ISOLATED MATERNAL HYPOTHYROXINEMIA AND ITS PERINATAL OUTCOME IN NORTH MACEDONIA

Maja Avramovska¹, Borislav Karanfilski², Goran Dimitrov³, Elena Dzikova³, Ana Daneva Markova³, Marija Hadzi Lega⁴, Gligor Tofoski³ and Aleksandar Sikole⁵

¹Dr. Trifun Panovski Clinical Hospital, Bitola, North Macedonia; ²National Committee for Iodine Deficiency, Ministry of Health, Skopje, North Macedonia; ³Department of Gynecology and Obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University of Skopje, Skopje, North Macedonia; ⁴Danat al Emarat Hospital for Women and Children, Abu Dhabi, Emirate of Abu Dhabi; ⁵Department of Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University of Skopje, Skopje, North Macedonia

SUMMARY – Isolated maternal hypothyroxinemia (IMH) is defined as the presence of low maternal total thyroxine (TT4) level in conjunction with normal maternal thyroid-stimulating hormone (TSH) level. The aim was to investigate whether IMH is associated with adverse pregnancy outcome in North Macedonia. Dried blood spot samples were obtained from 359 pregnant women meeting the inclusion criteria and analyzed for TT4 and TSH. Postpartum data were entered from their medical histories. Out of 359 women, 131 (37.42%) belonged to IMH group. There were statistically significant differences in birth weight (p=0.043), intrauterine growth restriction (IUGR) (p=0.028), Apgar score at 1 min <7 (p=0.018) and cesarean section for dystocia/disproportion (p=0.024) between the IMH and normal thyroid function (NTF) groups. In regression analysis, TSH was a significant variable predicting Apgar score (βst=0.05597, p=0.047), body mass index predicting birth weight (βst=0.02338, p=0.045) and TT4 predicting small for gestational age/IUGR (βst=-0.089834, p=0.029) in IMH group. TT4 was a strong predictor of birth weight (βst=-0.004778, p=0.003) and premature delivery (βst=0.028112, p=0.004) in NTF group. The impact of IMH in pregnancy remains controversial. IMH was associated with an increased maternal BMI and higher birth weight of neonates. Overweight could be a potential risk factor for thyroid dysfunction in pregnant women, and specifically IMH. The worst fetal outcome was seen in IMH mothers examined in second trimester. We found TSH, TT4 and BMI to be strong predictors of perinatal outcomes.

Key words: Isolated hypothyroxinemia; Perinatal outcome; Low birth weight; Preterm birth; Obesity

Introduction

A new controversy called isolated maternal hypothyroxinemia (IMH) arises in endocrinology¹, while in the meantime there is still a well-known debate about the recommendation for thyroid dysfunction screening during pregnancy. IMH defined as the presence of low maternal total thyroxine (TT4) concentration in the lower 5th or 10th percentile of the pregnancy related reference range, in conjunction with normal maternal thyroid-stimulating hormone (TSH) has recently been in the focus of interest². IMH during early pregnancy is associated with an increased risk of placental abruption, gestational diabetes, macrosomia, and preterm delivery³.

The causes of IMH have not been completely revealed, but the etiologies include iodine deficiency, obesity, and iron deficiency. Imbalance between the
pro- and anti-angiogenic factors could also be a factor, such as pro-angiogenic placental growth factor (PIGF) or anti-angiogenic soluble FMS-like tyrosine kinase-1 (sFlt) and vascular endothelial growth factor (VEGF), both important pregnancy-specific angiogenesis regulators. Obesity has also been recently associated with low free thyroxine (FT4) levels through incompletely understood mechanisms.

The 2011 guidelines for the management of thyroid dysfunction do not recommend universal screening of healthy women for thyroid dysfunction before pregnancy. Therefore, the aim of our study was to investigate whether IMH is associated with adverse pregnancy outcome in a pregnant population in the Republic of North Macedonia.

Subjects and Methods

Subjects

A total of 359 pregnant women meeting the criteria were enrolled and divided into three groups on the basis of gestational weeks, excluding women with twin pregnancy, personal history of chronic disease (hypertension, cardiac disease, and diabetes), as well as cigarette smokers and those with known thyroid disorders. They gave birth at the Department of Gynecology and Obstetrics in Skopje.

