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RISK OF NEONATAL HYPOTHYROIDISM IN NEWBORNS FROM MOTHERS EXPOSED TO CTPA DURING PREGNANCY: ANCILLARY DATA FROM A PROSPECTIVE OUTCOME STUDY.

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Word count for abstract: 213

Total word count: 1875

Short title: CTPA in pregnant women: effect on neonatal thyroid function

Number of tables: 1

Number of figures: 1

ESSENTIALS

- Neonatal hypothyroidism is a potential complication of CTPA use during pregnancy

- Analysis of this risk in a prospective management outcome study including pregnant women with suspected PE

- Collection of Guthrie tests performed in newborns from mothers who had CTPA for suspected PE during pregnancy

- No case of neonatal hypothyroidism in pregnant women investigated with CTPA for suspected PE was detected

ABSTRACT

Background

Neonatal hypothyroidism is often raised as a potential concern for the use of Computed Tomography Pulmonary Angiography (CTPA) in pregnant women with suspected PE.

Objectives

To assess the incidence of neonatal hypothyroidism among newborns from mothers exposed to CTPA.

Patients/Methods

Pregnant women with clinically suspected PE, included in a multicentre multinational prospective diagnostic management outcome study, based on pretest clinical probability assessment, high-sensitivity D-dimer testing, bilateral lower limb venous compression ultrasonography, and computed tomography pulmonary angiography (CTPA). Results of the Guthrie tests were systematically collected for newborns of all women who required CTPA as part of the diagnostic strategy. A TSH level above 15 U/ml was used to define hypothyroidism.

Results

Out of the 166 women included in the Swiss participating centers, 149 underwent a CTPA including 14 with twin pregnancies. Eight women suffered a pregnancy loss and results of the Guthrie could not be retrieved for 4 newborns. All TSH levels were reported as being below 15 U/ml. The incidence of neonatal hypothyroidism was 0/151 (0.0%, 95% CI: 0.0-2.5%).

Conclusions

We did not identify any case of neonatal hypothyroidism in our cohort of 149 pregnant women investigated for suspected PE using a CTPA. Along with previous literature data, this provides further reassuring data regarding the use of CTPA in this indication.

Keywords: pulmonary embolism, diagnosis, pregnancy, Guthrie test, hypothyroidism

INTRODUCTION

Pulmonary embolism (PE) remains one of the most common causes of maternal death in developed countries.[1,2] Besides the fact that pregnancy is associated with an increased risk of venous thromboembolism (VTE), one of the potential explanations is that diagnosing PE is particularly challenging during pregnancy. Pregnant women often present symptoms and signs that can suggest PE, such as physiologic shortness of breath or tachycardia.[3] There is very limited evidence in the literature to guide clinicians on how to manage pregnant women with suspected PE.[4,5] Two prospective management outcome studies using CTPA as imaging test have suggested that this test is safe to rule out PE in this population.[6,7] There is an ongoing debate on whether lung V/Q scan or CTPA should be preferred during pregnancy. In terms of fetal radiation, the doses received is lower with CT during early pregnancy and become equivalent by the end of pregnancy.[8-10] The dose to the mother's breast is significantly higher with CTPA throughout pregnancy.[11,12]

Potential harmful effects related to intravenous iodinated contrast agents on fetal thyroid function have also been put forward as a reason to prefer the V/Q scan.

While reduced intakes of iodine is the major cause of hypothyroidism, exposure of the fetus or the neonate to excess iodine may also result in hypothyroidism. High iodine levels block thyroid hormone synthesis through inhibition of the organification process. This is known as the Wolff-Chaikoff effect. Also excess iodine inhibits T4 and T3 secretion. These effects are

thought to be present in the thyroid tissues for some weeks. In a normal thyroid gland, after some days, the excess iodine induces downregulation of the sodium-iodide symporter and decreased intra-thyroid iodine concentration, leading to an escape from the Wolff-Chaikoff effect. However, the fetal thyroid gland is particularly sensitive to iodine overload because the ability to fully escape from the acute Wolff-Chaikoff effect does not mature until approximately 36 weeks. The risk of fetal hypothyroidism due to long-term maternal ingestion of iodides has been well documented in the past.[13-16] A theoretical risk of contrast-induced hypothyroidism in neonates exposed to iodinated contrast agents during the antenatal period exists but has never been assessed in in formal prospective study.[17]

