**57.500**
Std. dev.	3.173	3.917	10.559	50.267

3.3.2. Analysis of maternal functional status at the time of inclusion in the study

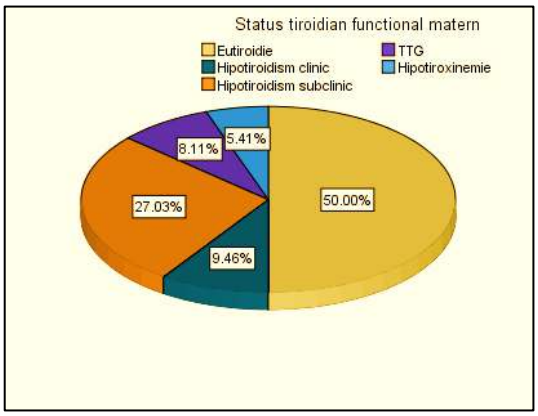


Figure no. 134 - Distribution of pregnant women according to maternal thyroid functional status

3.3.3. Assesment of the association between the degree of parturition of pregnant women at inclusion in the study and thyroid micronodules

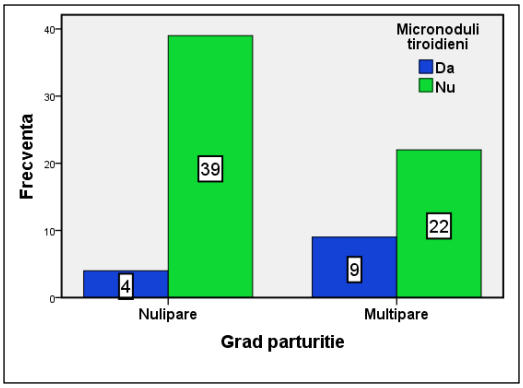


Figure 126 - Column-type graphical representation of the categorical variables degree of parturition of pregnant women and the presence of thyroid micronodules

3.3.4. Median values of maternal TSH depending on the range of values of CIU mcg / l

The median TSH for pregnant women with severe iodine deficiency (UIC <50 mcg/l) was 4.170 mIU/ml, moderate iodine deficiency (UIC = 50 -149 mcg/l) - 2.20 mIU/ml, pregnant women with adequate iodate intake (UIC = 150-249 mcg/l) - 1.82 mIU/ml, and pregnant women with more than adequate iodate intake (UIC = 250-499 mcg/l) had a median of 2.11 mIU/ml.

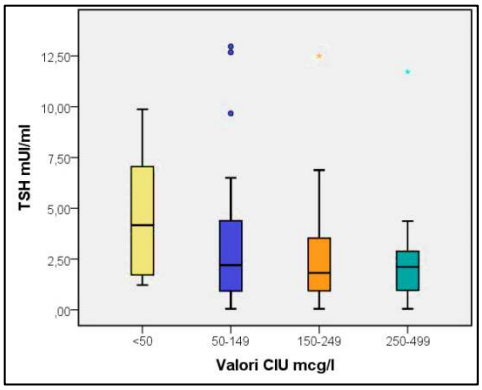
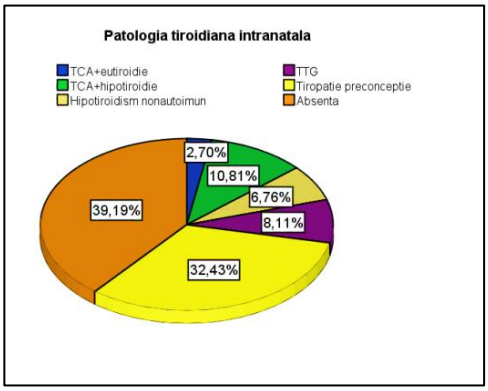


Figure 154 - Box-Plot graphical representation for TSH variable according to UIC value range mcg/l

3.3.5. Assesment of thyroid pathology



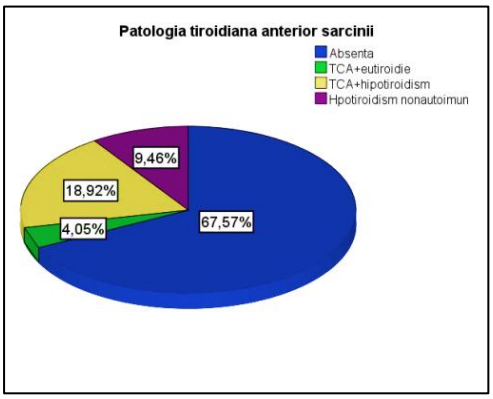
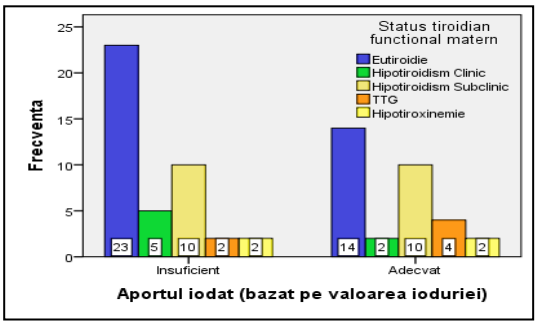


Figure 136 and **Figure 137** - Incidence of thyroid disorers during and before pregnancy



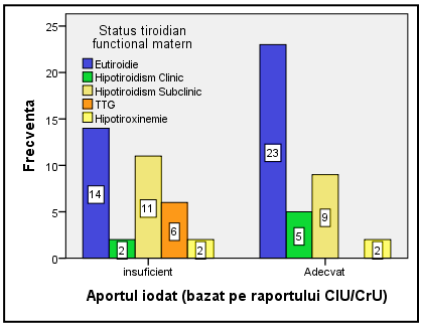


Figure 98 and Figure 112 - Column-type graphical representation of the categorical variables iodine intake based on UIC and UIC/Ucr ratio and maternal functional thyroid status

3.4. Analysis of maternal thyroid immune status

The prevalence of chronic autoimmune thyroiditis among pregnant women in the study was 36% of which 23% were diagnosed before pregnancy and 13% during pregnancy. We analyzed the variation of the median values of ATPO and ATG in relation to urinary iodine concentration, thyroid volume and neonatal parameters and iodine intake, iodine deficiency levels, iodine intake mode, consumption of iodine supplements, functional thyroid status and ecostructural changes.

