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## RESEARCH ARTICLE

# ULTRASONOGRAPHIC ASPECTS OF GOITER: A COMPARATIVE EPIDEMIOLOGICAL STUDY BETWEEN CHINESE AND CONGOLESE PREGNANT WOMEN WHO CONSULTED THE DEPARTMENT OF ENDOCRINOLOGY FOR THYROID DISORDERS

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**ABSTRACT**

**Aims:** Thyroid pathologies are correlated to genetics, environmental and reproductive factors including pregnancy that has an impact on the thyroid gland, especially when it occurs on an iodine deficient ground. This study aimed to compare the ultrasonographic aspects of goiter in Chinese pregnant women with those of Congolese who consulted the department of endocrinology for thyroid disorders.

**Methods:** Eighty pregnant women (40 Congolese and 40 Chinese) were retrospectively evaluated between February 2016 and March 2017 at the University Clinics of Kinshasa in Democratic Republic of Congo, and at the Qianfoshan Hospital in People's Republic of China. Thyroid ultrasound was performed using a 7.5-9MHz frequency linear-array transducer with a device of a Doppler function.

**Results:** Mean thyroid volume was recorded to be 12.1 ± 6.2 mL (range 4-28.6 mL) and 67.4 ± 7.7 mL (4-392.1 mL) in the Chinese group and Congolese respectively ($p<0.001$). 85% of Congolese subjects had goiter, while only 12.5% of Chinese subjects had it. Goiters were associated with sonographic Hashimoto's thyroiditis in the Chinese group, while 91.2% and 8.8% of goiters were respectively nodular and diffuse in the Congolese group. The thyroid parenchyma in the Chinese group was especially hypoechoic and heterogeneous with variable degree of vascularization, while in the Congolese group, beside hypoechogenicity and heterogenicity, we noted a normal vascularization.

**Conclusions:** Ultrasonography detected a higher prevalence of goiter in the Congolese pregnant women than in the Chinese.



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## INTRODUCTION

Thyroid diseases are more common in women than in men around the world (Morganti *et al*., 2005; Hansen *et al*., 2004). They occupy the second place after diabetes mellitus with a sex ratio of women/men that oscillates between 5/1 and 20/1 according to the authors (Henri Germain *et al*., 2005; Chabchoub *et al*., 2006). Various studies have shown that the development and onset of thyroid diseases are determined by the interaction of genetic, environmental and autoimmune factors (Hansen *et al*., 2004; Tome *et al*., 2012; McLeod *et al*., 2014; Hollowell *et al*., 2002; Mabika *et al*., 2008).

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Although these diseases have a universal distribution, their expression varies according to continents, countries, races and sex and within the same country it varies with the iodine content of the region (Hollowell *et al*., 2002; Vila *et al*., 2008). In terms of sex, the increase in need in iodine at puberty, during pregnancy and after childbirth explains in part the higher frequency with which thyroid disease appears in women (Vila *et al*., 2008; Tajtáková *et al*., 2003; Reid *et al*., 2013; De Groot *et al*., Stagnaro-Green *et al*., 2011). Several studies have correlated thyroid pathologies with reproductive factors, especially when pregnancies occur on an iodine deficient ground (Estaquio *et al*., 2006; Brunn *et al*., 1981; Knudsen *et al*., 2002; Habimana *et al*., 2014; Twite *et al*., 2010; Krohn *et al*., 2005). One of the factors that lead to the thyroid hypertrophy is the human chorionic gonadotropin (HCG)