Laboratory tests

From April to July 2017, a sample of five drops of heparinized blood (5 mL) was obtained from each woman and applied to a special type of filter paper. The next phase was drying of the samples for 24 hours and keeping them at constant temperature of -20 °C. Dried blood spot (DBS) samples were analyzed for TSH and TT4 by time-resolved fluoroimmunoassay method (GSP 2021-0010; PerkinElmer, Turku, Finland) at University Children’s Hospital, Zurich, Switzerland. Weight and relevant dietary factors were determined by a questionnaire, and body mass index (BMI) was used to classify maternal weight status.

Diagnostic criteria for thyroid dysfunction

Study women were divided into three groups depending on the trimester of pregnancy at the time of sampling, as follows: first trimester (up to 12 gestational weeks (g.w.)), second trimester (12-28 g.w.) and third trimester (28 g.w. to the end of pregnancy). According to the American Thyroid Association (ATA) guidelines for diagnosis and management of thyroid disease during pregnancy and postpartum, the assay specific reference values for TSH and TT4 were adapted by trimester and gestational weeks at 0.1-3.0/3.7 mIU/L and 65/97.5-165/247.5 nmol/L, respectively. We recorded TSH and TT4 matching values or deviations according to the ATA reference values (based on g.w.).

Diagnostic criteria for obstetric complications

Postpartum data were entered for all study women from their medical histories. Birth weight and length were measured by the obstetric midwife attending the birth, while the condition of the newborn after delivery and Apgar score were given by the neonatologist.

Preterm delivery was defined as delivery before 37 completed gestational weeks. Intrauterine growth restriction (IUGR) was defined as birth weight less than 10th percentile for gestational age. Low birth weight (LBW) was defined as weight equal to or less than 2,500 g, while large for gestational age (LGA) was a newborn with weight >4000 g. Apgar score was considered if Apgar score at 1 min was less than 7.

The aim of this study was twofold, i.e. first, to investigate whether IMH is associated with adverse pregnancy outcome in North Macedonia, and second, to compare adverse pregnancy outcomes between the IMH and normal thyroid function (NTF) groups.

This study was approved by the Ethics Committee of the School of Medicine, Ss. Cyril and Methodius University in Skopje at its 16th session held on January 24, 2019 (no. 03-242/3). All procedures were performed in accordance with the 1975 Declaration of Helsinki and Directive 2001/20/EC of the European Parliament and Council of April 4, 2001.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software version 19.1.3 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2019). Results were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), 95% confidence interval (CI) for median, n (number) and % (percent). We used Mann-Whitney U test or t-test for
Results

Demographic data

Fetal outcomes and mother characteristics are summarized in Table 1. Of the total of 359 woman, 131 (37.42%) women had IMH. The mean gestational age at delivery was similar in the two groups (38 weeks, p=0.808). When comparing mother characteristics, maternal BMI was statistically significantly higher in the IMH group (median 27.43 vs. 26.44, p=0.018). Compared to the NTF group, a significant increase in birth weight was noted in infants born to IMH mothers (p=0.043). Three women with low TT4 levels in pregnancy gave birth to babies with IUGR. The prevalence of LBW infants in the two groups was 13.3% and 12.87%, respectively, yielding no statistically significant difference (p=0.597).

The corresponding relative risk (RR) for preterm delivery was 0.77 (95% CI 0.41-1.43) and for LBW 0.97 (95% CI 0.55-1.70), compared to RR for IUGR, which was 0.55 (95% CI 0.15-2.01) and for Apgar score at 1 min <7, which was 0.76 (95% CI 0.29-1.97).

There was no age difference between the NTF and IMH groups (median age 29 both, p=0.274). Concerning fetal outcomes, there were statistically significant differences between the NTF and IMH groups in birth weight (p=0.043), IUGR (p=0.028) and Apgar score at 1 min (p=0.018). In maternal characteristics, there was a statistically significant difference in BMI between the NTF and IMH groups (p=0.018) (Table 1). Median BMI (kg/m²) was 26.44 in the NTF group and 27.43 in the IMH group. Obese woman had depressed TT4 range and were prone to hypothyroxinemia.

