CONTINUING MEDICAL EDUCATION

The Treatment of Illnesses Arising in Pregnancy

Michael Bolz, Sabine Körber, Toralf Reimer, Johannes Buchmann, Hans-Christof Schober, Volker Briesse

SUMMARY

Background: The treatment of pregnant women who have illnesses unrelated to pregnancy can cause uncertainty among physicians.

Method: We searched the PubMed database and specialty guidelines from Germany and abroad (the guidelines of the German Society for Gynecology and Obstetrics, the American Congress of Obstetricians and Gynecologists, and the Royal College of Obstetricians and Gynaecologists) over the period 2007–2016 for information on standards for the diagnosis and treatment of five illnesses that can arise in pregnancy: bronchial asthma, migraine, hypothyroidism, hyperthyroidism, and varicose veins.

Results: Any diagnostic tests that are carried out in pregnant women should be simple and goal-directed. The choice of drugs that can be used is limited. For many drugs, no embryotoxic or teratogenic effect is suspected, but the level of evidence is low.

Conclusion: When illnesses unrelated to pregnancy arise in pregnant women, attention must be paid to potential divergences from the typical disease course and to possible drug side effects on the fetus in order to prevent serious complications for both mother and child.

► **Cite this as:**

Bolz M, Körber S, Reimer T, Buchmann J, Schober HC, Briesse V: The treatment of illnesses arising in pregnancy. *Dtsch Arztebl Int* 2017; 114: 616–26.
DOI: 10.3238/arztebl.2017.0616

Illnesses unrelated to pregnancy are an important component of the (interdisciplinary) care of pregnant women. Uncertainty often arises about what diagnostic or therapeutic procedures can be performed and about the potential embryotoxic or teratogenic effects of drugs. This article is intended as an overview of five common and important maternal illnesses that can arise during pregnancy. Abnormal conditions that are explicitly linked to pregnancy, some of which are more common than the illnesses we discuss here (e.g., emesis and hyperemesis gravidarum, heartburn/gastroesophageal reflux disease), will not be considered in this review.

Learning objectives

This article is meant to provide the reader with

- an overview of the treatment of bronchial asthma, hypo- and hyperthyroidism, migraine, and varicose veins in pregnant women and
- knowledge of the standard treatment for each of these conditions.

Bronchial asthma

Asthma is the most common chronic lung disease among pregnant women, with a prevalence of 4–8% (1). As a rule, the disease remains stable in a third of patients during pregnancy, worsens in a third, and improves in a third (the “one-third rule”). Viral infections of the upper airways, discontinuation of inhaled corticosteroids, and active smoking are held to be risk factors for exacerbations (2).

Bacterial superinfection is common; when it occurs, antibiotic treatment is indicated. (For an overview of the use of antibiotics in pregnancy, see [e1].)

Inadequately controlled asthma that is present even before pregnancy is a major risk factor for the development

Department of Obstetrics and Gynecology, Klinikum Südstadt Rostock: Dr. med. Bolz, Dr. med. Körber, Prof. Dr. med. Reimer, Prof. Dr. med. Briesse

Department of Internal Medicine I, Klinikum Südstadt Rostock: Prof. Dr. med. Schober

Department of Child and Adolescent Psychiatry, Neurology, Psychosomatics and Psychotherapy, University Medicine Rostock and Clinic and Policlinic for Psychiatry and Psychotherapy, Health Care Center for Neurology, University of Rostock: Prof. Dr. med. Buchmann

Illnesses arising in pregnancy

Illnesses unrelated to pregnancy are an important component of the interdisciplinary care of pregnant women.

of pre-eclampsia at some time during pregnancy (relative risk [RR] 1.54 compared to pregnant women without asthma). Asthma is also associated with further complications of pregnancy, including intrauterine growth restriction (RR 1.46), small for gestational age (SGA) (RR 1.22), preterm delivery (RR 1.41), and birth defects (RR 1.11) [e2–e5]. These risks, however, are not a reason for women who want to have children to forego pregnancy.

There is no currently valid German guideline for the treatment of asthma during pregnancy. The national care guideline (*Nationale Versorgungsleitlinie, NVL*) for asthma, which included a chapter on pregnancy, expired on 31 December 2014; an update is not due to be published until 2018. The guideline of the Global Initiative for Asthma (GINA) can be recommended. A German-language pocket guide to this guideline (current as of 2016) is available.

Particular aspects of asthma in pregnancy

Asthma that is present during pregnancy must be optimally controlled. The treatment that was given before pregnancy should be continued, and marked acute exacerbations must be treated at once. To prevent sudden worsening of asthma, the German Standing Committee on Vaccination (*Ständige Impfkommission, STIKO*) recommends influenza vaccination from the first trimester onward. In the long-term treatment of the pregnant patient, the physician should periodically check the patient's need for and compliance with prescribed medication, and provide asthma education as needed. Any comorbidities that may arise, e.g., rhinitis or reflux, should be treated as necessary. Delays in diagnosis and treatment should be avoided. Patients who smoke should be encouraged to quit. The pregnant asthmatic patient should also undergo pulmonary function testing once per month. The initiation of desensitization treatment during pregnancy is contraindicated (3).

In a Cochrane analysis carried out in 2014, eight randomized trials on the treatment of asthma in pregnancy, involving a total of 1181 patients, were evaluated (4). No definitive conclusions could be drawn because some trials did not consider current treatment regimens and others were of insufficient power to detect differences in the perinatal status endpoint. Two approaches that were addressed in these trials are nevertheless of interest. One of these involved measurement of the fraction of exhaled nitrous oxide (FeNO) to predict sudden worsening of asthma (e6). A side benefit of this

measurement is that it enables a check on the necessary steroid dose and on patient compliance with medication; nonetheless, it is not reimbursed by most statutory health insurance carriers in Germany. Another approach discussed in the reviewed publications was improved asthmatic control through interdisciplinary counseling as part of the MAMMA trial (e7). In particular, counseling was coordinated by pharmacies. No recommendations for routine practice could be extracted from these trials, however, because of their low case numbers (n = 29 per arm).

