CASE REPORT

Pulmonary hypertension in a pregnant patient with thyrotoxicosis due to Graves' disease: considerations with respect to treatment

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SUMMARY

A 13 weeks pregnant 24-year-old patient with a history of Graves' disease presented with progressive dyspnoea existing for 4–6 weeks. Blood tests showed severe thyrotoxicosis and transthoracic echocardiography suggested severe pulmonary hypertension (PH) which was thought to be secondary to thyrotoxicosis. PH secondary to thyrotoxicosis is often reversible and may occur 3–14 months after normalisation of free T4 and T3 levels. The maternal mortality risk of PH in pregnancy is high despite modern treatment strategies (17–33%). In this case, PH was carefully monitored for 1 month. No changes in pulmonary artery pressure were found despite immediate treatment with propylthiouracil and β-blockade. We anticipated that the normalisation of pulmonary artery pressure would not occur during this pregnancy and that the risk of complications would remain high. In the interest of the mother an abortion was suggested. Termination of pregnancy took place at the gestational age of 16 weeks.

BACKGROUND

Pulmonary hypertension (PH) in pregnancy is associated with a high maternal mortality and morbidity risk. For this reason termination of pregnancy should be considered.[1] PH secondary to thyrotoxicosis is often reversible after normalisation of free T4 and T3 levels but it is not known when this can be expected (probably 3–14 months).[2–5] Therefore it is uncertain whether the risk of mortality in pregnant women with PH due to thyrotoxicosis remains high after adequate thyroid treatment is started. We report a case of PH in a 13-week pregnant patient admitted with thyrotoxicosis due to Graves' disease and the considerations with respect to continuation or termination of the pregnancy.

CASE PRESENTATION

A 24-year-old primiparous woman with a history of Graves' disease presented with progressive dyspnoea on exertion and a non-productive cough since 4–6 weeks. She also experienced palpitations and a sharp chest pain without radiation. She had stopped using thiamazol and levothyroxin on her own accord 6 weeks before because of a suspected pregnancy.

On examination the patient was dyspnoeic at rest, with a normal oxygen saturation, blood pressure 145/70 mm Hg and a tachycardia 110–120 bpm. Exophthalmos of the left eye was present. The jugular venous pressure was increased. Cardiac auscultation revealed a holosystolic murmur grade II/VI at the apex and an early crescendo–decrescendo systolic murmur at the left parasternal border. Pulmonary auscultation did not reveal rales or crackles. The extremities showed no signs of deep venous thrombosis or oedema.

INVESTIGATIONS

Blood analysis showed microcytic anaemia with a haemoglobin 6.2 mmol/L, no signs of inflammation and a severe hyperthyroidism due to Graves' disease with a thyroid-stimulating hormone (TSH) <0.01 mIU/L and fT4 >100 pmol/L, T3 >10 nmol/L, antithyrotropin TSH-binding inhibitor immunoglobulin receptor 16.0 IU/L (anti-TSH receptor fast ELISA (Biognost)).

The ECG showed a sinus tachycardia (115 bpm) with normal heart axis, conduction times and repolarisation. There were no signs of left ventricular hypertrophy or right ventricular strain.

A chest X-ray showed slight cardiomegaly. Transthoracic echocardiography (TTE) showed a dilated right ventricle with a normal systolic function. Estimation of the pulmonary artery pressure suggested severe PH with an expected systolic pressure of 63 mm Hg. The vena cava inferior was dilated and non-collapsing (29 mm). There was a mild mitral regurgitation grade II and no atrial septal defect was found.

The gestational age was determined at 12 weeks and 6 days by ultrasound.

DIFFERENTIAL DIAGNOSIS

Thyrotoxicosis as a result of non-treated Graves' disease was diagnosed.

Dyspnoea, palpitations and chest pain are often reported in hyperthyroidism but given the right ventricular overload and increased pulmonary artery pressure the following differentials were considered:

- Pulmonary embolism; especially since the patient was pregnant;
- PH secondary to thyrotoxicosis;
- Restrictive pulmonary disease caused by pulmonary parenchymal disease;
- HIV infection.

Doppler examination of both lower limbs and a thoracic CT angiography did not show deep venous thrombosis or pulmonary embolism, respectively. There was no pulmonary parenchymal disease. The patient was tested negative for HIV. Therefore, the diagnosis in this case was thyrotoxicosis in Graves' disease with secondary PH in a 13-week pregnant patient.

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OUTCOME AND FOLLOW-UP

Immediate treatment with metoprolol and propylthiouracil (PTU) (100 mg three times a day) was initiated. After 1 week the fT4 decreased to 38 pmol/L. From then on fT4 levels decreased only mildly to 27 pmol/L 1 month after admission. Follow-up by TTE did not show significant changes in estimated systolic pulmonary artery pressure.

The patient was informed about the increased maternal mortality risks due to persisting PH and was counseled to consider an abortion after PH was confirmed by invasive measurements. She refused to undergo a right heart catheterisation but expressed a consistent request to terminate the pregnancy. At 16 weeks of gestation an abortion was induced. At discharge thiamazol and levothyroxin were prescribed instead of PTU, metoprolol was continued.

In follow-up with TTE after 3 months of treatment the pulmonary artery pressure remained high.

