CME CREDIT *EDUCATIONAL OBJECTIVE:* To review the possible causes of dyspnea in a young pregnant woman

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A young pregnant woman with shortness of breath

A 21-YEAR-OLD WOMAN who is 12 weeks pregnant according to the date of her last menstrual period comes to the emergency department with shortness of breath and chest pain.

One week ago she began experiencing presyncope and shortness of breath on minimal exertion and then even at rest on most days. The shortness of breath worsened throughout the week, eventually limiting her daily activities to such a degree that she restricted herself to bed rest.

Her chest pain started today while she was sitting in church, without any apparent provocation. It is right-sided, sharp, and focal, and it does not radiate. At the same time, her shortness of breath was more severe than before, so she immediately came to the emergency department.

So far, she has had no prenatal care, and has lost 20 pounds due to nausea

This is her third pregnancy; she has had one live birth and one abortion. Her last pregnancy was full-term, with routine prenatal care and no complications. However, so far during this pregnancy, she has had no prenatal care, she has not taken prenatal vitamins, and she has been unable to maintain adequate nutrition because of persistent emesis, which began early in her pregnancy and continues to occur as often as two or three times daily. She has lost 20 pounds over the past 12 weeks.

She says she has no close contacts who are sick, and she has had no fever, diarrhea, dysuria, urinary frequency or urgency, palpitations, swelling of the legs or feet, blurry vision, or increase in neck girth. She says she does not smoke or use alcohol or illicit substances. Her only previous surgery was laser-assisted in situ keratoplasty (LASIK) eye surgery in 1998. She is allergic to seafood only. She has not eaten at any new places recently. She is up to date with her childhood vaccinations. She has no family history of hypercoagulability or venous thrombotic events.

PHYSICAL EXAMINATION

She is breathing rapidly—as fast as 45 breaths per minute. Her temperature is 37.2°C (98.9°F), blood pressure 95/60 mm Hg, oxygen saturation 100% while on 10 L of oxygen using a nonrebreather mask, pulse 102 beats per minute, and weight 55.9 kg (123.2 pounds). She appears alert, oriented, and comfortable, with a thin body habitus. She has no jugular venous distention, neck mass, or thyromegaly. Her lungs are clear to auscultation, with no wheezes or rales. The cardiovascular examination is normal. She has a regular heart rate and rhythm, normal S1 and S2 sounds, and no rubs, clicks, or murmurs. Pulses in the extremities are normal, and she has no peripheral edema. The neurologic examination is normal.

Electrocardiography shows sinus tachycardia with first-degree atrioventricular block.

DIFFERENTIAL DIAGNOSIS

1 At this point, which is the most probable cause of her symptoms?

- ☐ Pulmonary embolism
- ☐ Peripartum cardiomyopathy
- ☐ Acute coronary syndrome
- ☐ Aortic dissection
- ☐ Expected physiologic changes of pregnancy

Pulmonary embolism would be the most probable diagnosis, given the patient's pregnancy, shortness of breath, and tachycardia and the pleuritic quality of her chest pain.

Peripartum cardiomyopathy is also a possible cause, as it may present with profound shortness of breath and markedly decreased cardiac function. But it is much less likely in this patient because she is early in her pregnancy, and peripartum cardiomyopathy usually is seen during the last month of gestation or the first months after delivery.

Acute coronary syndrome is unlikely, given her young age and the lack of significant risk factors or a supporting history.

Aortic dissection is unlikely in view of her medical history.

Physiologic changes of pregnancy. Many pregnant women experience a sensation of not being able to catch their breath or expand their lungs fully, as the diaphragm is limited by the gravid abdomen. They also present with dyspnea, fatigue, reduced exercise capacity, peripheral edema, or volume overload.[1] However, these changes tend to occur gradually and worsen over time. This patient's degree of shortness of breath and its sudden onset do not seem like normal physiologic changes of pregnancy.