Clinical features

Shortness of breath and nocturnal coughing are the main manifestations of bronchial asthma. Auscultation reveals signs of obstruction (wheezes, rales, rhonchi). These symptoms and signs are partly or completely reversed after the inhalation of a β_2 -sympathomimetic agent. Asthma is classically associated with severe intolerance of beta-blockers. The treatment of asthma is essentially the same in pregnant as in non-pregnant patients.

An acute asthma attack in a pregnant woman is always an indication for in-hospital treatment and observation. Pharmacotherapy must be escalated or de-escalated depending on the severity of the attack and the extent of the clinical response (*Table 1*). Supplemental oxygen should be given at once, the goal being an O_2 saturation level above 95%.

The risk of birth defects, pre-eclampsia, preterm birth, or intrauterine growth retardation is not increased by the use of inhaled corticosteroids, theophylline, or short-acting β_2 -mimetic drugs such as salbutamol (6). The doses of these drugs need not be adjusted in pregnancy.

Oral glucocorticoids given in the first trimester increase the risk of fetal cleft lip or palate (0.3% versus 0.1%) (2). Systemic glucocorticoids increase the risk of diabetes but are nevertheless indispensable in the treatment of severe asthma and the life-threatening situations associated with it.

Inhaled corticosteroids are the cornerstone of the treatment of persistent asthma. They can be used safely in pregnancy; the largest body of evidence is available for budesonide (7). Only scant data are now available for the combination of inhaled corticosteroids with long-acting β_2 -agonists (formoterol) (e8). Inhaled anticholinergic drugs such as tiotropium bromide are increasingly used as an alternative. They should be

Asthma and pregnancy

Asthma is associated with complications of pregnancy including intrauterine growth restriction, smallness for gestational age (SGA), preterm delivery, and birth defects.

Treatment

The treatment of asthma is essentially the same in pregnant as in non-pregnant patients.

TABLE 1

Treatment recommendations for asthma attacks during pregnancy^{*1}

Substance class	Dosage
1 a) β2-mimetic agents (inhaled)	2–4 inhalations of a rapidly acting β2-mimetic agent (e.g., salbutamol, reproterol); repeat in 10–15 minutes as needed
1 b) Glucocorticoids	50–100 mg of prednisolone equivalent IV (repeat in 4–6 hours as needed)
1 c) Anticholinergic agents (drugs of 2 nd choice)	0.5 mg ipratropium bromide via nebulizer (better as a combined preparation with a β2-mimetic agent)
2) β2-mimetic agents^{*2} (systemic, for in-hospital use only)	SC or IV administration: terbutaline 0.25–0.5 mg SC q4h; reproterol 0.09 mg (= 1 mL amp.) via perfusor (5 amp./50 mL) at 2–10 mL/h ^{*3}
Theophylline	Should no longer be used, according to the GINA guideline (2015)

^{*1} modified from [5] and the National Disease Management Guideline on Asthma, 2nd Ed., Version 5

^{*2} β2-mimetic agents, glucocorticoids, and anticholinergic agents can be used both on an outpatient emergency basis and in the hospital.

^{*3} 5 ampoules in a 50 mL injection via perfusor, diluted with normal saline.

Note: There is also an IV bolus dosage for reproterol: 1 ampoule by slow IV push.

Amp., ampoule; IV, intravenous; SC, subcutaneous

given in pregnancy only for strict indications, as valid data on their use are currently still unavailable.

Theophylline in the recommended dose is not dangerous during pregnancy, but its role in the treatment of asthma is now only secondary (it is a weak bronchodilator with a very high side-effect potential, and its use necessitates measurement of serum levels). H1-antihistamines can be taken during pregnancy without any special restrictions (e9). Montelukast, a leukotriene receptor antagonist, has anti-inflammatory properties and can be used as an alternative to inhaled corticosteroids. The current recommendation is that montelukast treatment should not be started during pregnancy but should not be stopped during pregnancy either, if it was initiated beforehand and has met with therapeutic success (1).

The newer biological agents are coming into increasing use as additional treatments for severe bronchial asthma (step 5 in the treatment algorithm of the current GINA guideline). The monoclonal antibody omalizumab binds free human IgE in the blood and is used to treat severe allergic asthma. This drug was given to 191 women around the time of conception, or during pregnancy, without any observed increase in the rate of birth defects or intrauterine growth retardation (e10). Two further antibodies, mepolizumab and reslizumab, are new options for the treatment of severe eosinophilic asthma; both of them bind to the cytokine interleukin-5. No clinical data on their use in pregnancy are available.

Mode of delivery

Spontaneous delivery is to be preferred. Endogenous cortisol secretion during delivery makes asthma attacks during delivery very rare (5).

Special aspects of delivery in asthmatic mothers

During delivery, anti-asthmatic medication must be continued; short-acting β2-agonists with or without corticosteroids should be given. Intravenous fluid replacement is beneficial as well. Peridural anesthesia enables the optimal treatment of pain and may help reduce bronchospasm. The patient's pulmonary function and oxygen saturation should be evaluated as necessary. To prevent acute adrenal failure during delivery, the patient should be given a stress dose of glucocorticoid (20 mg of methylprednisolone every 8 hours for 1–2 days), especially if she has already been taking systemic glucocorticoids in the last few months (8).

If labor needs to be induced (e.g., with prostaglandin administration after post-partum bleeding), bronchoconstrictors must be avoided. Prostaglandin F2α has not been approved in Germany, but prostaglandin E2 or E1 may be given. The administration of fenoterol or oxytocin during delivery is not contraindicated (3).

Clinical experience has shown that asthma returns to the same level of severity as before pregnancy within 3 months of delivery (e11). Most anti-asthmatic medications can be safely taken during the breastfeeding

Inhaled corticosteroids

Inhaled corticosteroids are the cornerstone of the treatment of persistent asthma. They can be used safely in pregnancy; the largest body of evidence is available for budesonide.

During delivery

During delivery, anti-asthmatic medication must be continued; short-acting β2-agonists with or without corticosteroids should be given. Intravenous fluid replacement is beneficial as well.

period. The breast-fed newborn infants of mothers who take theophylline or antihistamines may become sleepy or irritable.