Median TSH was 0.500 mU/L in the NTF group and 0.400 mU/L in the IMH group, yielding a statistically significant difference (p=0.018), as well as in TT4 (118.85 nmol/L vs. 79.9 nmol/L, p=0.0001). Details on thyroid hormone levels, their IQR and 95% CI for the cohort are shown in Table 2.

Median TSH (0.500 mU/L) and TT4 (118.85 nmol/L) values in the NTF group refer to a represen-
Table 2. Maternal demographic and thyroid status according to thyroid function groups

|                        | Normal thyroid function | Isolated hypothyroxinemia | Mann-Whitney t-test |
|------------------------|-------------------------|---------------------------|--------------------|
| **Demographic and thyroid function values** |                        |                           |                    |
| **Age (years)**        | 29.0±5.2                | 28.30-29.69               | 0.1633             |
| **BMI (kg/m^2)**       | 26.7±4.62               | 26.09-27.32               | 0.0176             |
| **TSH (mU/L)**         | 0.500 (0.400-0.700)     | 0.500-0.595               | 0.0121             |
| **TT4 (nmol/L)**       | 118.85 (104.8-133.9)    | 115.5-120.79              | <0.0001            |

Results are expressed as mean ± SD (standard deviation), median, interquartile range (25\(^{th}\)-75\(^{th}\) percentile), 95% confidence interval (95% CI) for mean or median, number (N) and p-value; p = level of statistical significance; BMI = body mass index; TSH = thyroid stimulating hormone; TT4 = total thyroxine.

Regression analysis

Assessments (standardized coefficient $\beta$ ($\beta_{st}$), standard error of $\beta_{st}$, t, VIF (variance inflation factor) and p-value of significance) of the multiple regression model and correlation coefficients (coefficient of determination $R^2$ and multiple correlation coefficient) in the NTF and IMH groups are shown in Table 3.
Table 3. Multiple and logistic regression analysis of determinants of perinatal outcomes