Other possible causes of dyspnea in a pregnant woman include asthma, pleural empyema, pneumonia, and severe anemia. Asthma should be considered in anyone with a history of wheezing, cough, and dyspnea. Fever and sputum production would support a diagnosis of pneumonia or empyema. In addition, maternal heart disease (eg, endocarditis, pulmonary hypertension) complicates 0.2% to 3% of pregnancies.[1]

CASE CONTINUED

The emergency department staff decide to evaluate the patient for heart failure and pulmonary embolism.

Bedside echocardiography reveals an ejection fraction of 55% (normal range 50%–75%), normal heart function and size, and no valvular abnormalities.

Chest radiography is normal.

Lower-extremity duplex ultrasonography is negative for deep-vein thrombosis.

The D-dimer level is 380 ng/mL (normal range < 500 ng/mL).

The medical intensive care unit is consulted about the patient's continued tachypnea and the possible need for intubation. A ventilation-perfusion scan is performed to screen for pulmonary embolism, and it is negative.

An obstetric team performs Doppler ultrasonography at the bedside; a fetal heartbeat can be heard, thus confirming a viable pregnancy.

The patient has normal serum levels of the cardiac enzymes troponin T and creatine kinase-MB fraction, thus all but ruling out myocardial ischemia.

The patient is admitted to the hospital the next day, and a cardiology consult is obtained.

RULING OUT PULMONARY EMBOLISM

2 Has pulmonary embolism been definitively ruled out at this point?

☐ Yes
☐ No

The answer is no. The negative ventilation-perfusion scan and normal D-dimer test in this patient are not enough to rule out pulmonary embolism. The diagnosis of pulmonary embolism should be based on the clinician's estimation of the pretest probability of pulmonary embolism (which is based on presenting signs and symptoms), as well as on a variety of tests, including spiral computed tomography (CT), ventilation-perfusion lung scanning, and serum D-dimer testing. Signs and symptoms that may guide the clinician are chest pain (present in 70% of patients with pulmonary embolism), tachypnea (70%), cough (40%), shortness of breath (25%), and tachycardia (33%).[2] A history of pregnancy, malignancy, immobility, or recent surgery may also increase the pretest probability of pulmonary embolism. In many cases, one's clinical suspicion is highly predictive and is useful in diagnosing pulmonary embolism.

She is pregnant, dyspneic, tachycardic, and has pleuritic chest pain

The accuracy of the tests varies widely, depending on the pretest probability of pulmonary embolism. For instance, in a patient with a high pretest probability but a low-probability ventilation-perfusion scan, the true probability of pulmonary embolism is 40%, but in a patient with a low pretest probability and a low-probability scan, the probability is only 4%.

TABLE 1

The patient's initial laboratory values

TEST	VALUE	REFERENCE RANGE
Arterial blood gases		
pH	7.63	7.35–7.45
Pco_2	13 mm Hg	34–46
Pao_2	199 mm Hg	85–95
Basic metabolic panel		
Calcium	9.9 mg/dL	8.5–10.5
Carbon dioxide	23 mmol/L	(23–32)
Creatinine	0.5 mg/dL	0.70–1.40
Glucose	81 mg/dL	65–100
Potassium	4.4 mmol/L	3.5–5.0
Sodium	136 mmol/L	132–148
Blood counts		
Hemoglobin	9.9 g/dL	12.0–16.0
Mean corpuscular volume	74.1 fL	80–100
Platelet count	279×10^9/L	150–400
White blood cell count	8.13×10^9/L	4.0–11.0
Liver function tests		
Alanine aminotransferase	23 U/L	≤ 48
Albumin	3.9 g/dL	3.5–5.0
Thyroid studies		
T_3	314 ng/dL	94–170
T_4 (free)	2.7 ng/dL	0.7–1.8
TSH	0.008 µU/mL	0.400–5.500
Other tests		
Beta-hCG [a]	279,973 IU/L	5,000–200,000 at 10–12 weeks of gestation
Creatine kinase	55 U/L	30–220
INR	0.9	
Activated PTT	27.9 sec	24.4–31.7
Troponin T	< 0.01 ng/mL	0.0–0.10

hCG = human chorionic gonadotropin; INR = international normalized ratio; T_3 = triiodothyronine ; T_4 = thyroxine; PTT = partial thromboplastin time