hormone produced during pregnancy. This hormone that has a structural analogy with the thyroid stimulating hormone (TSH) stimulates the growth of thyroid follicular cells and the different stages of the thyroid hormonosynthesis, with as consequences in pregnant women; thyroid hypertrophy, nodules formation and risk of malignant degeneration (Wémeau *et al*., 2005; de Escobar *et al*., 2004). Thyroid hypertrophy during pregnancy poses serious diagnostic and/or therapeutic problems. Concerning the diagnosis, it should be noted that the somatic and behavioral changes easily evoke psychic or psycho-affective disorders. Biochemical and immunological disturbances that result can lead to misdiagnosis and poor treatment because of the false positives sometimes observed in the dosage of anti TSH receptor antibodies (De Groot *et al*., 2012; Stagnaro-Green *et al*., 2011; de Escobar *et al*., 2004; Okosieme *et al*., 2008). Only *in vivo* methods that do not use ionizing radiation can be performed during pregnancy, and Ultrasound technique is among these methods. Ultrasound technique offers the clinician many advantages: its non-aggressive nature, its great ability to detect thyroid nodules (even those less than 10mm in diameter), its great accessibility, the handling facilities, and its low financial cost. It also allows to specify the echostructure of the thyroid gland, to calculate the thyroid volume with good precision and to confirm the diagnosis of goiter as well as its impact on nearby structures (Stagnaro-Green *et al*., 2011; Twite *et al*., 2010; Kratky *et al*., 2013; Igl *et al*., 1981; Lutz and Buscarini, 2013; Royal, 1998 and Chaudhary and Bano, 2012). Despite the multiplicity of ultrasound scans in medical training in the Democratic Republic of Congo (DRC), the data referring to the echographic aspects of the thyroid gland during pregnancy are rarely available, while iodine metabolism disorders are frequently encountered in our consultations and are generally the cause of fertility disorders in the majority of women. Moreover, besides the benefit of treatment of pregnant women with thyroid pathologies, there are risks of interruption of pregnancy as well as disorders of somatic and psychomotor of fetal growth (de Escobar *et al*., 2004; Okosieme *et al*., 2008). The Chinese women are less exposed to obstetric factors than Western or Congolese women because of the limited births to two children. For that, this study aimed to compare the ultrasonographic aspects of goiter in Chinese pregnant women with those of Congolese who consulted the department of endocrinology for thyroid disorders, and to look for the possible clinical and Para clinical particularities that could be caused by the thyroid diseases in these two populations who present differences in terms of genetic, environmental and reproductive factors.

## MATERIALS AND METHODS

### Subjects

This is a retrospective and comparative study of 80 pregnant women (including 40 Congolese and 40 Chinese) who consulted for thyroid disorders in the department of endocrinology of the University Clinics of Kinshasa in Democratic Republic of Congo (DRC), and of the Shandong Provincial Qianfoshan Hospital in People's Republic of China (PRC) from February 2016 to March 2017. Eligibility criteria included pregnant women who consulted in the department of endocrinology for thyroid disorders and had performed thyroid hormone tests and a thyroid sonography. The subjects who did not undergo the thyroid sonography and those with non-exploitable records as well as non-Congolese and non-Chinese pregnant women were excluded from the study. The medical ethics committee of both the Shandong Provincial Qianfoshan Hospital in PRC and of the University Clinics of Kinshasa in DRC approved this study, and the confidentiality of the information has been taken into account.The demographic questionnaire concerned age, marital status, parity and the family history of thyroid pathologies. Clinical and biological characteristics included age, pregnancy rank as well as hormonal tests including TSH, free and total thyroxin (FT4 and TT4), and free and total triiodothyronine (FT3 and TT4).

**Image acquisition:** Thyroid ultrasonography of all pregnant women was performed by sonographers experienced in thyroid imaging. All the ultrasound machines were equipped with linear-array transducers with a frequency range of 7.5-9MHz, and Color Doppler module. The volume of the thyroid of each lobe was calculated according to the formula of the ellipse: height x width x thickness x $\pi$ / 6. The overall volume was obtained by the sum of the two volume lobes (Knudsen *et al*., 1999). The thyroid dimensions and the thyroid volume, the echogenicity and the echostructure of the parenchyma, the number of thyroid nodules, the vascularization and the presence or absence of cervical adenopathies were recorded. Goiter was defined by a volume of thyroid above 18 ml in women and was described as simple when its echogenicity was completely homogeneous (Brunn *et al*., 1981; Twite *et al*., 2010).