| REGRESSION ANALYSIS | Normal thyroid function | Isolated hypothyroxinemia |
|---------------------|-------------------------|---------------------------|
| **Multiple regression** |                         |                           |
| **Dependent 1** | Apgar score at 1 min |                         |
| Sample size | 218 | 131 |
| Coefficient of determination R² | 0.04323 | 0.0661 |
| Multiple correlation coefficient | 0.2079 | 0.2571 |
| Independent variables | βst Coeff. | Std. Error | t | VIF | p | βst Coeff. | Std. Error | t | VIF | p |
| Constant | 7.4418 | 8.2851 |
| TSH (mU/L) | 0.1822 | 0.2133 | 0.854 | 1.018 | 0.394 | 0.05597 | 0.2791 | 2.005 | 1.019 | 0.047 |
| TT4 (nmol/L) | -0.003837 | 0.002829 | -1.356 | 1.016 | 0.176 | 0.002208 | 0.00524 | 0.421 | 1.035 | 0.674 |
| Age (years) | 0.02982 | 0.012204 | 2.476 | 1.027 | 0.014 | -0.01424 | 0.01417 | -1.005 | 1.11 | 0.317 |
| BMI (kg/m²) | -0.00895 | -0.01351 | -0.662 | 1.017 | 0.508 | -0.01955 | 0.01717 | -1.142 | 1.15 | 0.256 |
| **Dependent 2** | Birth weight |                         |
| Sample size | 218 | 131 |
| Coefficient of determination R² | 0.07928 | 0.05004 |
| Multiple correlation coefficient | 0.2816 | 0.2237 |
| Independent variables | βst Coeff. | Std. Error | t | VIF | p | βst Coeff. | Std. Error | t | VIF | p |
| Constant | 3.0626 | 2.5583 |
| TSH (mU/L) | 0.11 | 0.1189 | 0.925 | 1.018 | 0.356 | 0.313 | 0.1886 | 1.660 | 1.019 | 0.099 |
| TT4 (nmol/L) | -0.004778 | 0.001577 | -3.029 | 1.016 | 0.003 | 0.001759 | 0.00354 | 0.497 | 1.035 | 0.620 |
| Age (years) | -0.003147 | -0.006715 | -0.469 | 1.027 | 0.640 | -0.009657 | 0.00957 | -1.009 | 1.11 | 0.315 |
| BMI (kg/m²) | 0.02331 | 0.007534 | 3.094 | 1.017 | 0.002 | 0.02338 | 0.01157 | 2.020 | 1.15 | 0.045 |
| **Logistic regression** |                         |                           |
| **Dependent 3** | Partus Prematurus Imminens (PPI): 1- positive; 0 - negative |
| Sample size | Positive: 28 (12.84%); Negative: 190 (87.16%) | Positive: 13 (9.92%); Negative: 118 (90.08%) |
| Coefficients and Standard Errors |                         |
| Variable | βst Coeff. | Std. Error | Odds ratio | Wald | p | βst Coeff. | Std. Error | Odds ratio | Wald | p |
| Constant | -4.6133 | 2.19866 | / | 4.4026 | 0.036 | -5.69072 | 2.89937 | / | 3.8518 | 0.049 |
| TSH (mU/L) | -1.06202 | 0.85085 | 0.3458 | 1.5580 | 0.212 | -0.41047 | 1.0973 | 0.6333 | 0.1399 | 0.708 |
| TT4 (nmol/L) | 0.028112 | 0.009846 | 1.0285 | 8.1523 | 0.004 | 0.02524 | 0.02141 | 1.0256 | 1.39 | 0.238 |
| Age (years) | 0.062743 | 0.04229 | 1.0648 | 2.2012 | 0.138 | -0.005364 | 0.05877 | 0.9947 | 1.2037 | 0.919 |
| BMI (kg/m²) | -0.07829 | 0.053226 | 0.9247 | 2.1636 | 0.141 | 0.064475 | 0.05877 | 1.0666 | 1.2037 | 0.273 |
| **Dependent 4** | SGA/IUGR: 1-positive; 0 - negative |
| Sample size | Positive: 9 (4.13%); Negative: 209 (95.87%) | Positive: 3 (2.29%); Negative: 128 (97.71%) |
| Coefficients and Standard Errors |                         |
| Variable | βst Coeff. | Std. Error | Odds ratio | Wald | P | βst Coeff. | Std. Error | Odds ratio | Wald | P |
| Constant | -1.2601 | 3.6773 | / | 0.117 | 0.732 | 10.7950 | 6.35612 | / | 2.8845 | 0.089 |
| TSH (mU/L) | -0.21146 | 1.20242 | 0.8094 | 0.0309 | 0.860 | -4.12985 | 4.11427 | 0.0161 | 1.0076 | 0.315 |
| TT4 (nmol/L) | -0.005648 | 0.016207 | 0.9944 | 0.1214 | 0.727 | -0.089834 | 0.04104 | 0.9141 | 4.7915 | 0.029 |
| Age (years) | 0.02996 | 0.06628 | 1.0304 | 0.2043 | 0.651 | -0.20726 | 0.14909 | 0.8128 | 1.9326 | 0.164 |
| BMI (kg/m²) | -0.076117 | 0.086722 | 0.9267 | 0.7704 | 0.380 | -0.057392 | 0.16456 | 0.9442 | 0.1216 | 0.727 |

βst Coeff. = β standardized coefficient; Std. error = standard error; VIF = variance inflation factor; TSH = thyroid stimulating hormone; TT4 = total thyroxine; BMI = body mass index; SGA/IUGR = small for gestational age/intrauterine growth retardation
Assessments (βst), standard error of βst, odds ratio, WALD and p-value of significance) of the logistic regression model in the NTF and IMH groups are also shown in Table 3.

There was statistical significance of the βst coefficient expressed by p value (0.014) for age as an independent variable predicting Apgar score in the NTF group. Because of their positive correlation, any BMI increase resulted in increased Apgar score at 1 min only in NTF women, whereas TSH showed positive predicting value for Apgar score at 1 min (p=0.047) in the IMH group.