Migraine

Migraine is characterized by recurrent bouts of headache, often of a pulsating character, usually unilateral, and of variable intensity. Associated symptoms included nausea, vomiting, photo- and phonophobia, and a general feeling of being unwell. Women are more commonly affected than men; 14% of women have migraine at some time in their lives. The prevalence of migraine is highest between the ages of 35 and 45 (e12, e13). A migraine attack that lasts longer than 72 hours is called status migrainosus (e14). In some 15% of patients, the headache is preceded by an aura.

The most important differential diagnoses of migraine in pregnancy are pre-eclampsia (pregnancy-induced hypertension and proteinuria) and eclampsia (pregnancy-induced epileptic seizures). Women with migraine typically suffer from less frequent and less intense attacks when they are pregnant (9). Women who have their first-ever migraine attack when pregnant (pregnancy-associated migraine) have an increased risk of stroke and myocardial infarction during pregnancy (10, 11) and should therefore be seen in consultation by a neurologist (12).

Treatment

Non-pharmacological interventions are preferred for the treatment of migraine during pregnancy. Multimodal approaches to the prevention and treatment of migraine are useful for pregnant women as for other sufferers. These include avoiding triggering factors, learning relaxation techniques, and making use of manual therapy and acupuncture (13, 14). The pharmacological prevention of migraine attacks with beta-blockers can be maintained during pregnancy, if necessary. There is good evidence for the efficacy of metoprolol (initially 50 mg/day, maintenance dose 100–150[200] mg/day), propranolol (initially 40 mg/day, maintenance dose 120–160 mg/day), and bisoprolol (5 mg/day).

When a pregnant woman is treated with a beta-blocker, there must be surveillance for the possible development of intrauterine growth retardation. Neonatal bradycardia may arise, and the newborn infant must therefore be kept under close observation for the first 24 hours after birth.

Further options for the pharmacological prevention of migraine attacks include analgesic drugs, magnesium, and non-steroidal anti-inflammatory drugs. These, however, should be given no later than the end of the 32nd week of gestation, as otherwise there is a danger of premature closure of the fetal ductus arteriosus. There is little evidence to support the administration of acetylsalicylic acid (100 mg/day) to prevent migraine attacks, which is an off-label use of this drug. Likewise, there is little evidence to support the administration of magnesium (200 mg bid) for this purpose.

Anticonvulsant drugs such as topiramate and valproic acid are associated with a higher risk of birth defects. The indications for their use should, therefore, be critically evaluated even before conception (15, e12–e16).

80% of migraine sufferers use non-prescription pain relievers to treat their acute migraine attacks, often without consulting a physician. The non-prescription drug of first choice to treat acute migraine attacks during pregnancy is acetaminophen (1000 mg/day up to a maximum of 3 g/day for 10–14 days). The evidence available to date indicates that acetaminophen is not teratogenic. There is evidence, however, of a higher likelihood of bronchial asthma after maternal use of acetaminophen during pregnancy (e17, e18). The non-prescription drugs of second choice to treat acute migraine attacks during pregnancy are ibuprofen and acetylsalicylic acid. Ibuprofen should be given in single doses of 200–600 mg, up to a daily maximum of 1200 mg. Ibuprofen should not be given during the third trimester due to the associated risk of premature closure of the ductus arteriosus in the fetus.

Triptans are the drugs of first choice for patients who are not pregnant but are not approved for use by pregnant women, even though there is no evidence that they cause birth defects. For sumatriptan in particular, there exists a large registry of pregnant women among whom no increase in the rate of complications in the first trimester can be seen (16). Sumatriptan is, therefore, the drug of third choice to treat acute migraine attacks (in a single dose of 50–100 mg p. o.).

Mode of delivery

Migraine per se is not an indication either for the induction of delivery or for cesarean section.

Migraine

The most important differential diagnoses of migraine in pregnancy are pre-eclampsia (pregnancy-induced hypertension and proteinuria) and eclampsia (pregnancy-induced epileptic seizures).

The treatment of migraine in pregnant women

Non-pharmacological treatments are preferred for the treatment of migraine during pregnancy.

The passage across the placenta of thyroid hormones and related substances (21). xxx indicates that TSH and rT3 do not cross the placenta. The dashed arrow for T3 and T4 indicates that the thyroid hormones cross the placenta only to a limited extent. TSH, thyroid-stimulating hormone

TABLE 2

Clinical manifestations of thyroid diseases

Disease	Manifestations
Goiter	Feeling of pressure, "a lump in the throat," dysphagia, frequent throat-clearing; with large goiters, dyspnea, stridor, venous congestion
Hyperthyroidism	Tachycardia, weight loss, heat intolerance, nervousness, tremor, visual symptoms
Hypothyroidism	Fatigue, weight gain, cold intolerance, constipation, slowness
Thyroiditis	Pain in the throat
Thyroid carcinoma	Thyroid nodule, enlarged lymph nodes, hoarseness

Thyroid dysfunction

Thyroid hormones make it possible to meet the increased energy requirement during pregnancy. They are extraordinarily important for fetal growth and development. An absolute deficiency of thyroid hormones during pregnancy leads to the syndrome of cretinism in the infant (17). Nearly 50% of pregnant women have a moderate iodine deficiency. The avoidance of iodine deficiency through daily supplementation with 100–150 µg of iodide compensates for the thyroid gland's elevated demand for iodine (25–50% higher than normal) and thus ensures

adequate thyroid hormone synthesis and the avoidance of hypothyroidism and goiter.

Both latent and overt hypothyroidism during pregnancy confer higher risks of spontaneous abortion (16.7%), intrauterine growth restriction, preterm birth (odds ratio [OR] 1.19), and intrauterine fetal death (0.65%) (18, e19, e20). Impaired neurocognitive development of the child due to hypothyroidism is irreversible (19). (Unrecognized) hypothyroidism elevates the risk of sterility.

Untreated maternal hyperthyroidism is associated with multiple risks for embryonal/fetal development, including pre-eclampsia, thyrotoxic crisis, spontaneous abortion (17.2%), intrauterine growth retardation, preterm birth (RR 1.24), and intrauterine fetal death (0.82%) (e19, e20). The treatment that is needed to lower maternal thyroid hormone levels promotes the development of hypothyroidism in the fetus (18).