3.4.1. Prevalence of thyroid dysfunction for pregnant women with chronic autoimmune thyroiditis

		positive TPOAb/TGAb		Total
		Da	Nu	
Thyroid functional status	Euthyroidism	9,5%	40,5%	50,0%
	Overt hypotiroidism	5,4%	4,1%	9,5%
	Subclinical hipotiroidism	**17,6%**	9,5%	27,0%
	Transient gestational thyrotoxicosis	1,4%	6,8%	8,1%
	Hypothyroxinemie	**2,7%**	2,7%	5,4%
Total		36,5%	63,5%	100,0%

The $\chi 2$ test of the association: $\chi 2calc = 14,565$, $df = 4$, $p = 0.006 < \alpha = 0.05$, pregnant women with subclinical hypothyroidism having the largest contribution to the result obtained.

3.4.2. Comparative analysis between median CIU values and CIU / CrU ratio for pregnant women with and without chronic autoimmune thyroiditis

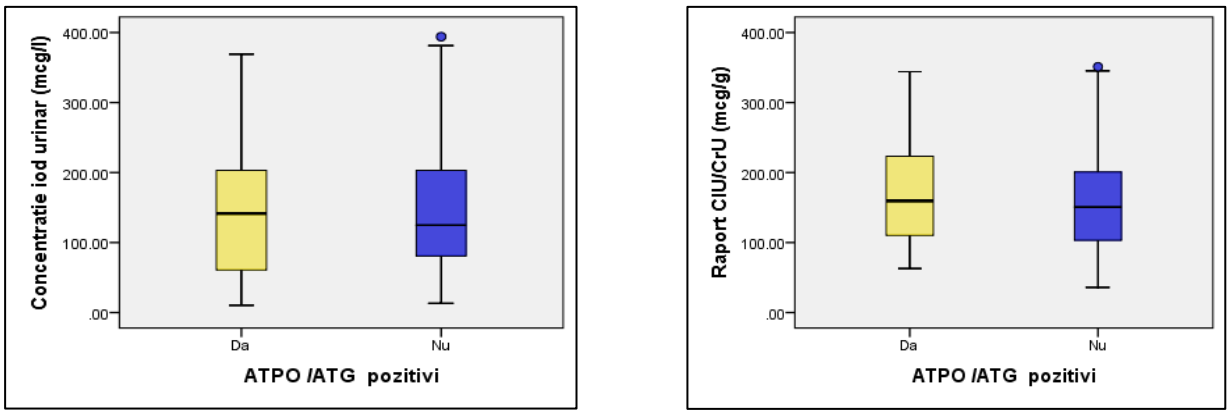


Figure no. 214 and 215 - Box-Plot graphical representation for the variable UIC (mcg / l) and the UIC/ UCr ratio distributed according to ATPO / ATG positive.

We identified the difference between UIC for pregnant women with and without TCA (141.4 mcg/l versus 124.9 mcg/l), but without statistical significance (p = 0.629), the same difference being found for the UIC/ UCr ratio (159, 48 mcg/g versus 150.82 mcg/g), also without statistical significance between the median values (p = 1,000).

3.4. 3. Distribution of pregnant women based on positive ATPO / ATG according to the range of values of CIU mcg / l

			ATPO/ATG pozitivi		Total
			Da	Nu	
Valori CIU (mcg/l)	**<50**	Frequency	**8**	7	15
		% of Total	**10,8%**	9,5%	20,3%
	50-149	Frequency	5	24	29
		% of Total	6,8%	32,4%	39,2%
	150-249	Frequency	5	7	12
		% of Total	6,8%	9,5%	16,2%
	250-499	Frequency	**9**	9	18
		% of Total	**12,2%**	12,2%	24,3%
Total		Frequency	27	47	74
		% of Total	36,5%	63,5%	100,0%

The $\chi 2$ test of the association: χ 2 calc = 8.029, df = 3, p = 0.045 <α = 0.05.

3.5. Evaluation of maternal-fetal and neonatal pathology

We analyzed the prevalence of gestational, perinatal, prenatal and neonatal pathology, but also the association with iodine intake, thyroid functional status, the presence of thyroid autoimmunity, but also the recommendation of thyroxine replacement therapy.

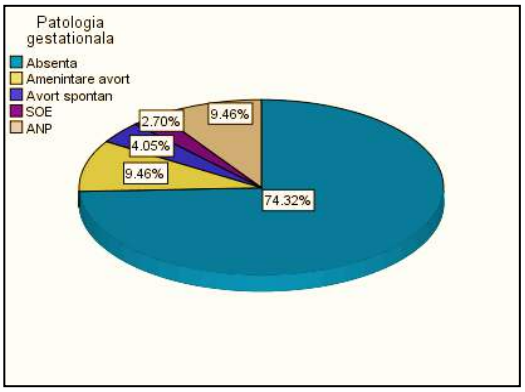


Figura nr. 226 **-** Pie representation for variable gestational pathology

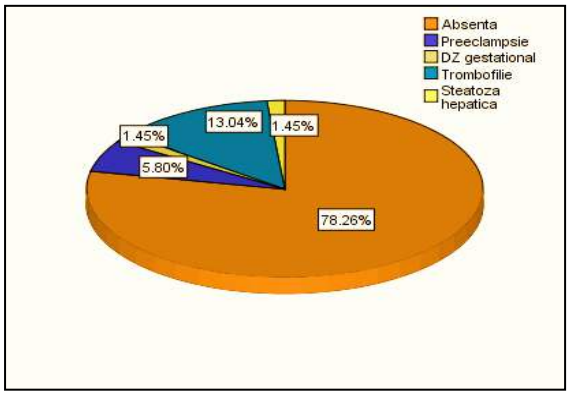


Figura nr. 228 - Pie representation for variable prenatal obstetrical pathology

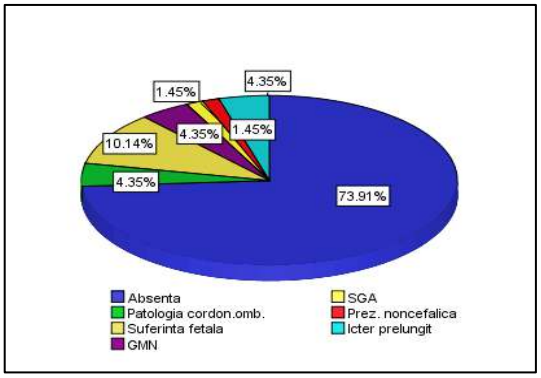


Figura nr. 230 - Pie representation for variable variable neonatal pathology

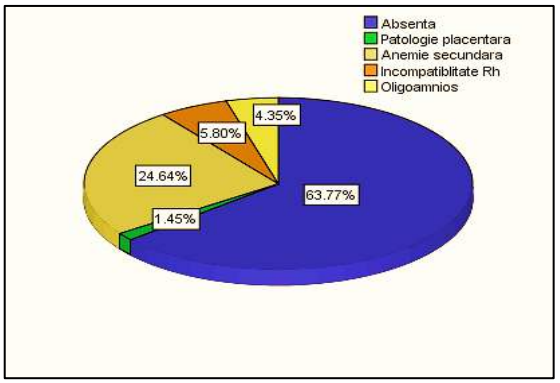


Figure 232 - Pie representation for the perinatal obstetrical pathology

3.5.1. Analysis of gestational and neonatal pathology in relation to maternal thyroid status, iodine intake based on iodide, the presence of antithyroid autoantibodies and the administration of thyroxine replacement therapy.