There was an inverse correlation (negative βst=-4.7779 coefficient) between TT4 and birth weight. This means that any reduction of maternal TT4 resulted in birth weight increase only in NTF women. BMI showed positive predictive value (p=0.002, p=0.045) for birth weight in both study groups. In predicting preterm birth, we found a strong positive impact of TT4 (p=0.004) only in the NTF group, but an inverse impact (negative βst=-0.08934, p=0.029) in the IMH group.

Based on their eβst value or exp βst (e=natural logarithm) of regression βst coefficients, in multiple regression analysis we calculated exp (βst)=1.030 for maternal age in predicting Apgar score at 1 min in the NTF group and exp (βst)=1.057 for TSH in predicting Apgar score at 1 min in the IMH group. Each unit increase of maternal age resulted in 3.0% rise in Apgar score at 1 min and each unit increase of TSH resulted in 5.7% rise in Apgar score at 1 min in the NTF and IMH group, respectively.

In logistic regression analysis, we calculated exp(βst)=1.028 and exp (βst)=1.09399 for TT4 in predicting preterm birth in the NTF group and TT4 in predicting SGA/IUGR in the IMH group. Each unit increase of TT4 resulted in 2.8% rise in the risk of preterm birth. Each unit increase of TT4 resulted in 9.39% decrease in the risk of SGA/IUGR.

Discussion

There are few studies that investigated IMH and adverse pregnancy outcomes. Available data are inconsistent, with conflicting results, but there is concern about the potential negative effects of early IMH on both the mother and the offspring.

In the study by Akbaba et al., which included 196 pregnant women from Turkey, IMH was detected in 38% of study women, which is similar to the results of our study, where we found IMH in 37.42% of the pregnant women from North Macedonia. Sufficient iodine intake is essentially important for the population, since iodine is the main constituent of thyroid hormones. Our country, due to the longstanding and effective preventive measures, has been considered iodine replete since 2003. So, in iodine-sufficient areas like this, the cause of IMH can be that pregnant women may not be consuming enough iodine daily (below the WHO recommended 250 μg/day) required for normal production of thyroid hormones. In the same study, there was no IMH woman detected in first trimester, whereas we recorded 4 such cases in first trimester. Akbaba et al. detected IMH in 32% of 59 patients in second trimester, which is identical to our results on second trimester. In third trimester, they found IMH in 50 (27%) of 185 women versus our result of 64.12% in third trimester.

However, in the study by Kalampoki et al., hypothyroxinemia was associated with birth weight greater than 4000 g, a finding similar to ours, showing that women with hypothyroxinemia give birth to heavier babies than euthyroid ones, with a statistically significant difference between the NTF and IMH groups (p=0.043) in our study. According to βst coefficients in our study, we believe that birth weight would increase by 2.35% and 2.36% for every unit increase of maternal BMI in the NTF and IMH groups, respectively. Also, birth weight would decrease by 0.482% for every unit increase of TT4 in the NTF group (p=0.023). The correlation between birth weight and TT4 in the IMH group was not statistically significant (p=0.620).

And the last but not the least, Casey et al. showed that IMH in the first half of pregnancy had no effect on perinatal outcomes, just like our study results where there were no neonates with Apgar score at 1 min <7, or IUGR, LBW, or preterm births in first trimester of IMH pregnancy. Casey et al. analyzed 233 women and found no excessive adverse pregnancy outcomes in women who had IMH in the first half of pregnancy. The results of our study showed a strong statistically significant (p=0.029) inverse correlation between TT4 and SGA/IUGR only in the IMH group. The negative βst result and exp (βst)=1.09399 for TT4 in predicting SGA/IUGR showed that each unit increase of
TT4 resulted in 9.39% decrease in the risk of SGA/IUGR. In other words, crucial results of regression analysis of determinants of perinatal outcomes in the IMH group were strong positive predictive impact of TSH on Apgar score at 1 min, strong positive predictive impact of BMI on birth weight, and inverse predictive impact of TT4 on SGA/IUGR.