[a] Quantitative serum intact and free beta-hCG

The Wells criteria can be used to calculate the pretest probability of pulmonary embolism. Given this patient's tachycardia and clinical presentation, her pretest probability according to the Wells criteria indicates increased risk. However, because her D-dimer test, lower-extremity Doppler test, and ventilation-perfusion scan were normal, pulmonary embolism is less likely.[3]

However, if one's clinical suspicion is high enough, further investigation of pulmonary embolism would proceed despite the encouraging test results.

CASE CONTINUED

Our patient's initial laboratory test results are listed in TABLE 1.

The cardiology consult team notes that her beta human chorionic gonadotropin (beta-hCG) level is much higher than would be expected at 12 weeks of pregnancy, and so they are concerned about the possibility of a molar pregnancy. In addition, her level of thyroid-stimulating hormone (TSH, or thyrotropin) is markedly low.

HYPERTHYROIDISM IN PREGNANCY

3 Which of the following would *not* explain this patient's markedly low TSH level?

- ☐ Graves disease
- ☐ Molar pregnancy
- ☐ TSH-secreting pituitary adenoma
- ☐ Gestational transient thyrotoxicosis
- ☐ Twin pregnancy

Hyperthyroidism (also called thyrotoxicosis) has many causes, including but not limited to Graves disease, pituitary adenoma, struma ovarii (teratoma), hCG-secreting hydatidiform mole, and thyroid carcinoma (which is rare).[4] In most of these disorders, the TSH level is low while the levels of thyroxine (T_4), triiodothyronine (T_3), or both are high.

Symptoms of hyperthyroidism are the effect of elevated T_4 and T_3 levels on the target organs themselves. Common symptoms include fever, tachycardia, tremor, stare, sweating, and lid lag. Other symptoms include nervousness, delirium, hypersensitivity to heat, flushing, palpitations, fatigue, weight loss, dyspnea, weakness, increased appetite, swelling of the legs, nausea, vomiting, diarrhea, goiter, tremor, atrial fibrillation, and cardiac failure.[4] In its extreme form, called thyroid storm, thyrotoxicosis can be life-threatening. The likelihood of an impending thyroid storm can be assessed by clinical variables such as the patient's temperature and heart rate and whether he or she has heart failure or gastrointestinal manifestations.[5]

Graves disease, the most common cause of hyperthyroidism in pregnancy, is due to stimulation of TSH receptors by antibodies against these receptors. Graves disease is possible in this patient, but a subsequent TSH receptor antibody test is negative.

Pituitary adenomas are one of the few causes of hyperthyroidism in which the TSH level is high, not low. Therefore, this is the correct answer.

Gestational transient thyrotoxicosis is a nonautoimmune condition that results in transient hyperthyroidism of variable severity.[6] Usually, it occurs in otherwise normal pregnancies without complications, but the initial manifestation is hyperemesis.[6] It can be differentiated from Graves disease by the absence of TSH receptor antibodies and by no history of thyroid disorder.[7] Common symptoms of gestational transient thyrotoxicosis include weight loss (or failure to gain weight), tachycardia, and fatigue.

The reason for the transient rise in T_4 may be that beta-hCG is structurally similar to TSH (and also to luteinizing hormone and follicle-stimulating hormone), so that it has mild thyroid-stimulating effects.[7] Sustained high levels of beta-hCG may in time give rise to the manifestations of thyrotoxicosis.

Molar pregnancy also can cause hyperthyroidism via elevated levels of beta-hCG. However, **twin pregnancy** is more common and can produce sustained levels of beta-hCG above 100,000 IU/L. In most cases of twin pregnancy, the TSH level is decreased and the T_4 level transiently elevated.[6] The elevated beta-hCG and the subsequent thyrotropic manifestations are thought to be directly related, and symptoms resolve when beta-hCG levels go down.[6]

In most cases of hyperthyroidism in pregnancy, the acute condition can be managed by a short (≤ 2-month) course of a beta-blocker. In rare cases, propylthiouracil treatment may be required. Gestational transient thyrotoxicosis is not associated with detrimental outcomes.