The secretion of thyroid hormones is stimulated by the influence of TSH (thyroid-stimulating hormone); in the bloodstream, thyroid hormones are coupled with thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin. Only the free (unbound) thyroid hormones are biologically effective. The ratio of free to bound thyroid hormone is roughly 1:1000 (Figure, Table 2).

Diagnostic evaluation

The diagnostic tests that can be applied during pregnancy are limited. fT3, fT4, TSH, anti-thyroperoxidase (anti-TPO) antibodies, anti-thyroglobulin antibodies (TAB), anti-TSH-receptor antibodies (TRAB), and thyroxine-binding globulin (TBG) can be measured in the laboratory (Tables 3 and 4), and ultrasonography, color-Doppler ultrasonography, and fine-needle biopsy of the thyroid gland can be considered as well. Radio-nuclide scintigraphy of the thyroid gland is contraindicated during pregnancy and breastfeeding, as is the thyrotropin releasing hormone (TRH) test. Nonetheless, if scintigraphy is performed during the first semester because of unawareness of pregnancy, there is no medical indication for a termination of pregnancy.

Hyperthyroidism—Hyperthyroidism arises in 0.1–1.0% of pregnancies (e21, e22). Its most common cause is Graves disease, i.e., autoimmune-mediated overstimulation of the thyroid gland by anti-TSH-receptor antibodies (TRAB). The manifestations can be expected to improve during the second and third trimesters; after delivery, however, the immunological condition generally

Thyroid diseases

An absolute deficiency of thyroid hormones during pregnancy leads to the syndrome of cretinism in the infant.

Untreated maternal hyperthyroidism

Untreated maternal hyperthyroidism is associated with risks for embryonal/fetal development including pre-eclampsia, thyrotoxic crisis, spontaneous abortion, intrauterine growth retardation, preterm birth, and intrauterine fetal death.

TABLE 3

Reference ranges for thyroid laboratory values in pregnancy (modified from [20])

	Not pregnant	First trimester	Second trimester	Third trimester
TSH (mU/L)	0–4	0–1.6	0.1–1.8	0.7–7.3
Free T4 (pmol/L)	11–23	11–22	11–19	7–15
Free T3 (pmol/L)	4–9	4–8	4–7	3–5

TSH, thyroid-stimulating hormone

TABLE 4

Typical laboratory constellations in selected thyroid diseases during pregnancy (modified from [20])

Disease	TSH	ft4	ft3
Hyperthyroidism	Undetectable	Very high	High
Hypothyroidism	High	Low	Low or normal
Subclinical (latent) hypothyroidism	High	Normal	Normal

TSH, thyroid-stimulating hormone

reverts to the state that prevailed before pregnancy. Rare causes of hyperthyroidism include toxic adenoma, toxic nodular goiter, carcinoma, subacute thyroiditis, and drugs (amiodarone, lithium).

The differential diagnosis of hyperthyroidism during pregnancy includes pregnancy-induced hyperthyroidism triggered by human chorionic gonadotropin (HCG) in the first and second trimester. This condition is caused by very high HCG levels (maximum in gestational week 12, ca. 210 000 mU/mL). HCG stimulates the TSH receptor, often resulting in (marked) intractable vomiting during pregnancy (hyperemesis gravidarum). In this situation, the laboratory test for anti-TSH-receptor antibodies (TRAB) is negative. The condition is self-limiting: from about the 17th gestational week onward, its manifestations disappear, and no treatment is needed to lower the thyroid hormone level (e23).

Untreated maternal hyperthyroidism may worsen into a thyrotoxic crisis in the setting of infection, stress around the time of delivery, or operative delivery (cesarean section). The manifestations of thyrotoxic crisis include fever, confusion, and cardiac decompensation (21).

Antithyroid antibodies cross the placenta and cause neonatal or fetal hyperthyroidism in about 10% of cases. Their half-life is three weeks, which explains the occurrence of (transient) hyperthyroidism in the neonate. Pregnant women with a known history of Graves disease must therefore be checked for the presence of antithyroid antibodies in the third trimester of pregnancy as well. Maternal hyperthyroidism is a clear indication for treatment. The lowest effective dose should be given, and laboratory checks should be repeated every four to six weeks. The administration of iodide is contraindicated in women with florid hyperthyroidism.

The drug of first choice is propylthiouracil (PTU) (50–100 mg/day). Under treatment, the ft4 value should revert to the upper normal range. Laboratory checks should be repeated every two to four weeks as needed. The liver enzymes should be regularly measured as well, as PTU is hepatotoxic.

The drug of second choice is thiamazole (5–20 mg/day). It should be borne in mind that thiamazole is embryotoxic if given during the first trimester. Approximately 1 in 100 to 1000 exposed children is affected. Some 200 cases of birth defects of various kinds have been reported, including choanal atresia,

Hyperthyroidism

Hyperthyroidism arises in 0.1–1.0% of pregnancies. Its most common cause is Graves disease.

Hyperemesis gravidarum

Very high levels of human chorionic gonadotropin can produce severe, intractable vomiting during pregnancy (hyperemesis gravidarum).

BOX

Individualized recommendations for screening for thyroid diseases during pregnancy (e23)

- **Pregnant women with a history of:**
 - Hypothyroidism
 - Hyperthyroidism
 - Prior postpartum thyroiditis
 - Prior thyroid surgery
 - Thyroid diseases in the family
 - Goiter
 - Infertility
 - Prior spontaneous abortion(s)
 - Prior preterm delivery
- **Pregnant women with:**
 - Known thyroperoxidase antibodies
 - Diabetes mellitus, type I
 - Other autoimmune diseases
 - Prior radiotherapy of the head and neck region
- **pregnant women who are symptomatic:**
 - Manifestations of hypo- or hyperthyroidism (including anemia, hypercholesterolemia, hyponatremia)

tracheo-esophageal fistula, aplasia cutis, hypoplasia of the nipples, and mental retardation; the link between these defects and the specific substance remains unclear. Thiamazole can, however, be given during the second and third trimesters.

Beta-blockers can be given in individual cases to inhibit the conversion of T4 to T3, e.g., propranolol in a dose of 20–40 mg every 6–8 hours. Thyroidectomy is indicated only in exceptional cases of treatment failure or suspected cancer. Radioiodine therapy is contraindicated during pregnancy (22–25).