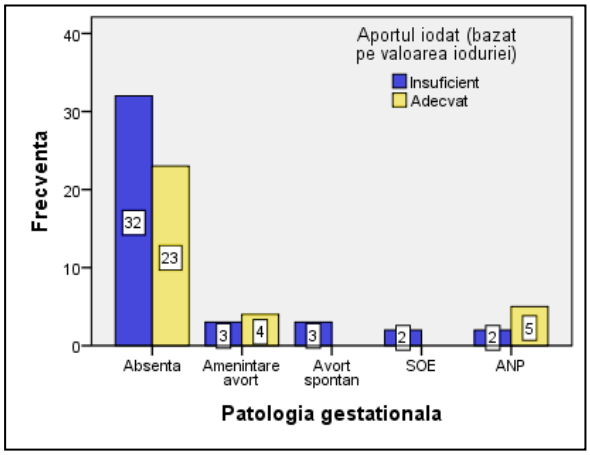


Figura nr. 236 – Colum graphical representation of variables iodine intake based on IUC and gestational pathology

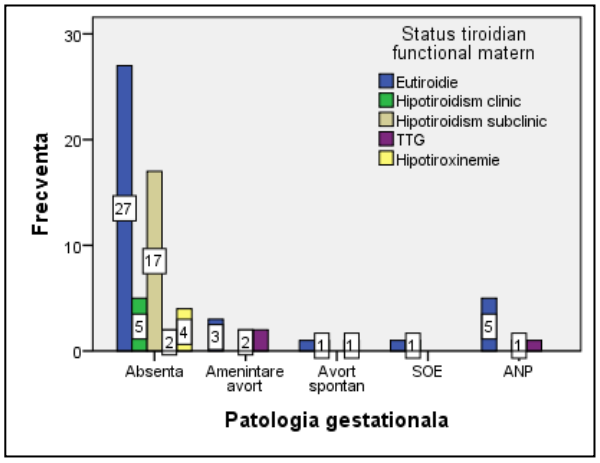


Figura nr. 241– Colum graphical representation of variables maternal thyroid functional status and gestational pathology

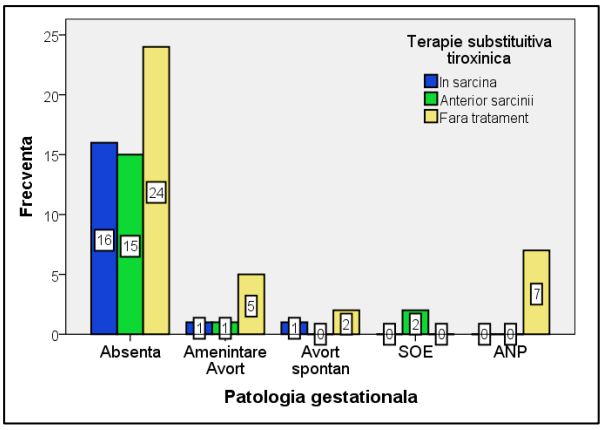


Figure no. 234 - Graphical representation Column of categorical variables tiroxine substitutiv therapy and gestational pathology

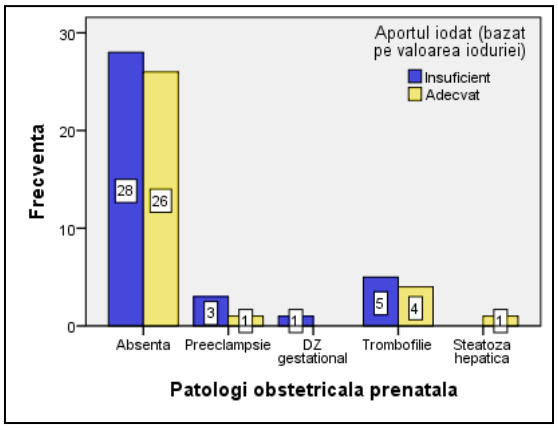


Figura nr. 238 – Colum Graphical representation of categorial variables iodine intake based on UIC and prenatal obstetrical pathology

3.5.2. Determination of urinary iodine concentration according to gestational pathology

Urinary iodine concentration (mcg/l)					
	Gestational pathology				
	Absence	Threat of abortion	Miscarriage	Stopped in evolution pregnancy	Threat of premature birth
N	55	7	3	2	7
Median	124,63	225,90	**83,070**	**91,10**	149,70

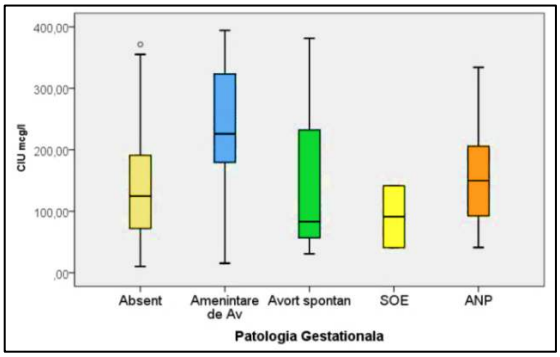
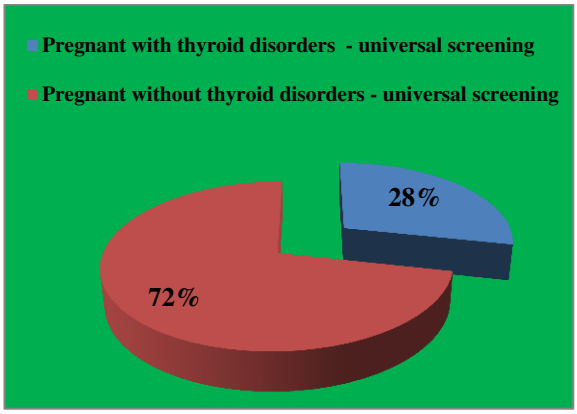


Figure no. 245 - Box-Plot graphical representation for the variable UIC (mcg/l) distributed according to gestational pathology.