DISCUSSION

Graves' hyperthyroidism complicates 1 in 500 pregnancies and tends to enter remission as pregnancy proceeds. Serum concentration of free T4 normalises usually after 8–12 weeks of adequate treatment.[6] In the first trimester of pregnancy treatment with PTU is advised because of the teratogenous effect of thionamides, methimazole and carbimazole. Treatment with PTU is associated with hepatotoxicity in both the mother and child, therefore switching to methimazole after the first trimester is advised.[7]

PH is increasingly found in thyrotoxicosis, both in Graves' disease as in nodular goiter. The underlying mechanism causing PH in thyrotoxicosis is still uncertain but may include:

1. Immune-mediated endothelial damage or dysfunction;
2. Endothelial injury as a result of increased cardiac output;
3. Increased metabolism of intrinsic pulmonary vasodilator substances.[2–5]

Pregnancy is associated with increased plasma volume and decreased systemic vascular resistance just like thyrotoxicosis and may therefore possibly add to the development of PH in thyrotoxicosis. The occurrence of thyrotoxicosis-related PH in pregnant women has not been described before though.

It has been reported that PH can be (partly) reversible after restoration to a euthyroid state. The exact time for PH to normalise is uncertain but it has been described after 3–14 months.[2 3 5]

The majority of maternal deaths in PH occur either during labour and delivery or within 1 month postpartum. At that time there is an increased risk of thromboembolic events, of a pulmonary hypertensive crisis. Owing to the additional haemodynamic changes resulting from pregnancy and delivery there is also an increased risk of right heart failure.

Maternal mortality is not related to the severity of PH. This disables the use of an acceptable pulmonary pressure.[8 9] A significantly higher maternal mortality was described between 1978 and 1996 in women with other forms of PH than in idiopathic or congenital PH (respectively 56%, 30% and 36%) but later studies do not support this finding.

Over the years maternal mortality rates in pregnant women with idiopathic, congenital and other forms of PH have improved. Still pregnancy carries a high mortality risk (30–50% between 1978 and 1996 and 17–33% between 1997 and 2007).

With the use of a standardised and multidisciplinary approach, calcium blockers, intravenous prostanoids and endothelin receptor antagonists after delivery, some pregnancies have been successfully managed in highly selected patients with well-controlled PH and normal or near-normal haemodynamics.[1 8 10–12] Since little is reported on the use of these new advanced therapies in thyroid disease-related PH they were not applied in our case.

Even though fT4 levels were decreasing in our patient after treatment with PTU and metoprolol started, pulmonary artery pressure did not change. Given the persistent not well-controlled, PH at 16 weeks of pregnancy it was anticipated that normalisation of pulmonary artery pressure would not occur during this pregnancy and that the risk of complications was high. Since the time window for legal and safe abortion was small, abortion was performed at the request of the mother. The fact that PH persisted even after 3 months of treatment supports this decision in retrospect. Perhaps with a higher initial dose of PTU (300–200 mg three times a day) thyrotoxicosis might have been controlled earlier but with an increased risk of hepatotoxicity for the mother and child.

This case shows the importance of early recognition of thyrotoxicosis and PH in pregnancy. With immediate initiation of treatment it is possible that a euthyroid state and normalisation of pulmonary artery pressure are reached before they form a threat to the safety of the mother in the third trimester.

A multidisciplinary team of obstetrics, pulmonologists and cardiologists should be involved in the treatment of pregnant thyrotoxic patients with PH. Since the exact course of PH in this specific group is unknown an individual approach with close monitoring of fT4 levels, PH and the safety of the mother is recommended.

Learning points

- Treatment for Graves' disease should not be interrupted because of pregnancy since it can result in a relapse and new thyrotoxicosis.
- Thyrotoxicosis is associated with pulmonary hypertension (PH). After normalisation of fT4 levels, PH can resolve.
- Although pregnancies have been successfully managed in selected patients with PH it still carries a high maternal mortality risk despite modern treatment strategies.
- With an early diagnosis of PH and adequate treatment of thyrotoxicosis in pregnancy, PH may normalise in time before questions about the safety of pursuing the pregnancy arise and abortion should be considered.
- A multidisciplinary team of obstetrics, pulmonologists and cardiologists should be involved in the treatment of pregnant thyrotoxic patients with PH, and close monitoring of fT4 levels, PH and the safety of the mother is recommended.

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REFERENCES

1 Regitz-Zagrsek V, Blomstrom Lundqvist C, Borghi C, *et al*. ESC guideline on the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2011;32:3147–97.

2 Nakchbandi IA, Wirth JA, Inzucchi SE. Pulmonary hypertension caused by Graves' thyrotoxicosis: normal pulmonary hemodynamics restored by (131)I treatment. *Chest* 1999;116:1483–5.
3 Hegazi MO, El Sayed A, El Ghoussein H. Pulmonary hypertension responding to hyperthyroidism treatment. *Respirology* 2008;13:923–5.
4 Ma RC, Cheng AY, Yee So W, *et al*. Thyrotoxicosis and pulmonary hypertension. *Am J Med* 2005;118:927–8.
5 Vallabhajousula S, Radhi S, Cevik C, *et al*. Hyperthyroidism and pulmonary hypertension: an important association. *Am J Med Sci* 2011;342:507–12.
6 Franklyn JA, Boelaert K. Thyrotoxicosis. *Lancet* 2012;379:1155–66.
7 Lazarus JH. Management of hyperthyroidism in pregnancy. *Endocrine* 2013 Oct 31. [Epub ahead of print]
8 Smith JS, Mueller J, Daniels CJ. Pulmonary arterial hypertension in the setting of pregnancy: a case series and standard treatment approach. *Lung* 2012;190:155–60.
9 Pieper PG, Hoendermis ES. Pregnancy in women with pulmonary hypertension. *Neth Heart J* 2011;19:504–8.
10 Jaïs X, Olsson KM, Barbera JA, *et al*. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *Eur Respir J* 2012;40:881–5.
11 Bedard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009;30:256–65.
12 Weiss BM, Hess OM. Pulmonary vascular disease and pregnancy: current controversies, management strategies, and perspectives. *Eur Heart J* 2000;21:104–15.