Breastfeeding is allowed while the mother is taking thyrostatic drugs, as long as they are taken in the following doses:

- PTU, no more than 150 mg/day (first choice);
- Thiamazole, no more than 20 mg/day.

Hypothyroidism—Subclinical hypothyroidism (TSH ≥ 4.0 mU/L) is present in roughly 3% of all pregnancies, and 0.3–0.5% of pregnant women suffer from clinically overt hypothyroidism. In 5.1–12.4% of cases, the cause

is an autoimmune disorder called Hashimoto's thyroiditis (e21, e22). Other causes include atrophic thyroiditis, congenital thyroid aplasia, iatrogenic hypothyroidism (status post thyroidectomy), drugs (thyrostatic agents), and, rarely, hypopituitarism.

The condition is usually recognized and treated before conception. If an increased dose of levothyroxine is needed during pregnancy, it is usually because the dose before conception was already insufficient.

The target value for TSH before conception should be between 2.5 and 4.0 mU/L. Targets ≤ 2.5 mU/L are not absolutely necessary (e24, e25). The euthyroid state is a prerequisite for a normal course of pregnancy. Thyroid hormones are substituted with L-thyroxine at a dose of 1.2–2.0 μg per kilogram of body weight daily, including during the breastfeeding phase. The necessary initiation and titration of treatment must take place before the 8th gestational week, as it has been found that the initiation of treatment between the 8th and 20th gestational week does not result in any improvement of the children's cognitive abilities at age 5 (e26).

Pregnant women with antithyroid antibodies are at elevated risk (up to 40%) of post-partum thyroiditis (PPT). It is therefore recommended that their TSH values should be checked 3 and 6 months after delivery (e27, e28).

Screening for thyroid disease during pregnancy

There have not been any studies indicating the benefit of universal screening for thyroid disease during pregnancy. Situations in which individuals may be advised to undergo testing are listed in the *Box*.

Mode of delivery

Women with thyroid disease can give birth normally. For women with large goiters, a prepartal anesthesiological consultation is recommended in order to determine whether there is any impediment to intubation.

Varicose veins (chronic venous insufficiency)

Varicose veins are a component of the syndrome of chronic venous insufficiency (primary varicosis). They are not an obligatory manifestation of the syndrome. The main symptoms are heavy and tired legs, ankle edema, a feeling of restlessness in the legs, and nocturnal leg cramps. The prevalence of varicosis is 20–30% in primiparae and 50% in multiparae (e29). Obesity markedly increases the tendency of varicose veins to

Graves disease

Pregnant women with a known history of Graves disease must therefore be checked for the presence of antithyroid antibodies in the third trimester of pregnancy as well.

Long-term monitoring

Pregnant women with antithyroid antibodies are at elevated risk of post-partum thyroiditis. Their TSH values should therefore be checked 3 and 6 months after delivery.

become thrombosed. The greater saphenous vein is most commonly affected. Intradermal telangiectasiae are visible on the skin surface; if they are present in a network-like pattern, they are called reticular varices. Varicosis arising after venous thrombosis is called secondary varicosis. Complications of varicosis that can arise during pregnancy include thrombophlebitis, thrombosis, and pulmonary embolism. The risk of thrombosis and pulmonary embolism in pregnancy is 0.2 % (26). Thrombophlebitis is a superficial inflammation of epifascial veins with the secondary development of thromboses. Small, possibly subclinical pulmonary emboli may result. The skin changes that accompany varicosis include stasis dermatitis, induration, white atrophy, and ulcerations.

The following sites of involvement are important in pregnancy because of the possibility of hemorrhagic complications: suprapubic varicosis, varicosis vulvae (differential diagnosis, Klippel-Trenaunay-Weber syndrome), uterine and ovarian varicosis (spontaneous hemoperitoneum!), and hemorrhoids (27–30). The alarm signs for superficial thrombophlebitis include sudden pain and swelling or a persistent “charley-horse” of the legs. Clinical signs of thrombosis that can be seen during pregnancy also include the following:

- Livid discoloration; patchy skin pigmentation; atrophic, tense, and shiny skin
- Pain in the groin, over the adductor canal, in the popliteal fossa, the calf, the ankle, or the sole of the foot
- Calf pain on plantar flexion (Homans sign)
- Pratt’s warning veins (dilated pretibial veins)
- Painful pretibial Meyer pressure points
- Pain in the sole of the foot: Payr sign elicited by simultaneous pressure and plantar flexion.

Any suspicion of thrombosis during pregnancy calls for immediate diagnostic evaluation. No diagnostic algorithm for thrombosis during pregnancy and the postpartum period has yet been tested. Duplex ultrasonography of the femoral and pelvic veins is the diagnostic test of first choice. The D-dimer test cannot be interpreted accurately during pregnancy because of the physiologic rise in D-dimers. Echocardiography additionally enables the detection of pulmonary emboli. Magnetic resonance imaging (MRI) is a further diagnostic alternative during pregnancy. The treatment of deep vein thrombosis (DVT) and/or pulmonary embolism during pregnancy is with low-molecular-weight heparin, which should be given until 6 weeks

postpartum. Vitamin K antagonists are contraindicated during pregnancy. There have not yet been any systematic studies of non-vitamin-K-dependent oral anticoagulants during pregnancy (26).

According to a recent meta-analysis, among women with superficial thrombophlebitis during pregnancy, 18% will develop a deep vein thrombosis and 7% will have a pulmonary embolism (31). For comparison, the overall prevalence of deep vein thrombosis in pregnancy is only 0.08–0.29%, or 1.56% among pregnant women with more than three days of bedrest (32). Obese pregnant women with thrombophlebitis are at particularly high risk. Further risk factors for deep vein thrombosis include maternal age over 35, multiple pregnancy, pre-eclampsia, trauma, emergency cesarean section, and high peripartur blood loss.

No treatment for chronic venous insufficiency is supported by high-level evidence. The most important therapeutic measure is to stabilize the connective tissue from outside with compressive stockings. In addition, mobilization and intermittent positioning of the legs above the torso are recommended.