3.5.3. Thyroid screening of pregnant women in the study

Comparative analysis between universal and targeted screening for the diagnosis of tiropathies during pregnancy



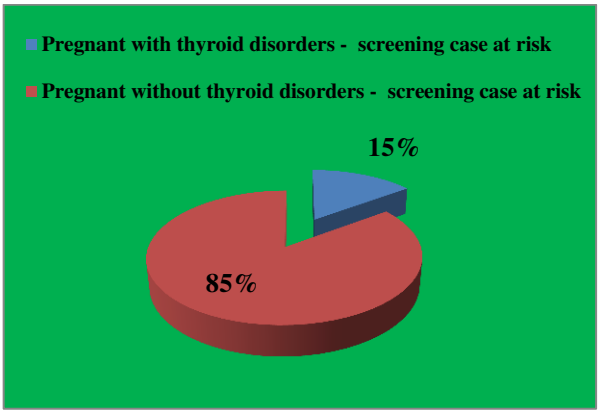


Figure 252 and Figure 253 - Pie representation between comparative analysis of universal screening versus targeted cases at risk screening

The thyroid pathology diagnosed in pregnancy for all 74 pregnant women was 21 cases (28.38%) - in universal screening. In targeted screening of cases at risk according to the recommendations of the guidelines, we identified from 74 pregnant women - 47 cases with at least one risk factor, and from this group we identified only 11 cases of thyroid disease, representing 14.86% of the total number of pregnant women.

CHAPTER 4
Interpretation of results and discussions

The motivation of this study started from the lack of information and data on the iodine nutritional status of pregnant women from areas without iodine deficiency, the perimarine area of Romania, Dobrogea region. National population studies presents a series of results from regions considered endemic for iodine deficiency, most of which were performed on pregnant women in the last trimester of pregnancy.

Also, the spectrum of thyroid diseases in sufficient areas in iodine is characterized by the prevalence of autoimmune thyroid disease, and in pregnancy conditions is of great interest to the endocrinologist because it requires regular monitoring with the initiation or adjustment of appropriate therapy. Although the Dobrogea region is characterized as a non-endemic area for

iodine deficiency, iodine intake in conditions of high iodine needs, such as pregnancy, can present a number of variability depending on many associated factors. The use of iodized or non-iodized salt, iodinated supplements, consumption of sea -foods are just some of the elements that can influence the nutritional status of iodine.

The originality of the present study can be considered the fact that it is the only study in the last 25 years that evaluates the iodine nutritional status of pregnant women at the beginning of pregnancy in the perimarine area of Romania, but also identify an iodine deficiency among pregnant women from Dobrogea, a known area without iodine deficiency.

Limiting elements: serum hormonal values not adapted by all laboratories specific quarter, lack of information about the iodinated status of pregnant women before pregnancy.

4.1. General characteristics of the study group - demographic data, background, iodine intake, maternal and neonatal parameters

Of all the pregnant women in the study only 82.4% consume iodized salt, the remaining 17.5% do not consume salt at all or only non-iodized salt. Although the indicator of the effectiveness of the iodine deficiency disorder prevention programs recommended by the WHO is the use of iodized salt in over 90% of households [13].

The frequency of pregnant women who used iodine supplements (150 mcg/day) was 33.8% (25 cases). According to the international guidelines the daily intake of iodine in pregnancy should increase to 250 mcg, so it is recommended to administer prenatal supplements with iodine content between 150 and 200 mcg / day in both iodine-deficient and iodine-sufficient areas [3, 5].

Out of a total of 74 pregnant women who entered the study, 69 pregnant women completed the pregnancy, because in 5 cases the pregnancy was interrupted by miscarriage - 3 cases (2 cases in the first trimester and 1 case in the second trimester) and 2 cases of stopped pregnancies all evolving in the first trimester.

4.2. Determination of iodine status indicators

The median urinary iodine concentration for the entire study group of 74 pregnant women, was 133.03 mcg / l (IQR: 69.11; 204.65 mcg / l), a characteristic value of insufficient iodine intake. Values obtained are similar to the most recent national study from 2016-2017 on a population of 665 pregnant women, but originating from endemic areas of Romania with a median iodide of 116 mcg / l specific to insufficient iodine intake [5].

An insufficient iodine intake with the predominance of a moderate iodine deficiency is found in the largest national study conducted in 2005 by National Institute for Mother and Child Health-Bucharest and UNICEF Romania (median UIC - 73µg/l) [25].

But the general population of Romania is characterized according to the median UIC in school-age children by an **adequate iodine intake** according to recent data from 2020 in the global iodine network - IGN (Iodine Global Network) (UIC median in school-age children of 255 mcg/l) [28.29]. A number of studies have sustain that UIC in school-age children cannot be used to define iodine status in pregnancy, suggesting that in addition to iodine-sufficient geographical regions, additional iodine supplementation during pregnancy and lactation is recommended [71].

Increasing the glomerular filtration rate during pregnancy by about 50% and urinary volume/24 h, will also be associated with increased renal iodine excretion, thus an optimal indicator of the iodine nutritional status better during pregnancy, minimizing variations caused by differences in volume and urinary dilution, is the ratio between the concentration of urinary iodine to urinary creatinine (UIC / UCr ratio) [72,73,74].

In the present study, the median UIC/UCr ratio was 152.83 mcg / g (IQR: 102.55, 211.21), thus exceeding very little the reference level of 150 mcg/g characteristic to an adequate iodine intake for pregnant women.

Iodine intake based on UIC value identified 56.7% of cases with insufficient intake and 43.2% with adequate intake. Iodine intake based on the UIC / UCr ratio identified only 47.3% of pregnant women with insufficient intake and 52.7% with adequate intake. Thus, the evaluation based only on UIC reveals a higher prevalence by 9.4% compared to the evaluation based on the UIC / UCr ratio of insufficient iodinated intake, overestimating the iodine deficit in pregnancy.

The distribution of pregnant women according to the range of UIC values with the determination of the severity of the iodine deficiency identified severe iodine deficiency that(median CIU below 50 mcg/l) in 16.2% of cases, moderate iodine deficiency (median UIC between 50 - 149 mcg/l) presented in 40.5% of cases, the rest of the pregnant women had an adequate iodinated intake (median UIC between 150 - 249 mcg/l) being present in 21.6% of cases and an iodine intake more than adequate (median UIC between 250 - 499 mcg/l) was identified in 21.62%.

Very different results were presented in 2016 in the study conducted by Ursu et al. 7 on a group of 118 pregnant women from endemic and non-endemic areas in which severe iodine deficiency in only 1.7% in cases and moderate iodine deficiency was described in only 28%, but all were assessed in the last trimester of pregnancy comparatively with the present study performed in the first 2 trimesters of pregnancy.