**Thyroid function and serum levels of thyroid hormones:** The state of euthyroidism, hypothyroidism or hyperthyroidism was defined on the basis of the TSH rates according to the values of international references for pregnant women Level I-USPSTF (Stagnaro-Green *et al*., 2011): first trimester: 0.1–2.5mIU/L, second trimester: 0.2-3.0mIU/L and third trimester: 0.3–3.0mIU/L.

### Statistical Analysis

The data were entered and analyzed on the computer using the software SPSS version 17, Inc., Chicago, IL. Means ± SD were calculated for the quantitative variables. The ANOVA test was used for comparison of patient's groups; the statistical significance was set at 0.05 for a 0.95% confidence interval.

## RESULTS

**Epidemiological characteristics:** This study involved 80 women (including 40 Chinese and 40 Congolese) who consulted the Department of Endocrinology for thyroid disorders during pregnancy. The average age of the subjects was 32.2 ±4.9 (range 23-48) years overall. It was 30.9±4.2 (range 24-40) years for the Chinese population, and 33.5±5.4 (range 23-48) years for the Congolese (p=0.991). We identified the majority of subjects in first trimester of pregnancy; 60% and 62.5% of patients in the Chinese group and Congolese respectively. Multiparity has characterized the Congolese population; the majority of subjects (60%) had at least 3 births in the past, versus (vs) to the Chinese population which was characterized by the primiparity (57.5%) (Figure 1 and Figure 2).

### Thyroid function in each population

We noted 25% of subjects with dysthyroidism in the Congolese group versus 52.5% in the Chinese. Figure 3 shows thyroid

function in each population.The thyroid function profile was characterized by a prevalence of hypothyroidism higher to that of hyperthyroidism in Chinese subjects (30% of hypothyroidism vs 22.5% of hyperthyroidism). The opposite was noted in Congolese groupin whom the prevalence of hyperthyroidism was higher than that of hypothyroidism (17.5% of hyperthyroidism vs 7.5% hypothyroidism) (Figure 3).

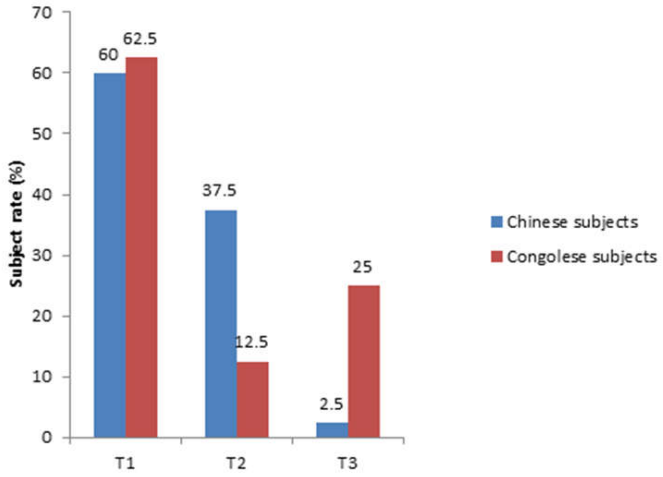


**Figure 1. The distribution of subjects at each stage of pregnancy: First (T1), second (T2) and third (T3) trimester of pregnancy**

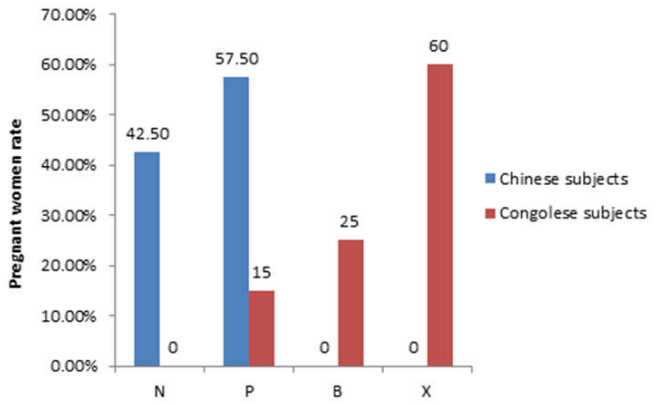


**Figure 2. The distribution of pregnant women according to the parity: Nulliparous (N), primiparous (P), two deliveries in the past (B) and at least tree deliveries in the past (X)**