There is only low-level evidence for various pharmacological and physical treatments to relieve the symptoms of venous insufficiency during pregnancy. These include rutoside, reflex-zone massage, and Kneipp therapy in the form of “alternating showers” (thermal conditioning) (32). The supplementary local application of botanical ointments, including horsechestnut and yarrow extract, may be helpful as well.

Patient education and prevention are important. Pregnant women should not sit for more than one hour at a time without taking a 5–10 minute mobilization break. In the physical therapy department, aquajogging and bicycling in the supine position are indicated. Nicotine, alcohol, hot baths, prolonged sun exposure, leg massages, and long journeys should be prophylactically avoided. Brush massages of the legs promote the development of telangiectasiae.

Horváth et al. (33) recommend the prophylactic treatment of women at high risk with low-molecular-weight heparin (exoxaparin) in a dose of 1 to 1.5 mg/kg body weight, twice per day; the target parameter is an anti-factor-Xa activity of 0.5 four hours after the injection.

For women with marked varicosis vulvae (i.e., varicosis affecting the labia and/or vagina), a cesarean section can be considered in individual cases. However, the risk of thrombosis is markedly higher (by a factor of

Superficial thrombophlebitis

The alarm signs for superficial thrombophlebitis include sudden pain and swelling or a persistent “charley-horse” of the legs.

Risk factors for thrombophlebitis

- Obesity
- Maternal age >35
- Multiple pregnancy
- Pre-eclampsia, trauma, emergency cesarean section, and high peripartur blood loss

5 to 10) in the postpartum period (26). The term “varicosis” refers to the entire syndrome of chronic venous insufficiency. Obese pregnant women with superficial thrombophlebitis are at especially high risk and need thrombosis prophylaxis with low-molecular-weight heparin.

Conflict of interest statement

Prof. Buchmann has received honoraria from Allergan for preparing scientific presentations.

The remaining authors state that they have no conflict of interest.

Manuscript dates

Manuscript received on 24 January 2017; revised version accepted on 31 July 2017.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

1. Kwon HL, Triche EW, Belanger K, Bracken MB: The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006; 26: 29–62.
2. Giles W, Murphy V: Asthma in pregnancy: a review. *Obstet Med* 2013; 6: 58–63.
3. Rey E, Boulet LP: Pregnancy plus: asthma in pregnancy. *BMJ* 2007; 334: 582–5.
4. Bain E, Pierides KL, Clifton VL, et al.: Interventions for managing asthma in pregnancy. *Cochrane Database Syst Rev* 2014; 10: CD010660.
5. Gillissen A, Worth H: Asthma in der Schwangerschaft. *Dtsch Med Wochenschr* 2008; 133: 1977–80.
6. Murphy VE, Schatz M: Asthma in pregnancy: a hit for two. *Eur Respir Rev* 2014; 23: 64–8.
7. Schatz M, Dombrowski MP: Asthma in pregnancy. *N Engl J Med* 2009; 360: 1862–9.
8. Briesse V, Bolz M, Reimer T: Krankheiten in der Schwangerschaft, Handbuch der Diagnosen von A-Z. 2nd edition. Berlin: de Gruyter 2015.
9. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M: Headache and migraine during pregnancy and puerperium: the MIGRA-study. *J Headache Pain* 2011; 12: 443–51.
10. Jamieson DG, Cheng NT, Skliut M: Headache and acute stroke. *Curr Pain Headache Rep* 2014; 18: 444.
11. Kuo CY, Yen MF, Chen LS, et al.: Increased risk of hemorrhagic stroke in patients with migraine: a population-based cohort study. *PLoS One* 2013; 8: e55253.
12. Fox AW, Diamond ML, Spierings EL: Migraine during pregnancy: options for therapy. *CNS Drugs* 2005; 19: 465–81.
13. Airola G, Allais G, Castagnoli Gabellari I, et al.: Non-pharmacological management of migraine during pregnancy. *Neurol Sci* 2010; 31 (Suppl 1): 63–5.
14. Melchart D, Linde K, Fischer P, et al.: Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. *Cephalalgia* 1999; 19: 779–86.
15. Jentink J, Loane MA, Dolk H, et al.: Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 2010; 362: 2185–93.
16. Loder E: Safety of sumatriptan in pregnancy: a review of the data so far. *CNS Drugs* 2003; 17: 1–7.
17. Fitzpatrick DL, Russell MA: Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North* 2010; 37: 173–93.
18. Abalovich M, Amino N, Barbour LA, et al.: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2007; 92: 1–47.
19. Bolz M, Körber S, Schober HC, Briesse V: Schilddrüsenerkrankungen in der Schwangerschaft und im Wochenbett. *Arztebl Mecklenburg-Vorpommern* 2012; 22: 168–73.
20. Collins S, Arulkumaran S, Hayes K, et al.: (Ed.) Oxford Handbook of Obstetrics and Gynecology. (2nd edition) Oxford University Press. 2008; 238.
21. Earl A, Crowther CA, Middleton P: Interventions for hyperthyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013; CD008633.
22. Inoue M, Arata N, Koren G, Ito S: Hyperthyroidism during pregnancy. *Can Fam Physician* 2009; 55: 701–3.
23. Patil-Sisodia K, Mestman JH: Graves hyperthyroidism and pregnancy: a clinical update. *Endocr Pract* 2010; 16: 118–29.
24. Embryotox: Thiamazol. www.embryotox.de/thiamazol.html (last accessed on 5 January 2017).
25. Embryotox: Propylthiouracil. www.embryotox.de/propylthiouracil.html (last accessed on 5 January 2017).
26. S2-Leitlinie Diagnostik und Therapie der Venenthrombose und Lungenembolie, 10.10. 2015, AWMF Leitlinien-Register Nr. 065/002, Klasse S2k) www.awmf.org/leitlinien/detail/II/065-002.html (last accessed on 1 March 2017).
27. Díaz-Murillo R, Tobías-González P, López-Magallón S, Magdaleno-Dans F, Bartha JL: Spontaneous hemoperitoneum due to rupture of uterine varicose veins during labor successfully treated by percutaneous embolization. *Case Rep Obstet Gynecol* 2014; 2014: 580384.
28. Haynes MC, Lu BY, Winkel AF: Ovarian vein thrombophlebitis related to large uterine myoma. *Obstet Gynecol* 2014; 123(2 Pt 2 Suppl 2): 450–3.
29. Kawata E, Kondoh E, Kawasaki K, et al.: Utero-ovarian varices and absent inferior vena cava in pregnancy. *J Obstet Gynaecol Res* 2015; 41: 631–4.
30. Yara N, Masamoto H, Ibrah Y, et al.: Diffuse venous malformation of the uterus in a pregnant woman with Klippel-Trénaunay Syndrome diagnosed by DCE-MRI. *Case Rep Obstet Gynecol* 2016; 2016: 4328450.
31. Di Minno MN, Ambrosino P, Ambrosini F, Tremoli E, Di Minno G, Dentali F: Prevalence of deep vein thrombosis and pulmonary embolism in patients with superficial vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost* 2016; 14: 964–72.
32. Smyth RM, Aflaifel N, Bamigboye AA: Interventions for varicose veins and leg oedema in pregnancy. *Cochrane Database Syst Rev* 2015; 10: CD001066.
33. Horváth B, Skrapits J, Bódis J: Obstetrical management of an extremely overweight pregnant woman (184kg bw) with special attention on thromboprophylaxis. *Case Rep Obstet Gynecol* 2013; 2013: 689549.