The similar distribution of pregnant women according to the range of values for the UIC / UCr ratio showed differences, namely a percentage of only 4.1% had a severe iodine deficiency (<50 mcg / g), 43.2% of pregnant women had had a moderate iodine deficiency, and adequate and more than adequate iodine intake accounted for 40.5% and 12.2% of cases, respectively.

The evaluation of neonatal TSH in the 69 newborns revealed an average of 4.26 mIU/l with the interquartile range between 3.54-4.84 mIU/l. Out of the total of 69 newborns, only 13 presented TSH values over 5 mIU/l, this prevalence of 18.8% representing a mil iodine deficiency of the region. However, neonatal TSH is more the expression of iodine nutritional status during pregnancy, being the period with the highest need for iodine and thyroid hormones, so there may be differences with median iodide in school-age children that more accurately reflects the iodine status of the general population [13] .

Evaluation of the degree of goiter at the time of inclusion in the study of pregnant women revealed a prevalence of 25.68% characteristic for a moderate iodine deficiency, but this is not the expression of recent iodine intake, being an indicator that reflects the long-term iodine consumption history and pregnancy in this woman being an additional stimulus for goitrogenesis.

4.3. Analysis of the association and distribution of UIC and UIC / UCr ratio according to the studied variables

In the case of the analysis of the iodine intake modality according to the UIC / UCr ratio, we found a statistically significant difference in the distribution of the median in the analyzed categories (p = 0.049). The highest values of the median UIC / UCr ratio were recorded in pregnant women with iodized intake by iodinated supplements (228 mcg / g) and those with consumption of iodized salt and iodine supplements (197.7 mcg / g) specific to an adequate iodate intake, and the lowest value was recorded in pregnant women who never consume iodized salt and do not use iodine supplements (103.8 mcg / g - insufficient iodate intake).

The determination of UIC according to the consumption of iodinated supplements found a value for pregnant consuming iodinated supplements of 198.1 mcg / l (specifies adequate iodate intake) compared to pregnant who do not consume iodine supplements who had a very low value of UIC - 115 mcg / l (corresponding to an insufficient iodinated intake), with a statistically significant difference both in the distribution of the median UIC (p = 0.001) and between the values of the median (p = 0.014). We found similar results for the UIC / UCr ratio of pregnant women with and without iodine supplements (206.5 mcg / g versus 133 mcg / g), with statistically significant differences between the median values (p = 0.049), as well as in the case of the distribution of the ratio values (p = 0.005).

The median UIC values for pregnant women who did not complete the pregnancy were 82.1 mcg / l corresponding to insufficient iodine intake and moderate iodine deficiency. The remaining 69 pregnant women who completed the pregnancy had a median of 141.2 mcg /l also corresponding to an insufficient intake, but values closer to the lower limit of the appropriate iodate intake level (150 mcg /l).

4.4. Analysis of iodine nutritional intake

We found an association following the statistical analysis between the iodine intake based on UIC and pregnant women who consumed iodine supplements during pregnancy ($p < 0.001$). The use of iodinated supplements being responsible for the adequate iodized intake of pregnant women (Standard Residue = 2.2). The same significant association was between iodine intake based on the UIC / UCr ratio and pregnant women consuming iodinated supplements ($p = 0.018$).

Analysis of the association between iodine intake (based on UIC) and completed pregnancies showed a statistically significant association ($p = 0.043$) between pregnant women with insufficient iodinated intake and unfinished pregnancies, iodine deficiency being a risk factor for miscarriage and recurrent abortion [5].

4.5. Analysis of the functional and ecostructural status of the maternal thyroid

Slightly higher values of the median TSH showed pregnant women who did not complete the pregnancy (pregnant women with abortion or stopped pregnancy in evolution) compared to pregnant women who completed the pregnancy (2.87 versus 2.12 µUI / mL), but without statistically significant differences ($p = 1,000$), knowing that overt and subclinical hypothyroidism is associated with an increased risk of miscarriage and stopped pregnancy in progress [75,76]. The recommendation to initiate thyroxine treatment in pregnancy was for 18 pregnant women who had a median TSH of 5.07 µUI/mL, and for pregnant women who were already on thyroxine replacement therapy and needed to adjust the dose, the median TSH was of 3.53 µUI / mL, with a statistically significant difference in the distribution of median values between the analyzed categories ($p = 0.001$).

Maternal functional thyroid status of pregnant women at inclusion in the study was: overt hypothyroidism - 9.49%, subclinical hypothyroidism - 27.03%, TGT -8.11% and isolated hypothyroxinemia in 5.41%. Both the ATA[5] and Endocrine Society[3] guidelines show an incidence of overt clinical hypothyroidism between 0.3% - 0.5% and subclinical hypothyroidism between 2 - 3%, lower values than the results obtained in the present study .

Statistical analysis between TSH and ATPO revealed a weak positive correlation between the values of the two variables ($p = 0.001$, Spearman coefficient $\rho = 0.375$), not the same result was obtained with ATG value ($p = 0.6411$, Spearman coefficient $\rho = 0.055$).

The thyroid morphological evaluation of the pregnant women included in the study identified a predominance of hypoechoicity (40.54%) and unhomogeneous ecostructure (58.11%). Following the statistical analysis we found a statistically significant predominance of hypo and hyperechoicity in the first trimester of pregnancy compared to the second trimester ($p = 0.034$).

The association between parity and the presence of nodular formations was a statistically significant one ($p = 0.028$) regarding the higher incidence of micronodules in multiparous pregnant women compared to nulliparous pregnant women (12.2% versus 5.4%).

Although the median values of thyroid volume were lower in the first trimester compared to the second trimester (6.93 versus 7.80 ml), still no statistically significant differences between the medians ($p = 0.690$). Both goiter and thyroid volume are considered an indicator of iodine deficiency in the general population, an aspect that has peculiarities in the population of pregnant women, which also has a adaptive process of goitrogenesis to an increased need for thyroid hormones in pregnancy especially for proper trophoblastic function of the placenta. [77].

Smoking pregnant women had a slightly higher level of TSH, but no significant differences compared to non-smoking pregnant women (p = 0.813), smoking being a risk factor for the development of Graves disease and ophthalmopathy, there is also an association between Hashimoto's thyroiditis, thyroid dysfunction postpartum and smoking.

Thyroid pathology diagnosed during pregnancy was recorded in 21 cases (28.3%) with the predominance of chronic autoimmune thyroiditis (13.5%) associated with euthyroidism in 2.7% and hypothyroidism in 10.8% of cases, non-autoimmune hypothyroidism presented 6.76% of cases and TGT in 8.11% of all studied cases.