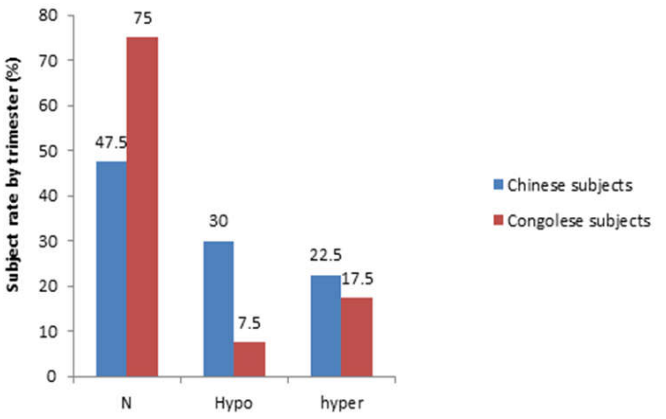


**Figure 3. The thyroid function in each group: Euthyroidism (N), hypothyroidism (Hypo) and (Hyper)**

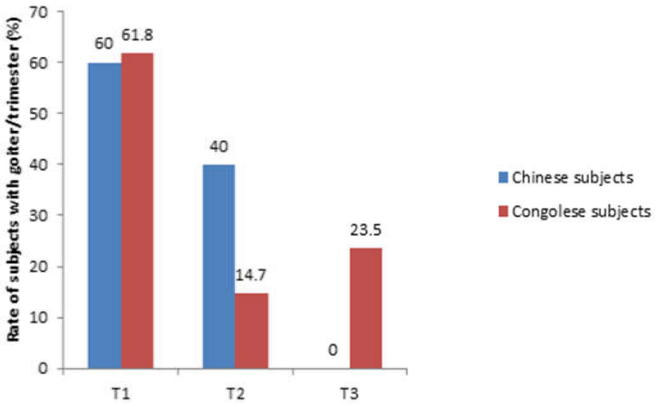


**Figure 4. The distribution of goiter according to gestational age: First trimester (T1) second timerster (T2) and third trimester (T3)**

### Size or volume of the thyroid gland

Comparing the mean thyroid volume between both populations, it was found to be 12.1 ± 6.2 mL (range 4-28.6 mL) and 67.4 ± 7.7 mL (4-392.1 mL) in the Chinese group and Congolese respectively; this difference was statistically significant ($p<0.001$). We noted 34 of the 40 (85%) Congolese subjects with a thyroid volume well above the upper limit of the normal, while only five of 40 (12.5%) Chinese subjects had goiter. Sixteen of the forty Chinese subjects (40%) had a thyroid volume less than 10 mL, whereas only one Congolese subject had a thyroid volume less than 10ml. The majority of these subjects with goiter were in the first trimester, 60% of Chinese subjects and 61.8% of Congolese subjectsrespectively (Figure 4).

### Sonographic features of thyroid gland and sonographic diagnoses

Thyroid parenchyma in both populations was especially hypoechoic and heterogeneous to sonography (Table 1). This heterogeneous echogenicity was accompanied by a hypervascularisation to the Doppler in 72.7% cases in the Chinese population, and only 4.3% of cases in the Congolese.A hypoechoic and heterogenic thyroid parenchyma was mainly associated to the diagnosis of ultrasonographic Hashimoto's thyroiditis (45%) in the Chinese group, and to the goiter (52.5% or 21 subjects) in the Congolese group (Table 1 and 2).

### Related features

Secondarysonographicfindings were found to be associated withdifferent thyroid pathologies. Cervical adenopathies (which were considered as benign) were found to be associated with 14 (77.7%) cases of sonographic Hashimoto's thyroiditis. It was found that the plunging and/or compressive characters in 12 (37.5%) Congolese subjects who had goiter (Insert Table 3).