Corresponding author

Dr. med. Michael Bolz
Universitätsfrauenklinik, Klinikum Südstadt Rostock
Südring 81, D-18059 Rostock, Germany
michael.bolz@klinikusued-rostock.de

Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref3717

Thrombosis prevention

Patient education and prevention are important.
Pregnant women should not sit for more than one hour at a time without taking a 5–10 minute mobilization break.

FURTHER INFORMATION ON CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education. Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (Länder). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire. See the following website: cme.aerzteblatt.de

Participants in the CME program can manage their CME points with their 15-digit "uniform CME number" (einheitliche Fortbildungsnummer, EFN). The EFN must be entered in the appropriate field in the cme.aerzteblatt.de website under "meine Daten" ("my data"), or upon registration. The EFN appears on each participant's CME certificate.

This CME unit can be accessed until 10 December 2017, and earlier CME units until the dates indicated:

- "Cystic Fibrosis" (issue 33–34/17) until 12 November 2017,
- "Ileus in Adults" (issue 29–30/17) until 15 October 2017,
- "Latent Hypothyroidism in Adults" (issue 25/17) until 17 September 2017.

CLINICAL SNAPSHOT

Multiple Organ Failure in a Young Asylum-Seeker

A 24-year-old Somali asylum-seeker was admitted via the emergency room with high fever and multiple organ failure. The laboratory findings were indicative of a severe acute infection, acute renal failure, and disseminated intravascular coagulopathy. The diagnosis of louse-borne relapsing fever, caused by *Borrelia recurrentis* in the setting of infestation with *Pediculus humanus humanus*, was made microscopically with a blood smear/thick-drop preparation, and on the molecular level by PCR. Pappenheim staining enabled the visualization of multiple spirochetal (screw- or spiral-shaped) bacteria. Relapsing fever borne by body lice has become more common recently in the setting of the current wave of immigration to Germany. Patients present with attacks of high fever, and the diagnosis is made based on a blood smear obtained during a fever spike. Doxycycline is the antibiotic of choice; treatment with this drug, however, can lead to life-threatening immune-mediated side effects (the Jarisch-Herxheimer reaction). The direct or indirect demonstration of *Borrelia*

recurrentis is reportable. Our patient developed acute respiratory distress syndrome (ARDS) and required artificial ventilation because of a Jarisch-Herxheimer reaction, but was extubated within a week and was able to leave the intensive care unit in stable condition.

Dr. med. Mathias Schmid, Prof. Dr. med. Christoph Dodt, Klinikum Bogenhausen, München, mathias.schmid@klinikum-muenchen.de

Conflict of interest statement

The authors state that they have no conflict of interest.

Translated from the original German by Ethan Taub, M.D.

Cite this as:

Schmid M, Dodt C: Multiple organ failure in a young asylum-seeker. Dtsch Arztebl Int 2017; 114: 625. DOI: 10.3238/arztebl.2017.0625

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the most appropriate answer.

Question 1

Pregnant women with chronic asthma are at increased risk of which of the following?

- a) Intrauterine growth retardation
- b) Postmature birth
- c) Umbilical cord prolapse
- d) Breech presentation
- e) Multiple pregnancy

Question 2

Which of the following should not be given to women in Germany who have asthma and are in labor, because it is not approved for this purpose?

- a) Oxytocin
- b) Prostaglandin F₂alpha
- c) Prostaglandin E₁
- d) Prostaglandin E₂
- e) Peridural anesthesia

Question 3

Which of the following is a leading manifestation of migraine?

- a) Syncope with eclampsia
- b) Spontaneous absence seizures
- c) Predominant occurrence during sleep
- d) Recurrent bouts of intense headache lasting 4–72 hours
- e) Spontaneous attacks of ptosis recurring over many months

Question 4

What disease is a differential diagnosis to be ruled out in a woman who has migraine during pregnancy?

- a) Hypotension
- b) Diabetes mellitus type 1
- c) Dysarthria
- d) Depression
- e) Pre-eclampsia

Question 5

What diagnostic test for thyroid disease is contra-indicated during pregnancy and breastfeeding?

- a) Measurement of the serum TSH level
- b) Ultrasonography
- c) Color-Doppler ultrasonography
- d) Thyroid scintigraphy
- e) Fine-needle biopsy

Question 6

A 25-year-old woman is admitted to the hospital in the 13th week of gestation with hyperemesis gravidarum, a 2-kg weight loss, and marked circulatory disturbances. The following laboratory results are obtained: TSH 0.05, fT₄ and fT₃ in the upper range of normal, TRAK and TPO negative.

What is the correct diagnosis?

- a) Hypothyroidism
- b) Graves disease
- c) Hashimoto's thyroiditis
- d) Symptomatic goiter
- e) HCG-triggered hyperthyroidism of pregnancy

Question 7

Untreated maternal hyperthyroidism during pregnancy increases the risk for which of the following in the mother?

- a) Hypotension
- b) Increased weight gain
- c) Postmature birth
- d) Pre-eclampsia
- e) Delivery of an infant with macrosomia

Question 8

What is the risk of postpartal thyroiditis in a pregnant woman who is positive for anti-TPO antibodies?