Evaluation of thyroid pathology before pregnancy identified the predominance of autoimmune pathology with overt and subclinical hypothyroidism (18.92%) or euthyroidism (4.05%) and non-autoimmune hypothyroidism in only 9.46%.

We also found an association between thyroxine treatment and the type of iodine intake (p = 0.002), the increased contribution to the statistical value being the absence of iodine salt consumption in the category of pregnant women with thyroxine treatment initiated before pregnancy (RS = 2.5), most pregnant women being diagnosed prior to pregnancy with CAT.

4.6. Assessment of thyroid autoimmunity in pregnancy

Following the evaluation, we found that 36.5% of cases had positive values of antithyroid autoantibodies (ATPO and ATG), being the cases diagnosed before pregnancy and the cases diagnosed during pregnancy with CAT, 23 % - diagnosis before pregnancy and 13 % new cases diagnosis during pregnancy. The prevalence of autoimmune pathology in pregnancy according to the ATA guideline is considered to be between 2 -17% for unselected pregnant women [3,78], being even higher in cases with a history of recurrent abortions reaching approx. 17-33% [79.80].

Most pregnant women were diagnosed with CAT were established in the first trimester of pregnancy compared to the second trimester (24.3% versus 12.2%), but without a significant association (p = 0.339).

We identified a statistically significant association between positive ATPO / ATG and thyroid echogenicity (p = 0.002), pregnant women with CAT had the highest prevalence of hypoechoicity compared to pregnant women without CAT (24.3% versus 16.3%). Unhomogeneous ecostructure also predominated among pregnant women with CAT compared to homogeneous structure (28.4% versus 8.1%), with the presence of a statistically significant association between positive thyroid autoantibodies and thyroid ecostructure (p = 0.009).

The distribution of pregnant women with CAT according to the range of UIC values identified a significant prevalence of thyroid autoantibodies for pregnant women with UIC values between 250-500 mcg / l (12.25%) (p = 0.045). More than adequate iodine values may be a cause of worsening thyroid autoimmune pathology with the association of hypothyroidism due to the direct stimulatory effect of excess iodine on immune cells or increased thyroglobulin iodination with increased immunogenicity [81.82]. Another mechanism of iodine excess associated with CAT that will cause TSH to increase is significant chronic inhibition of deiodinase-II activity in the hypothalamus and pituitary gland by chronic increased iodine intake, which will decrease T3 production in the hypothalamus and pituitary gland with subsequent increase in TSH production [83].

Median TSH values were higher in the category of pregnant women with CAT compared to pregnant without autoimmune thyroiditis (3.73 versus 1.69 mIU / ml), with statistically significant differences in the distribution of TSH values (p = 0.001) and medians (p = 0.001), associating in addition to the risk of thyroid autoimmunity and the risk of hypothyroidism on the evolution of pregnancy.

Assessment of thyroid functional status for pregnant women with CAT identified the highest prevalence for subclinical hypothyroidism 17.6%, euthyroidism in 9.5%, overt hypothyroidism in 5.4%, hypothyroxinemia in 2.7%, and TGT in 1.4 %. Statistical analysis between CAT and thyroid

functional status identified a significant association (p = 0.006) the largest contribution to the statistical result was determined by subclinical hypothyroidism (Standard Residue = 2.1).

4.7. Evaluation of maternal-fetal and neonatal pathology in relation to the iodinated and functional status of maternal thyroid

Maternal-fetal pathology and iodine intake

The analysis of gestational pathology in relation to iodine intake based on UIC revealed that all cases of miscarriage and stopped evolving pregnancy had **insufficient iodized intake**, but without a statistically significant association (p = 0.154), also for iodine intake based on the UIC / UCr ratio (p = 0.336).

Analysis of neonatal pathology for pregnant women with insufficient iodine intake (based on UIC) identified the highest incidence of fetal distress compared to pregnant women with adequate intake (7.2% versus 3%), and prolonged jaundice was more common among pregnant women with adequate iodate intake (3%). However, we did not register any significant association between iodine intake based on UIC and neonatal pathology (p = 0.069).

The absence of an association between gestational pathology and the range of values of UIC with the assesment of iodine deficiency was identified in the statistical analysis (p = 0.243). All pregnant women with miscarriages and stopped evolving pregnancy had severe and moderate iodine deficiency. Pregnant with threat of premature birth had severe iodine deficiency in 2.7% of all pregnant women and the threat of abortion in 1.4% severe deficiency and 2.7% moderate deficiency.

The lowest value of the median UIC was registered in the category of pregnant women with spontaneous abortion - 83.07 mcg/l and pregnancies stopped evolving - 91.1 mcg / l corresponding to an insufficient iodine intake.

The lowest median UIC in the analysis of prenatal pathology was recorded in pregnant women with thrombophilia - 79.4 mcg / l corresponding to an insufficient iodine intake and moderate iodate deficiency. However, pregnant women with preeclampsia had a median value of 270.3 mcg / l specific to an iodinated intake more than adequate.

The median UIC for pregnant women with newborns with low birth weight was 79.4 mcg /l specific to an insufficient iodine intake and moderate iodine deficiency. The highest value of the median UIC was recorded in pregnant women with newborns with fetal distress and RCIU - 265.1 mgc/l corresponding to a more than adequate intake, these being pregnant women who also associated with CAT.

Maternal-fetal pathology and maternal thyroid functional status

The highest incidence of pregnant women with perinatal pathology (secondary anemia, Rh incompatibility, amniotic and placental fluid pathology) was identified in the pregnant with subclinical hypothyroidism compared to isolated hypothyroxinemia and overt hypothyroidism (13% versus 2.9% and 1.4 %), but without a significant association (p = 0.980).

Newborns from mothers with subclinical hypothyroidism had a higher incidence of neonatal pathology (umbilical cord pathology -2.9%, fetal distress with IUGR - 2.9%, LBW -14% and SGA - 1.4%) compared with overt hypothyroidism (fetal distress - 1.4%) and isolated hypothyroxinemia (LBW - 1.4%). However, statistical analysis did not show a significant association between thyroid functional status and neonatal pathology (p = 0.867). A recent meta-analysis supports the association between IUGR and subclinical hypothyroidism, with 1,5 times increased risk, but did not identify any association with overt hyperthyroidism, isolated hypothyroxinemia or positive ATPO values [84].