## DISCUSSION

In the present study, the mean age of Congolese pregnant women (33.5 ± 5.4 years) and that of Chinese (30.9 ± 4.2 years) were superimposable, but slightly higher than that reported by Rajesh Rajput *et al*. (23.79 ±3.47 years) (Rajput *et al*., 2015). This age range corresponds to one of the critical periods of working life for women (the reproductive period especially) during which various factors (pregnancy, childbirth

**Table 1. Ultrasonographic features of thyroid parenchyma**

| Countries | Echostructure | Frequency | % | Valid % | Cumulative % |
|---|---|---|---|---|---|
| Chinese group | | | | | |
| NE | | 18 | 45 | 45 | 45 |
| HH | | 22 | 55.0 | 55.0 | 100.0 |
| Total | | 40 | 100.0 | 100.0 | |
| Congolese group | | | | | |
| NE | | 17 | 42.5 | 42.5 | 42.5 |
| HH | | 23 | 57.5 | 57.5 | 100.0 |
| Total | | 40 | 100.0 | 100.0 | |

**Abbreviations: NE**=Normal echostructure; **HH**=Hypoechogeneous and heterogeneous.

**Table 2. Distribution of diagnosis according to the echostructure**

| Diagnostics/group | NE | HH | Total |
|---|---|---|---|
| Chinese group | | | |
| Normal thyroid | 14 | - | 14(35%) |
| Hashimoto's thyroiditis | - | 18 | 18(45%) |
| Thyroid with hypervascularization | 1 | - | 1(2.5%) |
| Isolated nodules | 4 | 3 | 7(17.5%) |
| Total | 19 | 21 | 40(100%) |
| Congolese group | | | |
| Normal thyroid | 2 | - | 2(5%) |
| Nodular/multinodular/Diffuse goiter | 13 | 21 | 34(85%) |
| Isolated nodules | 2 | 2 | 4(10%) |
| Total | 17 | 23 | 40(100%) |

**Abbreviations: NE**= Normal echostructure. **HH**=Hypoechogeneous and heterogeneous.

**Table 3. Ultrasonographic diagnosis according to the secondary features**

| Diagnostics/groups | Nothing to report | CA | Pl/comp. character | T. calcif. | Total |
|---|---|---|---|---|---|
| Chinese subjects | | | | | |
| Normal thyroid | 2 | 12 | - | - | 14(35%) |
| Hashimoto's thyroiditis | 4 | 14 | - | - | 18(45%) |
| Thyroid hypervascularisation | - | 1 | - | - | 1(2.5%) |
| Thyroid with nodules | 3 | 4 | - | - | 7(17.5%) |
| Total | 9 | 31 | | | 40(100%) |
| Congolese subjects | | | | | |
| Normal thyroid | 2 | - | - | - | 2(5%) |
| Nodular/Diffuse goiter | 20 | - | 12 | 2 | 34(85%) |
| Thyroid with nodules | 4 | - | - | - | 4(10%) |
| Total | 25 | - | 13 | 2 | 40(100%) |

**Abbreviations: CA**= cervical adenopathy; **Pl/comp. character=**Plunging/compressive character of goiter; **T. calcif=**Thyroid parenchymal calcification.