The CTPE-pregnancy study was the first published prospective management outcome study which assessed the safety of a sequential diagnostic strategy in pregnant women with suspected PE.[6] This strategy was based on the assessment of clinical probability with the simplified Geneva score, D-dimer measurement, compression ultrasonography of the lower limb veins, and computed tomography pulmonary angiography (CTPA). In Switzerland, a systematic screening of several neonatal condition, including congenital hypothyroidism is performed at birth by the measurement of capillary thyroid stimulating hormone (TSH) levels. To study the effect of iodinated contrast agents used for CTPA in pregnant women, we prospectively collected TSH measurements in babies born from mothers who underwent CTPA for a suspected PE in the CT-PE pregnancy study.

METHODS

Study population

We used data from a multicenter, multinational prospective diagnostic management outcome study. We screened outpatient pregnant women presenting at one of the participating centers with a clinical suspicion of PE, as defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause. Exclusion criteria were: age below 18 years, allergy to iodinated contrast agent, impaired renal function (defined by a creatinine clearance below 30 ml/min as per the Cockcroft-Gault formula), diagnosis made prior to

presentation, indication for or already on full dose anticoagulation, and inaccessibility for follow-up. The study was performed in two countries (France and Switzerland) and 11 centers actively included patients. The study was approved by the Ethics Committee according to legislation at each study site. A written informed consent was obtained from all participating women.

Diagnostic work-up

The pretest probability of PE was determined using the revised Geneva score. A D-dimer test was performed in all women, using a highly sensitive D-dimer assay (Vidas® D-dimer assay, BioMérieux, Marcy l'Etoile, France). PE was deemed excluded in women with a non-high pretest probability and a negative D-dimer test (i.e. D-dimer < 500 µg/L). Women with a high pretest probability, and those with a non-high pretest probability and a positive D-dimer test, underwent bilateral CUS. When a proximal DVT (popliteal vein and/or above) was found, PE was considered as confirmed without further testing. Women with a negative CUS underwent CTPA. The protocol for CTPA consisted of an evaluation of the pulmonary arteries up to and including the subsegmental vessels. Only multidetector CT machines were used. The acquisition parameters for CTPA were: injection of a total volume of 100 ml of non-ionic contrast material (iodine concentration, 300 to 350 mg per milliliter) with a power injector at 3 to 5 ml per second; imaging 9 to 20 seconds after initiation of the contrast-material injection; scanning performed at 1.0 to 1.3 mm per section with a pitch of 1.25 to 1.75, 120 KV, and 115 to 260 mA; and reconstruction of images at 0.6 to 0.8 mm intervals. The complete diagnostic algorithm is depicted in Figure 1.

Follow-up

Patients with a negative diagnostic work-up were considered as not having PE and thus left without anticoagulant treatment and underwent clinical follow-up for three months. They were instructed to contact the study team in case of any new or worsening symptoms. An independent adjudication committee (three members) reviewed all the suspected VTE events, blinded from the initial diagnostic work-up.

Study analysis

Although neonatal screening was performed in both countries, results were not systematically collected in the French participating centers, this analysis is restricted to babies born from women included in the Swiss participating centers. Results of the Guthrie tests were obtained at follow-up or when data were not available at follow-up, through the central Labor (Zürich, Switzerland). Results are provided as negative when the TSH measurement were below 15 U/ml. The actual TSH value is given in case of abnormal results. Women using medications which could have an influence on the babies thyroid function (levothyroxine, amiodarone) were excluded.

The analysis was performed using babies as a unit. We estimated the proportion of newborns with an abnormal TSH result using exact proportions along with the 95% confidence interval (CI).

RESULTS

The study flow chart is depicted in Figure 1.