The higher incidence of gestational pathology was recorded in pregnant women with subclinical hypothyroidism for the threat of abortion - 2.7% and threat of premature birth -1.4%,

pregnant women with overt hypothyroidism present miscarriage in 1.4% and the pregnancy stopped evolving in 1.4%. (p = 0.280). The risk of miscarriage and recurrence abortion increases with increasing TSH levels, amplified by the presence of positive thyroid autoantibodies [85], also the risk of premature birth is associated with subclinical hypothyroidism, isolated hypothyroxinemia and hyperthyroidism [86, 87].

Maternal-fetal pathology and indication for thyroxine substitution

Pregnant women with an indication of thyroxine substitution in pregnancy as a result of the diagnosis of overt or subclinical clinical hypothyroidism associated with CAT had a higher incidence of perinatal pathology compared to pregnant women with thyroxine treatment initiated before conception (8.6% versus 5.7%), but without a significant association (p = 0.601). In the case of prenatal pathology, we recorded a higher incidence for pregnant women with thyroxine treatment initiated before pregnancy compared to thyroxine treatment initiated during pregnancy (4.3% versus 2.9%), but without a significant association (p = 0.713).

Gestational pathology had a higher incidence among pregnant women with thyroxine treatment initiated before pregnancy compared to pregnant women with therapy initiated during pregnancy (4.1% versus 2.8%), with a statistically significant association between gestational pathology and thyroxine treatment (p = 0.030), the largest contribution being offered by the category of pregnant women with thyroxine treatment before pregnancy and adjusted late (RS = 2.2). Studies show a significant decrease in the risk of miscarriage and premature birth at the early initiation of thyroxine replacement therapy [58], as well as a decrease in the incidence of gestational pathology (abortion and premature birth) in euthyroid pregnant women (TSH <4.2 mIU / L) with CAT and initiation of thyroxine therapy in the first trimester of pregnancy [88].

Maternal-fetal pathology and chronic autoimmune thyroiditis

We did not identify an association between gestational pathology and positive TPOAb / TGAb (p = 0.211), although thyroid autoimmunity is associated in many studies with an increased risk of miscarriage and premature birth [79].

In the case of pregnant women with CAT, the analysis in relation to gestational pathology showed a lower prevalence compared to pregnant women without thyroid autoimmunity (6.8% versus 19.1%). In the case of neonatal pathology, umbilical cord pathology predominated (2.9%), fetal distress (2.9%) and LBW (2.9%) in the case of pregnant women with CAT. We did not identify a statistically significant association between neonatal pathology and the presence of positive TPOAb / TGAb values (p = 0.687).

4.8. Thyroid screening in pregnancy

Controversies over the identification of cases at risk for thyroid disorders versus universal thyroid screening in pregnancy have created numerous debates in international endocrinology societies. Interpretation of functional thyroid status using only high-risk case screening can underdiagnose up to approx. 30 - 40% of thyroid dysfunctions support a series of studies [67,68].

We evaluated the pregnant women included in the study according to the presence or absence of risk factors according to the recommendations of ATA[5] and the European Society of Endocrinology [3]. The frequency of pregnant women without risk factor was reduced -36.5% and most pregnant women had at least 1 risk factor in 63.5% of cases.

Following the universal screening of the entire group, we identified 21 pregnant women with thyroid dysfunction (autoimmune / non-autoimmune hypothyroidism, TGT) representing 28.38% of the total studied group. Compared to the screening of cases with high risk, we identified only 11 cases of de novo thyropathies representing 14.86% of the total number of cases. Thus, there is a risk of missing 10 cases of pregnant women with thyroid diseases, representing a percentage of 13.5% of undiagnosed cases, a percentage similar to the specialized studies [67, 68, 89].

CHAPTER 5
Conclusions

1. The evaluation of the iodine nutritional status of a group of pregnant women from the perimarine area of Romania, geographical territory declared without iodine deficiency, finds iodine values lower than normal in 56.7% of cases and even after adjusting iodine values to urinary creatinine the percentage of pregnant women with subnormal iodide remains significantly increased - 47.3%.

2. Assessment of the severity of iodine deficiency depending on the value of urinary iodine, found a predominance of moderate iodine deficiency (iodine between 50 - 149 mcg/l) found in 40.5% of cases and severe iodine deficiency (iodine below 50 mcg /l) present in 16.2% of pregnant women.

3. The causes of iodine deficiency in a non-endemic area can be individual pathological situations involving iodine bioavailability or failure to ensure iodine from food intake - low iodine foods, confusion between iodized salt and non-iodized salt, ignoring iodinated supplements administered during pregnancy.

4. For pregnant women from Dobrogea, the adequate consumption of iodized salt in the households was 82.4%, a value below the level recommended by the WHO (> 90%) accepted as an effective criterion for eliminating the iodized deficiency.

5. 18 years after the implementation of the USI programs in 2002 and inclusion of Romania in the countries with adequate iodine intake among the general population, starting with 2014, the effectiveness of iodine deficiency prevention programs can be maintained by combining both iodized salt intake and the use of iodine supplements, even in iodine-sufficient areas of the perimarine region of the country, especially in pregnancy under conditions of high iodine requirement.

6. Serum values of TSH in newborns recorded a 18.8% above the limit of 5 mIU/L correlated with a mild iodine deficiency, being considered a more accurate indicator of iodine deficiency than iodine status among the population. We did not identify serum TSH values above 20 mIU/l for any of the newborns - considered the maximum level that raises the suspicion of congenital hypothyroidism.

7. The ratio of urinary iodine/urinary creatinine concentration is an optimal and useful indicator for iodine nutrition during pregnancy, being a way to effectively assess iodine intake in pregnant women, but also for the population of a studied territory and characterized under this parameter. Inadequate iodine nutrition before pregnancy should also be considered.

8. In the group of studied pregnant women, from the point of view of thyroid pathology, 36.5% had chronic autoimmune thyroiditis. For 23% of cases the diagnosis was established before pregnancy and 13.5% was diagnosed during pregnancy. There is an increased incidence of chronic autoimmune thyroiditis among pregnant women with the possibility of onset of the disease during pregnancy. Adequate or excess iodine intake during pregnancy in cases of thyroid autoimmunity raises the issue of the effect of excess iodine intake on the onset or worsening of the disease.

9. The prevalence of the use of iodinated supplements in the studied group of pregnant women was 33.8%, the lowest consumption being identified in the category of pregnant women with positive thyroid autoantibodies. Individualization of iodine supplements is necessary during pregnancy to prevent agravation of chronic autoimmune thyroiditis. It should be mentioned that among pregnant women with chronic autoimmune thyroiditis, predominated iodine intake more than adequate (urinary iodine 250-500 mcg/l). Iodine supplementation is necessary for the prevention and treatment of IDD, which must be maintained at a safe level and performing urinary

iodine in the first trimester of pregnancy regardless of the living environment of the pregnant woman could allow a more rigorous prescription of iodine supplements.

