ASSESSING THE EFFECTIVENESS AND BENEFITS OF THYROID DISEASE SCREENINGS IN PREGNANCY THROUGH HEALTH INSURANCE DATA

Ján BIELIK[1] – Vladimíra KMEČOVÁ[2] – Matej BIELIK[3] – Marián FAKTOR[2]

[1] *Faculty of Healthcare, Alexander Dubcek University of Trenčín, Trenčín*
[2] *Health Insurance Company Dôvera, a.s., Bratislava*
[3] *KAMEAT, s.r.o., Endocrinologic Out-patient Department, Nové Mesto nad Váhom*
Corresponding author email address: jan.bielik@tnuni.sk

Abstract
Background: Thyroid screening in pregnancy in Slovakia is governed by the Slovak Ministry of Health Guidelines for the diagnosis and treatment of thyroid autoimmune diseases in women during pregnancy (Journal of the SR 39, 2009, p. 33-39).
Goal: The main aim of this work was to find out the adherence to the professional provisions of this "Guidelines" in gynecological practice and consequently their clinical effectiveness and cost effectiveness. The secondary objective was to compare the results with the results of an analogous study from 2011.
Methods: The evaluation included women from the records of the health insurance company Dôvera, a.s. with diagnoses E.00 to E.07 who first visited a gynecologist in 2016, with no endocrinology record from 2015. During the gynecologist's visit, a blood sample was taken for TSH and aTPO (4434-determination of ultra-sensitive TSH). Women who were referred by gynecologist for endocrinological examination within 3 months of TSH collection were included in the trial and were followed up until the end of 2017. As other group were separately evaluated pregnant women who had a documented visit to the endocrinologist in 2015 or in 2016.
Results: The group consisted of 16 891 women. 5 901 women (34.9%) had documented TSH sampling (up to 3 months after examination). 526 women (3.1%) had a subsequent endocrinological examination. In this group, 210 women (1.2%) were prescribed thyroid drugs. Of these, 6 were treated with thyreostatic therapy (2.9%) and 204 women were treated with thyroid replacement therapy (97.1%). The cost of TSH and blood collection at a gynecological clinic in this group was € 47 857.11, of aTPO - € 67 271.40, of USG thyroid examinations - € 6 423.70, of endocrine examinations - € 13 314.00 and of medicine - € 1 055.37. A total of 2,587 (15.3%) women had thyroid disease before pregnancy, with 905 of them taking thyroid drugs (5.4%).
Conclusions: Thyroid pathology screening in pregnant women indicates low feasibility of screening for thyroid diseases by gynecologists (34.9%). New thyroid disease has been diagnosed in 3.1% of women in this group, with 1.2% of women requiring medical treatment. The cost of newly diagnosed thyreopathy was € 258.40, and the cost of treatment of one case of newly diagnosed and treated thyreopathy was € 647.30. The screening program is clinically and economically effective, although the low level of laboratory examinations in gynecologists appears problematic.

Key words: Thyreoid diseases. Pregnancy. Screening.

1 Introduction

Thyroid diseases are the most common endocrinopathies, affecting approximately 5 – 10 % of our population, resp. 10 to 15 % of middle-aged to older women. Thyroid hormones are important for normal growth and development of the body, function of the central nervous system, regulation of a variety of homeostatic functions including energy and thermos regulation. They affect performance and quality of life, weight, may be responsible for cardiovascular complications [1, 2].

We distinguish two basic types of diseases. On one hand, diseases leading to deterioration of thyreoid function, such as hyperthyroidism, hypothyroidism, and thyroid inflammation, on the other hand, a change in the size of the thyroid and the presence of focal changes, i.e. a goiter diffuse or nodose. Dysfunction is diagnosed by determining thyroid hormone levels, antibodies and possibly inflammatory parameters, structural failure by ultrasonography [3].

Thyroid activity is controlled by the hypothalamic-pituitary system's negative feedback mechanism. Thyroid hormones (thyroxine and triiodothyronine forming therefrom) are, from the beginning of prenatal development, essential for proper development of the CNS, hypothalamic-pituitary-thyroid axis, lung, bone, postnatal intellect, etc. In women of reproductive age occurs manifest hypothyroidism (with laboratory findings of increased TSH and reduced FT4 in serum) in about 3 %. If manifest hypothyroidism is not adequately treated, it is associated with impaired fertility, increased abortion, and premature births, with a risk of delayed (especially psychoneural) fetal development and neonatal morbidity [4]. The risk assessment of pregnancy - so-called subclinical hypothyreosis (SCH) - has become problematic. A systematic review that analyzed the results of 21 studies summarized evidence of adverse clinical effects of SCH during pregnancy and the effect of levothyroxine treatment to alleviate complications. Pregnant women with SCH were found to be at higher risk of abortion, placental abruption, neonatal deaths compared to euthyroid pregnant [5].