and breastfeeding) interact and stimulate growth and development of the thyroid. These factors increase the need for thyroid hormones and, on the other hand, lead to the hyperplasia of thyroid follicular cells with reduced thyroid uptake of iodine following the resulting hyperestrogenemia. These factors could partially explain the increase in risk of thyroid pathology during this age group (Pedersen *et al*., 1993; Tunbridge *et al*., 1977). Seventy-five percent (75%) of Congolese pregnant women who consulted had a normal thyroid function (See Figure 3), while only 47.5% of Chinese pregnant women who consulted had thyroid function within normal range. Thirty percent (30%) of Chinese subjects were in hypothyroidism and 22.5% were in hyperthyroidism, contrary to what was observed in Congolese subjects (where hypothyroidism accounts for 7.5% and hyperthyroidism 17.5% of cases). The profile of thyroid function in Chinese group in our study corresponds to that of several other authors who reported the prevalence of hypothyroidism higher in Asian countries (including China and India) than in west (Dhanwal *et al*., 2013; Bandela *et al*., 2013). The predominance of the autoimmune process and the increased iodine intake in diet may be a reason for this higherprevalence of hypothyroidism observed in Chinese pregnant women (Poppe and Glinoer, 2003; Teng *et al*., 2011). The present study shows a higher prevalence of goiter in the first trimester of pregnancy (60% of Chinese subjects and 61.8% of Congolese subjects with goiter). This could be explained by the iodine loss (placental transfer, elevation of renal clearance in Iodine), hyperestrogenemia, and the action of chorionic hormone gonadotropin during the first weeks of pregnancy (Zimmermann *et al*., 2008). Concerning the mean thyroid volume, Nils Knudsen *et al*. (1999) reported in their series a mean thyroid volume of 11.9 ml in an area with low iodine intake. These values are close to those found in Chinese subjects in our series (12.1 ± 6.2 ml, extremes 4-28.6 ml) and those reported by Berghout *et al*. (1994) and by Brander and Kivisaari (1989). However, Berghout *et al*. (1994) found no change in thyroid volume prior to or during pregnancy in healthy pregnant women living in areas with adequate intake of Iodine (10.3 ± 5.1 mL before pregnancy, 10.6 ± 4.4 mL in the first trimester, 9.6 ± 3.8 mL in the second trimester and 9.4 ± 3.0 mL in the third trimester of pregnancy). Curiously, all these values remain far lower than those found among Congolese subjects, in whom the range is from 4 to 392.1 mL, with an average of 67.4 ± 7.7 mL. This volumetric discordance may be the consequence of an autoimmune process in the Chinese subjects, as shown by the predominance of chronic lymphocytic thyroiditis suspected in these patientswith cervical adenopathies (in 77.7% of Chinese subjects with sonographic Hashimoto's thyroiditis) and tendency of decrease

in volume (up to less than 10mL in 37.5% of Chinese subjects with suspicious of sonographic Hashimoto's thyroiditis).

But, besides iodine deficiency, possible raisons for the severe hypertrophy of the gland during pregnancy in Congolese group could include: the presence of goitrigens in diet (such the consumption of cassava roots and leaves without sufficient protein intake), deficiency in nutrient (Selenium and Iron), multigravida/multiparity, use of pesticides, the genetic predisposition or the existence of an infra-clinical anomaly that would have escaped the attention of the clinician and whose appearance would be favored by many physiological factors that interact during pregnancy as demonstrated in other studies (Rajput *et al*., 2015; Thilly *et al*., 1992; Knudsen *et al*., 2002; Das *et al*., 2011; Soares *et al*., 2008; Hansen *et al*., 2005). Our hypothesis is reinforced by the observations of Rasmussen *et al*. (1989) who reported an increase in thyroid volume from 20.2 ± 2.2 mL to 24.1 ± 2.2 mL in the second trimester and at the end of pregnancy without the volume of the gland reaching 30 mL in an iodine-poor environment, with a reduction to 18.4 ± 2.0 mL in postpartum period. Looking at these data more closely, we see that the increase in the size of the thyroid gland observed during pregnancy for almost all of the Chinese subjects did not go beyond 18 ml set as the upper limit of a normal thyroid in women (Brunn *et al*., 1981). On the other hand, we noted that 34 of the 40 Congolese subjects in our series (85%) had a thyroid volume well above the upper limit of the normal and thus had a goiter, while only 6 patients (15%) had a normal size gland in this group (Brunn *et al*., 1981). These figures contrast with those published by Twite *et al*. in their study in which only 5.4% of the Congolese pregnant women had goiter (Twite *et al*., 2010). In clinical examination, Rajesh Rajput and al. found goiter 8% of women (Rajput *et al*., 2015).