Between August 2008 and July 2016, 395 pregnant women were included in the study. Of them, 166 were included in the Swiss participating centers.

There were 23 (13.9%) women included during the first trimester of their pregnancy, 69 (41.6%) during the second and 74 (44.6%) during the third trimester.

CTPA was not performed in 17 women: 14 women with a non-high PTP and negative D-Dimer, 1 with a high PTP and proximal DVT on CUS, and two due to protocol violations. None of the included mothers were using drugs having a potential impact on the thyroid function of their babies. Therefore, 149 women including 14 with twin pregnancies, were included in the analysis. The results of the Guthrie test could not be retrieved for four newborns, and there were 8 pregnancy losses. Altogether, 151 Guthrie results were available.

All Guthrie levels were reported as being below 15 U/ml. The proportion of newborns with neonatal hypothyroidism was: 0/151 (0.0%, 95% CI: 0.0-2.5%).

DISCUSSION

Among women included in the CT-PE pregnancy study,[6] we did not identify any case of neonatal hypothyroidism in newborns of mothers who underwent a CTPA during the pregnancy for a suspected PE.

Congenital hypothyroidism, which can be definitive or transient, has an incidence of one in 2000 to one in 4000 newborns in the USA, and is the most common and treatable cause of mental retardation.[18] Thyroid function during the intra-uterine period is essential for the neurologic development of the fetus as highlighted by the fact that the fetal gland begins to produce thyroxine under the influence of the TSH between 10 and 12 weeks of gestation.[19] Congenital hypothyroidism may be a result of athyreosis, thyroid dysgenesis, or defects in pathways for biosynthesis of thyroid hormones. Transient congenital hypothyroidism may be due to placental transfer of maternal antibodies, or excessive iodine exposure. As iodine crosses the placenta, a potential adverse effect on the fetal thyroid gland from maternal intravenous administration of iodinated contrast agent resulting in neonatal hypothyroidism has been postulated.[20] Indeed, some reports of transient congenital hypothyroidism have been described, for example after amniofoetography with iodinated contrast agents.[15] On the other hand, some small series did not report hypothyroidism in babies born from mothers receiving iodinated contrast medium during pregnancy.[17] Therefore, the issue is still highly debated and has been put forward to avoid CTPA during pregnancy and prefer V/Q scan instead.[21]

Depending on the generation of the CTPA and the protocol used, 75-150 ml of iodinated contrast medium is administered intravenously. The iodine content of iodinated contrast media varies from 320 to 350 mg/mL and is much higher than the recommended daily allowance of 150 µg for adults and 220-290 µgr for pregnant and lactating women.[22]

V/Q scan has been the cornerstone for PE diagnosis for more than 3 decades and is often proposed in pregnant women with suspected PE, starting with a perfusion scan and adding a ventilation phase only in case of perfusion abnormality.[23] However, this kind of strategy has never been validated in a properly conducted prospective study. Moreover, the availability of the test is limited to tertiary care centers.

CTPA has become the reference standard test for PE diagnosis outside pregnancy[24,25] and has recently also been used in pregnant women with suspected PE.[6,7] Indeed, the sequential use of an assessment of pre-test probability, D-dimer measurement and CTPA, has been tested in two management prospective studies, which confirmed the safety of this diagnostic approach.[6,7]

Therefore, our prospective data suggesting no detected case of neonatal hypothyroidism in our cohort could further reassure clinicians on the safety of CTPA for PE diagnosis during pregnancy. Of course, breast's maternal radiation associated with the use of CTPA is significantly higher than with V/Q scan, and there is an ongoing debate regarding the long term risk of such an irradiation. However, the risk-benefit balance of using CTPA in pregnant women seems acceptable as misdiagnosing PE during pregnancy may have immediate dramatic consequences for the mother and her baby.