Our findings demonstrated overweight to be a risk factor for hypothyroxinemia in pregnancy, similar to the study by Furnica et al. The prevalence of IMH was increased among pregnant women with BMI >24 kg/m². It is thought that obesity stimulates peripheral deiodinase activity as an adaptation process to increase energy expenditure, resulting in an increased conversion of FT4 to FT3, and weight loss has been shown to be associated with changes in thyroid hormone levels, including decreases in FT3 level.

In many studies, elevated BMI was found in pregnant women with hypothyroxinemia. A Chinese study found that BMI ≥25 kg/m² may act as an indicator of hypothyroxinemia. Korevaar et al. also suggest that higher BMI might lead to lower thyroid function capacity. In our study, pregnant women with IMH had higher BMI (27.43 vs. 26.44 kg/m²) than women with normal thyroid function (p=0.018).

Korevaar et al. showed that IMH women had a 2.5-fold increased risk of premature delivery. In contrast, our study did not reveal any association with this complication, just like the study by Furnica et al., or a statistically significant difference between NTF and IMH groups (p=0.448). Contrary to this, a study conducted in a large Dutch pregnancy cohort, where the effects of thyroid dysfunction on the risk of premature delivery were investigated, showed that IMH was associated with an increased risk of premature delivery. Among the many endpoints studied, only the risk of abruptio placentae was found to be 2.3 times increased in mothers with IMH (p=0.026). Nonetheless, the ATA guidelines do not currently recommend treatment of IMH, while the recent European Endocrine Society guidelines leave it to the discretion of the care giver.

Our study had several strengths. First, none of the IMH women was prescribed levothyroxine, so a bias regarding the treatment of hypothyroxinemia could be excluded. A large sample size was another advantage of this study. Besides these strengths, our study also had some limitations. First, we did not evaluate thyroid peroxidase antibodies or thyroglobulin antibodies, which are also connected to negative neonatal outcomes. Although the association between IMH and iodine deficiency is still controversial, another limitation of the study was that we did not measure urinary iodine level.

In conclusion, the definition and impact of hypothyroxinemia in pregnancy remain controversial. The prevalence of IMH during pregnancy was of 37.42% in our unselected Macedonian population of pregnant women. IMH was associated with an increased maternal BMI and higher neonatal birth weight. Overweight could be a potential risk factor for thyroid dysfunction in pregnant women, in particular hypothyroxinemia. Also, the worst fetal outcome (LBW, pre-term delivery, and Apgar score at 1 min <7) was recorded in IMH mothers examined in second trimester. Isolated hypothyroxinemia is a variable magnitude, caught at one point of intersection and may not persist throughout pregnancy, so it would not be a significant predictor of perinatal outcome. It has greatest impact on babies with higher birth weight and occurs in obese mothers. Concerning strong correlation of the thyroid parameters of TSH and TT4, and maternal BMI, they may be used as predictors of some perinatal outcomes (Apgar score at 1 min, birth weight, and SGA/IUGR) in women with isolated hypothyroxinemia.

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IZOLIRANA HIPOTIROKSINEMIJA MAJKE I PERINATALNI ISHOD U SJEVERNOJ MAKEDONJI

M. Avramovska, B. Karanfilski, G. Dimitrov, E. Dzikova, A. Daneva Markova, M. Hadzi Lega, G. Tofoski i A. Sikole

Izolirana hipotiroksinemia majke (IMH) je prisutnost niske koncentracije ukupnog tiroksina (TT4) u majke u kombinaciji s normalnim mačjim hormonom za stimulaciju štitnjače (TSH). Cilj naše studije bio je ispitati je li IMH povezan sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodom trudnoće u Sjevernoj Makedoniji. U 359 trudnica koje su zadovoljile kriterije uzeti su uzorci osušene kapi sa štetnim ishodem trudnoće u Sjevernoj Makedoniji.

Sažetak

IZOLIRANA HIPOTIROKSINEMIJA MAJKE I PERINATALNI ISHOD U SJEVERNOJ MAKEDONJI

M. Avramovska, B. Karanfilski, G. Dimitrov, E. Dzikova, A. Daneva Markova, M. Hadzi Lega, G. Tofoski i A. Sikole

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