Regarding the clinical forms of goiter, it must be noted that all goiters in the Chinese group were associated with Hashimoto thyroiditis, while 91.2% of the goiters were nodular and 8.8% were diffuse in the Congolese group. In our study, the diagnosis of Hashimoto's thyroiditis was sonographic. This diagnosis is generally accepted by several authors who reported that thyroid ultrasound has a higher specificity than the positivity of antithyroid antibodies in the diagnosis of Hashimoto's thyroiditis (Kratky *et al*., 2013; Rago *et al*., 2001). The ultrasonographic abnormalities demonstrated in Chinese subjects that led to the diagnosis of Hashimoto's thyroiditis were as follows: hypoechoic and heterogeneous echostructure with echogenic lines and a variable degree of vascularization on Doppler ultrasound (Kratky *et al*., 2013; Rago *et al*., 2001). As co-morbidity, unilateral or bilateral cervical adenopathy deemed benign was found in 77.8% of cases in the Chinese group (14/18 cases), and 6 of them (33%) had a thyroid volume of less than 10ml. These characteristics reinforce the hypothesis of the process of an inflammatory disease (Cosgrove, 2012; Brant and Helms, 2012; Baskin *et al*., 2012). Isolated thyroid nodules were rarely found in the study populations: 7 cases out of 40 (17.5%) in the Chinese group and 4 out of 40 cases in the Congolese group (10%). More than 85% of Congolese subjects had multinodular goiter, while among the Chinese, the thyroid nodules were most commonly associated with Hashimoto's thyroiditis (45%). The identification of isolated thyroid nodules is clinically important, given the high risk of malignancy (up to 20%) of any solitary nodule (Wémeau *et al*., 2011). Several factors, including multiparity, multiple pregnancies and especially iodine deficiency, even if relative, could explain the difference between both populations in term of nodulogenesis (Krohn *et al*., 2005). In Congolese population, goiter was diagnosed in 58.8% of cases with the following ultrasound signs: hypoechoic and heterogeneous structure with normal vascularization of the thyroid parenchyma on Doppler ultrasound. These signs distinguished euthyroid goiter from hypervascular goiter of Graves' disease, where the echostructure may be normal or hypoechoic in a diffuse manner, if not in a homogeneous or heterogeneous way. Our study had several strengths. It presents the first findings of comparison study between Congolese (of Democratic Republic of CONGO) and Chinese pregnant women with thyroid disorders.

This study has shown the role of the sonographic exploration in the study of goiter and the factors associated with it. Moreover, it explains the mechanism behind the increase in thyroid volume in both populations: in the Congolese context, the swelling of the thyroid gland being reactive (given the low iodine intake in a young pregnant woman), however, concerning the Chinese pregnant women, it results from an autoimmune process reflected by the predominance of Hashimoto's thyroiditis with tendency to atrophy of the gland as seen on ultrasound (which is seen in Congolese women generally menopausal or of advanced age). These differences in pathophysiological mechanisms explain clearly the differences in the ultrasound patterns observed in two populations studied.

Our study also had several limitations. The sample of our study is not representative of both Chinese and Congolese populations as a whole, and then not reflecting the reality of the phenomenon in both communities. Cases are rare to find, and it is due firstly to the failure to meet the eligibility criteria (many of these women had not undergone a thyroid sonography during pregnancy) and secondly by the likely ignorance and neglect of the thyroid symptoms especially by the Congolese pregnant women. These realities explain the small size of our sample. Another weakness of this study is the fact that thyroid ultrasounds have not been performed by a single sonographer.

In conclusion, the sonography detected a higher prevalence of goiter in the Congolese pregnant women than in the Chinese who consulted the department of the endocrinology for thyroid disorder during pregnancy (85% Congolese versus 12.5% Chinese subjects with goiter). More than 60% of subjects with goiter were in the first trimester of the pregnancy. The thyroid gland of Congolese subjects is six times larger than that of Chinese subjects, whose volume does not exceed 20 ml by ultrasound. Factors that may explain the occurrence of goiter and the differences observed in terms of thyroid echostructure were mainly autoimmunity in Chinese group and iodine deficiency in Congolese group. This may justify the association of sonography with biological tests in the diagnosis of thyroid disorders during pregnancy.

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