Two fundamental opinions on screening were discussed in the professional public. The first view was to advocate the choice of risk group screening that should be undertaken in patients with a history of hypothyroidism,

hyperthyroidism, postpartum thyroiditis, or lobectomy, with a positive family history of thyroid disease, in the presence of goiter, in patients with a body mass index of more than 40 kg/m^2 , over 30 years of age, in presence of type 1 diabetes mellitus or other autoimmune diseases, in conditions after head or neck irradiation, infertile patients, history of miscarriage or preterm labor, amiodarone, lithium, cytokines treatment [6]. The second view has advocated for universal screening [7-9], which was reinforced in particular by the finding that up to 30 % of subclinical or clinical thyreopathy in pregnancy was not captured in women with a risk profile [10].

2 Methods and results

Slovakia is a country where, based on expert discussion, it was believed that the solution to the problem is to implement a universal screening for thyroid diseases in the population of pregnant women. Screening has been underway since 2009 on the basis of the Ministry of Health Expert Guidance for the diagnosis and treatment of autoimmune diseases in pregnant women (Professional Guidance). According to this "the patient's screening is performed in the gynecological clinic at the first examination, at the desired pregnancy, optimally by the 10th week of pregnancy." It is recommended that TSH (thyreostimulating hormone) and thyreoperoxidase autoantibodies (TPOAb) be indicated for screening. If results are positive, the patient is referred to a specialized endocrinologic clinic at which the endocrinologist indicates further examination of free thyroxine (fT4), free triiodothyronine (fT3), anti-thyroglobulin (TGAb) and TSHrAb autoantibodies. At the endocrinological clinic every patient who is dispensarized with a known thyroid disease and who is planning to conceive will be instructed to undergo check-up in an endocrinologic clinic after confirmation of pregnancy [11].

Table 1 shows a summary of treatment for newly detected hypothyroidism and Table 2 for hyperthyroidism. The cost of TSH and blood collection at the gynecological clinic in this group was € 47 857.11, of USG thyroid examinations - € 6,423.70, of endocrinological examinations - € 13 314 and of pharmacotherapy- € 1 055. 37. However, the costs of aTPO (€ 5 901x11,40) in the amount of approximately € 67 271,40, which are not recorded in the database of the health insurance company, but in the relevant laboratories, must also be added to these costs. We assume that if the gynecological clinic was examining for TSH, aTPO examination was also indicated. The total cost was € 135 921.58. The cost structure is shown in Table 3.

Table 1 *Overview of treatment in pregnant women with newly diagnosed hypothyroidism*

Pharmacotherapy in pregnant women with newly diagnosed hypothyroidism	**Patients**	**Packages ($\bar{x}$)**	**Reimbursement (€)**
Euthyrox 100 µg	16	2.50	118.40
Euthyrox 112 µg	4	1.75	23.52
Euthyrox 125 µg	2	1.00	7.48
Euthyrox 137 µg	2	1.00	8.22
Euthyrox 25 µg	85	2.49	159.00
Euthyrox 50 µg	95	2.01	286.50
Euthyrox 75 µg	34	2.44	186.75
Euthyrox 88 µg	10	2.00	52.80
L-Thyroxin 100 Berlin-Chemie	3	3.00	27.00
L-Thyroxin 150 Berlin-Chemie	1	2.00	9.00
L-Thyroxin 50 Berlin-Chemie	21	2.05	64.50
L-Thyroxin 50 Berlin-Chemie	3	1.00	4.50
L-Thyroxin 75 Berlin-Chemie	9	2.00	40.47
Average dose 74,5 ug/d	**285**	-	**988.14**

Note: The total number of included women was 204. A group of 285 was formed to account for the same person switching to another drug or dose of the drug.

Table 2 *Overview of treatment in pregnant women with newly diagnosed hyperthyroidism*

Pharmacotherapy in pregnant women with newly diagnosed hyperthyroidism	**Patients**	**Packages (n)**	**Reimbursment (€)**
Thyrozol	4	4.3	24.43
Propycil	2	8.0	42.80
Total	**6**	-	**67.23**

Table 3 *Cost structure*

Cost	**Number**	**€**
Gynecology (TSH, blood sample)	5901	47 857.11
Endocrinology USG	514	6 423.70
Endocrinology examinations	526	13 314.00
Endocrinology drugs	210	1 055.37
Total		**68 650.18**
ATPO	5091 (assumed)	**67 271.40**
Total		**135 821.58**

Amount in full 2 587 women (15.3%) were registered by endocrinologist before pregnancy: 905 (5.4%) of them were taking thyroid drugs. The cost of one case of newly diagnosed thyreopathy was € 258.40, and the cost of treatment of one case of newly diagnosed and treated thyreopathy was € 647.30, € 660.30 per one hypothyroidism, € 22 653.60 per hyperhyroidism. These results as well as the results of the 2011 study, including the cost of one case of newly revealed thyreopathy as well as one case of hypothyroidism and hyperthyroidism, are shown summarized in Table 4.