- a) Up to 5%
- b) Up to 10%
- c) Up to 25%
- d) Up to 40%
- e) Up to 65%

Question 9

For what type of varicosis should a primary cesarean section be considered, on an individual basis?

- a) Superficial thrombophlebitis
- b) Extreme varicosis vulvae
- c) Reticular varices
- d) Varicosis after thrombosis
- e) Suprapubic varicosis

Question 10

Which of the following is an absolute indication for thrombosis prophylaxis with low-molecular-weight heparin during pregnancy?

- a) Varicosis in the third trimester
- b) Varicosis in the first trimester
- c) Obesity plus superficial thrombophlebitis
- d) Intradermal telangiectasiae
- e) Suprapubic varicosis

Additional material for:

The Treatment of Illnesses Arising in Pregnancy

Michael Bolz, Sabine Körber, Toralf Reimer, Johannes Buchmann, Hans-Christof Schober, and Volker Bries

Dtsch Arztebl Int 2017; 114: 616–26. DOI: 10.3238/arztebl.2017.0616

eREFERENCES

- e1. Schaefer C: Medikamentöse Therapie in Schwangerschaft und Stillzeit – aktueller Kenntnisstand und Empfehlungen. Frauenheilkunde up2date 2015; 9: 2–8.
- e2. Murphy VE, Namazy JA, Powell H, et al.: A meta-analysis of adverse perinatal outcomes in women with asthma. BJOG 2011; 118: 1314–23.
- e3. Murphy VE, Wang G, Namazy JA, et al.: The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. BJOG 2013; 120: 812–22.
- e4. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M: Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. Eur Respir J 2013; 41: 1082–90.
- e5. Wang G, Murphy VE, Namazy J, et al.: The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2014; 27: 934–42.
- e6. Powell H, Murphy VE, Taylor DR, et al.: Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomized controlled trial. Lancet 2011; 378: 983–90.
- e7. Lim AS, Stewart K, Abramson MJ, Walker SP, Smith CL, George J: Multidisciplinary approach to management of maternal asthma (MAMMA): a randomized controlled trial. Chest 2014; 145: 1046–54.
- e8. Eltonsy S, Kettani FZ, Blais L: Beta2-agonists use during pregnancy and perinatal outcomes: a systematic review. Resp Med 2014; 108: 9–33.
- e9. Etwel F, Faught LH, Rieder MJ, Koren G: The risk of adverse pregnancy outcome after first trimester exposure to H1 antihistamines: a systematic review and meta-analysis. Drug Saf 2017; 40: 121–32.
- e10. Namazy JA, Schatz M: The treatment of allergic respiratory disease during pregnancy. J Investig Allergol Clin Immunol 2016; 26: 1–7.
- e11. Schatz M, Harden K, Forsythe A, et al.: The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988; 81: 509–17.
- e12. Deutsche Migräne- und Kopfschmerzgesellschaft (DMKG), Deutsche Gesellschaft für Neurologie (DGN), der Berufsverband der Neurologen (BDN), die Deutsche Gesellschaft für Psychologische Schmerztherapie und –Forschung (DGPSF), die Österreichische Kopfschmerzgesellschaft (ÖKSG) und die Schweizer Kopfwehgesellschaft (SKG): Gemeinsame S1-Leitlinie: Kopfschmerz bei Übergebrauch von Schmerz- und Migränemitteln. www.dmgk.de/files/dmgk.de/Empfehlungen/Leitlinie_Kopfschmerz_Medikamentenuebergebrauch_2012.pdf (last accessed on 24 August 2017).
- e13. Bries V, Bolz M, Reimer T: Krankheiten in der Schwangerschaft. Handbuch der Diagnosen von A–Z. Berlin, Boston 2010: De Gruyter.
- e14. Gaul C: Migräne: Diagnose, Therapie, Prophylaxe. Frauenarzt 2015; 56: 132–7.
- e15. Embryotox: Valproinsäure. www.embryotox.de/valproinsaeure.html, (last accessed on 18 December 2016).
- e16. Silberstein SD: Topiramate in migraine prevention: A 2016 perspective headache 2017; 57: 165–78.
- e17. Evers S, Weatherall M, Jefferies S, Beasley R: Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy 2011; 41: 482–9.
- e18. Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J: Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol 2016; 45: 2009–17.
- e19. Sheehan PM, Nankervis A, Araujo Junior E, et al.: Maternal thyroid disease and preterm birth: systematic review and meta-analysis. J Clin Endocrinol and Metab 2015; 100: 4325–31.
- e20. Andersen SL, Olsen J, Laurberg P: Hypothyroidism and pregnancy loss: comparison with hyperthyroidism and diabetes in a Danish population based study. Clin Endocrinol 2016; 85: 962–70.
- e21. Springer D, Jiskra J, Limanova Z, et al.: Thyroid in pregnancy: from physiology to screening. Crit Rev Clin Lab 2017; 54: 102–16.
- e22. Führer D: Schilddrüsenerkrankungen und Schwangerschaft. Internist 2011; 52: 1158–66.
- e23. Stagnaro-Green A: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21: 1081–125.
- e24. Cai YY, Zhong L, Guan J, et al.: Outcome of in vitro fertilization in women with subclinical hypothyroidism. Reprod Biol Endocrinol 2017; 15: 39.
- e25. Plowden TC, Schisterman EF, Sjaarda LA, et al.: Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss, or live birth. J Clin Endocrinol Metab 2016; 101: 2358–65.
- e26. Casey BM, Thom EA, Peaceman AM, et al.: Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med 2017; 376: 815–25.
- e27. Argatska A, Nonchev B, Orbetzova M, et al.: Postpartum thyroid dysfunction in women with autoimmune thyroiditis. Gynecol Endocrinol 2016; 32: 379–82.
- e28. Heufelder AE, Hofbauer LC: Die Thyreotiden. Dtsch Arztebl 1998; 95: A-466–76.
- e29. Dindelli M, Basellini A, Rabaiotti E, et al.: Epidemiological analysis of the incidence of varicose pathology in pregnancy. Ann Obstet Gynecol Med Perinat 1990; 111: 257–64.