10. The functional thyroid status of the pregnant women in the study was characterized by subclinical hypothyroidism (27.03%), overt hypothyroidism (9.49%) and hypothyroxinemia (5.41%). An incidence of 17.6% of subclinical hypothyroidism due to autoimmune was found, a characteristic percentage foor patients from regions without iodine deficiency. Although the consumption of iodinated supplements was not associated with the altered maternal thyroid functional status, a significant influence was achieved on the iodine status in pregnancy assessed by urinary iodine values.

11. Determining the functional status of the thyroid in pregnancy requires the interpretation of serum values of thyroid hormones according to specific trimester reference intervals, the most appropriate approach being to correlate with the geographical region of origin of pregnant women to identify thyroid dysfunction as accurately as possible.

12. There are particular variations in thyroid volume, ecostructure and echogenicity in pregnancy in relation to iodine intake and iodine deficiency levels, age and parity, trimester of pregnancy. These elements support thyroid imaging assessment along with thyroid functional status starting with the first trimester of pregnancy. There was a statistically significant predominance of thyroid micronodules among multiparous pregnant women compared to nulliparous pregnant women (12.2% versus 5.4%). The low intake of seafood and the low consumption of iodized salt of pregnant women in the Dobrogea area can influence the thyroid volume separated from the physiological thyroid adaptation in pregnancy.

13. In all cases of unfinished pregnancies (miscarriage or recurrent abortion, stopped evolving pregnancy) was found an insufficient iodinated intake (urinary iodne <150 mcg / l) with moderate iodine deficiency (urinary iodine between 50-149 mcg / l). Most cases with a threat of abortion and a threat of premature birth had an adequate iodine intake (urnary iodine> 150 mcg / l).

14. An increased involvement of subclinical hypothyroidism has been identified in gestational (4%), prenatal (4.3%), perinatal (13%) and neonatal (8.6%) pathology. Pregnant women with thyroxine treatment initiated preconception and not adapted to pregnancy conditions or adapted late associated an increased incidence of gestational pathology (4%). Neonatal pathology (fetal distress, low birth weight, umbilical cord pathology) predominated among pregnant women with chronic autoimmune thyroiditis (8.7%).

15. The assessment of the population of pregnant women only by targeted screening of cases considered at risk for thyroid disorders developed during pregnancy (in our study 14.8%) may miss a significant number of cases compared to universal screening (in the studied group 28.3%), data that underline the risk of underestimation of thyroid pathology of pregnancy.

16. Universal screening of thyroid status and thyroid autoimmunity performed during the first trimester of pregnancy is a medical priority activity with a preventive effect for the maternal-fetal unit in terms of thyroid pathology need to be extended to pregnant women from geographical areas declared with adequate intake of iodine.

17. Maintaining collaboration between family physicians, obstetricians, neonatologists and endocrinologists is essential in preventing and reducing the incidence of maternal-fetal pathology by early detection of thyroid hormonal imbalance or iodine deficiency or thyroid autoimmunity, which has a major impact on health of the mother and the child.

18. Under the conditions of universal salt iodization even in geographical areas with adequate iodine intake such as the perimarine area, the possibility of iodine deficiency and thyroid disorders, including in pregnancy, requires regular explorations on this parameter, with monitoring of iodine status indicators.

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1. Circo Eduard, **Scrinic Olesea**, Seceleanu Mihaela- „Structural and functional changes of maternal thyroid in pregnancy" – Current Health Sciences Journal, volum 40, Supliment 5, pg. 29 - 34, 2014, **ISSN**: 2067-0656.
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4. **Scrinic Olesea,** Ibadula Seila, Circo Eduard - „Materno- fetal features in a group of pregnant women diagnosed with chronic autoimmune thyroiditis and vitamin d deficiency" - 6th SWS International Scientific Conference on Social Sciences, ISCSS 2019, Volum 6, Book number 3, pg. 553-560 **ISBN:** 978-619-7408-93-5 ; **ISSN:** 2682-9959
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List of posters, oral presentations presented at national and international scientific events

1. **Olesea Scrinic**, Seila Ibadula, Eduard Circo -„ Screeningul tiroidian la gravide - activitate profilactică obligatorie" - al X-lea Congres al Asociației de Endocrinologie Clinică din România, 02-05 septembrie **2015**, Constanta.
   Volum de rezumate: N1/2015, Ediția 10/2015, ISSN: 2457-6883 **- comunicare orala**
2. **Scrinic Olesea**, Ibadula Seila, Gheorghita Raluca, Ilie Mihaela, Circo Eduard - „Evaluation of serum thyroglobulin during pregnancy - a marker of thyroid echostructure modification" - Revista Fiziologia - Physiology, **2015**, Supliment, ISSN 1223- 2076 **- poster**
3. Circo, Eduard; Seila, Ibadula; **Olesea, Scrinic**- „Small gestational age - implications of chronic autoimmune thyroiditis in pregnancy" - EUROPEAN JOURNAL OF PEDIATRICS Volume: 176 Issue: 11 Pages: 1481-1481, Meeting Abstract: 719 Published: NOV **2017**; IF: 2,24 **- poster**
   https://program.eventact.com/Lecture/155019/3030363
4. Ibadula Seila, **Olesea Scrinic**, Eduard Circo - „Particularităţi materno-fetale la un lot de gravide diagnosticate cu tiroidita cronica autoimuna si hipovitaminoza D" - Al XIII-lea Congres al Asociaţiei de Endocrinologie Clinică din Români, 5 – 8 septembrie **2018**, Teatrul Elisabeta, București.
   Volum de rezumate: N2/2018, Ediția 13/2018, ISSN: 2457-688 **- comunicare orala**
5. **Olesea Scrinic**, Eduard Circo, Seila Ibadula - „Screeningul in sarcina trebuie să includă determinarea nivelului seric de vitamina D?" - Al XIV-lea Congres Asociației de Endocrinologie Clinică din Romania (AECR), Sinaia, 5-7 Septembrie **2019**.
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6. **Olesea Scrinic**, Seila Ibadula, **Eduard Circo** - „Functional thyroid changes in the first trimester of pregnancy in a normal iodine intake area" - 21st European Congress of Endocrinology, 18 - 21 May **2019** Lyon, France.
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7. **Scrinic Olesea**, Ibadula Seila, Delia Corina, Circo Eduard - „Iodine status in a group of pregnant women with chronic autoimmune thyroiditis having as provenience perimarine area of Romania" - 22nd European Congress of Endocrinology - Online , 05 - 09 Sep **2020**, European Society of Endocrinology.
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