Our study has strengths and limitations. This was a prospective study and we had *a priori* decided to systematically collect newborns outcomes. We were able to retrieve results through a centralized laboratory which performs tests for all newborns in Switzerland. This ensures the use of the same pre-analytics variables and the same assay for all newborns. Also, all included pregnant women underwent a standardized diagnostic algorithm, using a similar CTPA protocol and the same contrast agent throughout the conduct of the study.[6]

Despite being the largest prospective study on PE diagnosis in pregnancy collecting newborns outcomes, our sample size remains limited. We were only able to exhaustively collect all Guthrie tests results for women included in Switzerland. This prevented us to provide very narrow estimates of the risk. However, our results are in line with those of a retrospective study including 344 women who underwent CTPA for suspected PE. In this study, all newborns had a normal T4 at birth, and only one newborn had a transient abnormal TSH, that normalized after few days.[17]

In summary, we did not identify any case of neonatal hypothyroidism in our cohort of 149 pregnant women investigated for suspected PE using a CTPA. Along with previous literature data, this provides further reassuring data regarding the use of CTPA in this indication.

AUTHOR'S CONTRIBUTIONS

AKNOWLEDGMENTS

CONFLICT OF INTEREST SECTION

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Table 1. Characteristics of included patients

Characteristics	Patients
	n=149
Female gender, n, (%)	149, 100
Age in years, median (IQR)	33, (29-36)
Trimester of pregnancy	
First, n (%)	17, (11.4)
Second, n, (%)	60, (40.3)
Third, n, (%)	72, (48.3)
BMI (kg/m^2)	25.1 (6.0)
Personal history of VTE, n, (%)	11, (7.4)
Familial history of VTE, n, (%)	15, (10.1)
Active malignancy, n, (%)	0, (0.0)
Surgery within one month, n, (%)	2, (1.0)
Bedridden for > 72 hours during the last 4 weeks, n, (%)	15, (10.1)
Travel > 6 hours, n, (%)	5, (3.4)
Chest pain, n, (%)	95, (63.8)
Dyspnea, n, (%)	108, (72.5)
Syncope, lipothymia, n, (%)	19, (12.8)
Hemoptysis, n,%	5, (3.4)
Clinical signs or symptoms of DVT, n, (%)	14, (9.4)
Heart rate, bpm, mean (SD)	90 (17)
O2 saturation, %, mean (SD)	98.4 (1.6)
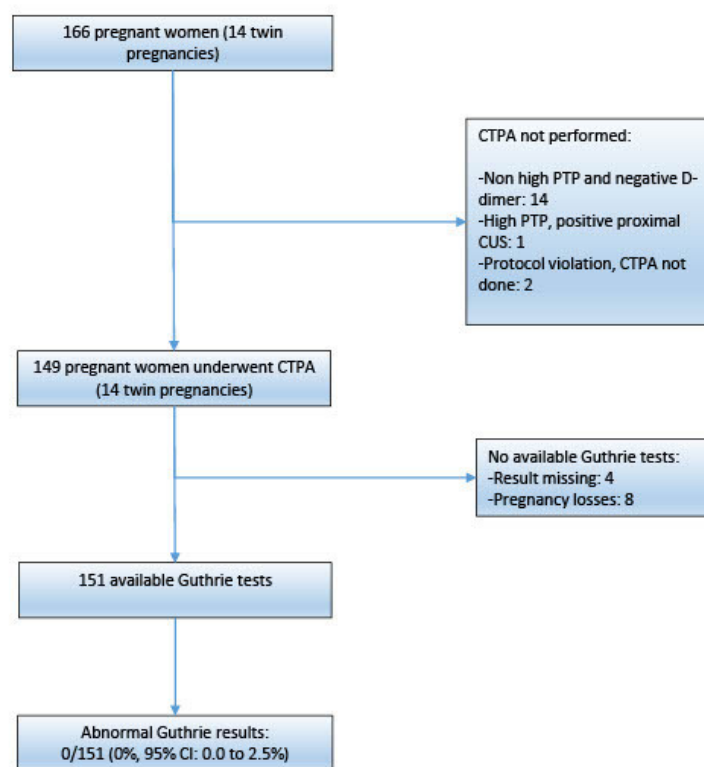
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