Case continued

Our patient's TSH level is low and her free T_4 and T_3 levels are elevated. Her high beta-hCG level may be stimulating the thyroid gland and may account for the low TSH value, as well as for her tachycardia, emesis, shortness of breath, and weight loss.

After an obstetric consult, it is determined that our patient has a viable pregnancy. However, further investigation with transvaginal ultrasonography reveals that she has two viable, single-placenta, intrauterine gestations, separated by a thin chorionic membrane.

Beta-hCG and free T_4 levels are significantly higher in twin pregnancies than in single pregnancies, especially in the early stages.[6] In our patient, the twin pregnancy led to the elevated beta-hCG, which eventually manifested as thyrotoxicosis, which caused the shortness of breath, hyperemesis, weight loss, tachycardia, and nausea.

Shortness of breath in patients with thyrotoxicosis is well recognized but not well explained. It may be caused by decreased lung compliance, engorged capillaries in the lung, or left ventricular failure, as well as by chest pain due to increased myocardial demand or coronary artery vasospasm.[4] The dyspnea is present at rest and during exertion, and the high metabolic rate is thought to lead to an inappropriate response of the ventilatory system.[3,8]

The hCG is high for her pregnancy date: molar pregnancy?

WHAT TREATMENT?

4 How would you treat this patient at this point?

- ☐ No drug therapy, just supportive care
- ☐ Propranolol (Inderal)
- ☐ Levothyroxine
- ☐ Propylthiouracil

Several types of drugs are used to manage hyperthyroidism.

Antithyroid drugs such as propylthiouracil, methimazole (Northyx, Tapazole), and carbimazole block thyroid hormone synthesis by inhibiting thyroid peroxidase. Propylthiouracil also blocks peripheral conversion of T_4 to T_3. Side effects of these agents include abnormal sense of taste, pruritus, urticaria, agranulocytosis, and hepatotoxicity.[4]

Usually, hyperthyroidism is treated with propylthiouracil at the smallest effective dose. This has been proven to be safe to the fetus and mother during pregnancy.[9] Propylthioura-

cil and the other drugs in its class cross the placenta, but propylthiouracil crosses at one-quarter the rate of the other two.[9]

Beta-blockers are effective in the acute phase of thyrotoxicosis against tachycardia, hypertension, and atrial fibrillation. They also decrease conversion of T_4 to T_3, which is an added benefit. Beta-blockers can be tapered as thyroid hormone levels decrease.

A short course of a short-acting beta-blocker would be an option for our patient and would decrease her symptoms, although she does not have the typical markedly elevated T_4 or T_3 levels. In the long term, a beta-blocker would present a fetal risk, but short courses can be tolerated without incident.[9]

Radioactive iodine 131 is used in patients with Graves disease. ^{131}Iodine therapy is safe for most adults, but in pregnancy its use is contraindicated. Fetal thyroid tissue is thought to be present after 10 weeks of gestation and could be damaged by the use of radioactive iodine. Another warning with the use of radioactive iodine is that patients should avoid close contact with other adults for a few days after treatment, and should avoid close contact with children and pregnant women for 2 to 3 weeks after treatment because of the risk of exposure to radiation emanating from the thyroid gland.

Levothyroxine is a treatment for hypothyroidism, not hyperthyroidism.

CASE CONTINUED

Our patient is treated with propranolol and monitored for several days in the hospital, during which her symptoms markedly improve. She is discharged without complications.

TAKE-HOME POINTS

The evaluation of shortness of breath in adult patients can be difficult, given the many possible causes. It is especially challenging in pregnant patients, since normal physiologic changes of pregnancy may produce these symptoms.

In many instances, cardiomyopathy must be suspected if a pregnant patient complains of shortness of breath. However, it is not the only possible cause.

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