Table 4 *Summary of the results of the 2016 study and their comparison with the results from 2011*

Parameter	2016/2017	2011/2012
„Thyroid“ examined women in gynecological clinics ratio (%)	34.9	37.1
Known thyreopathy (%)	15.3	2.2
Known treated thyreopathy (%)	5.4	1.5
New thyreopathy (%)	3.1	2.0
New treated thyreopathy (%)	1.2	1.1 – 1.4
New treated thyreopathy ratio to untreated (%)	38.7	54.9 – 70.9
Cost of one new thyreopathy (€)	258.40	507.20
Cost of one new treated thyreopathy (€)	647.30	811.00
Cost of one new treated hypothyroidism case (€)	666.30	811.00
Cost of one new treated hyperthyroidism case (€)	22 653.60	69 747.00

3 Discussion

The consequences of thyroid dysfunction on the mother are: fertility problems, endometriosis, ovarian failure, spontaneous abortion, premature labor, preeclampsia, placental abruption, hypertension, postpartum bleeding. The consequences of thyroid dysfunction on the fetus are: fetal death, intrauterine growth retardation, fetal hypothyroidism, increased risk of sepsis, respiratory distress syndrome, increased perinatal mortality, cardiomyopathy, reduced birth weight, neonatal hypothyroidism, slowed neuropsychological development, impaired postpartum adaptation [7].

In our study, the low, only 34.9 % share of “thyroid” examined women in gynecological out-patient departments, i.e. 5 901 out of 16 891 pregnant women, was an unpleased surprise. On the other hand, the results showed a high 3.1 % discovery of new thyroid diseases (526 out of 16 891), with more than a third requiring medical treatment - a total of 1.2 %. Surprising, the incidence of known thyropathy was 15.3 % of the overall population (2 587 out of 16 891), with a total of 905 women receiving medication - i.e. 5.4 % of the whole file. In epidemiological terms this means that the incidence of thyroid diseases in pregnant women was 18.4 %. Due to the fact that the average age of women at 1st birth in 2015 was 27.8 years [12], we can translate our findings into the category of 30 to 35 years old women.

Interestingly, though in the negative sense, it was found that the proportion of thyroid-treated pregnant women in 2016 was even lower than in 2011, i.e. 34.9 % vs 37.1 %. Although the difference is not statistically significant, we expected a higher proportion. In terms of cost-effectiveness, costs in 2016 were significantly lower than in 2011, in the case of newly diagnosed thyreopathy – 258.40 € vs 507.20 €, as well as in case of newly diagnosed thyreopathy with treatment needed – 647.30 € vs 811.00 €. To compare, an estimate of the cost of capturing one occult blood in colorectal carcinoma screening was reported to be approximately € 820 in 2008 [13].

The importance of disease screening cost is assessed from the direct medical cost point of view (as mentioned above) as well as from the point of view of costs, which are recalculated to the so-called “1 year of quality adjusted life year” (QALY). In this case, we can refer to the work of English authors who calculated the cost of obtaining 1 QALY for universal screening at £ 7 138 and for screening groups at risk at £ 6 753 [14]. A comprehensive review of the issue of thyroid screening in pregnancy has been reported by Taylor et al. in 2018 [15].

Universal thyroid screening in pregnancy fulfills criteria for beneficial and cost-effective screening program and holds promising for improving fetal and maternal outcomes. However, the areas of uncertainty remain especially with regard to the significance of borderline biochemical abnormalities and whether the correction of such abnormalities can improve outcomes. And consensus is unlikely to be reached without further controlled trials and such trials should aspire to recruit women pre-conception or as early as possible in pregnancy. In the interim regular audit of existing screening programs will be crucial in gaining insights into the practicalities of universal thyroid screening in pregnancy. For centers a universal or high-risk screening integrating thyroid autoimmunity into decision making is essential [15].

The fact that we have a need for an average thyroxine dose of about 75 µg, as indicated for newly diagnosed thyreaptia, also endorses the aforementioned recommendations. This dose may be reflected in a clinical evaluation of a so-called moderate hypothyroidism, according with the outcomes of Zaborek et al., according to which a dose of 100 to 150 µg, depending on body weight (1.6 µg/kg/d), may be considered as the average thyroxine dose required after total strumectomy [16].

4 Conclusion

Universal screening of thyroid diseases in pregnant women, carried out according to the Professional Guidelines of the Ministry of Health, can be evaluated, in accordance with the prevailing outputs of foreign authors, as clinically justified and cost effective. However, its greatest limitation is the low proportion of gynecological clinics involvement - 34.9 %, in 2016 paradoxically lower than in 2011 - 37.1 %. In order to improve the situation, it would be appropriate (voluntarily or through sanctions) to achieve a full obligation to examine for TSH and aTPO in gynecological clinics, with a timely notification of these results (e.g. within 5 days of collection) and in case of pathological values, immediate referral to endocrinological examination (or an appointment made by phone). On the other hand, it would be necessary to provide additional security (either voluntarily or through sanctions) to improve the availability of endocrinological care (e.g. within 5 days when the appointment was made by the gynecologist or the patient). In a way, the supportive finding that the average daily dose of thyroxine indicated for newly diagnosed hypothyroidism was about 75 µg is cautionary and suggestive of this proposition, which can be assessed clinically as moderately severe hypothyroidism. From this point of view, the universal screening of thyroid diseases in pregnant women is a sound investment on behalf of both pregnant women and their children's health.

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