Short-Term Evaluation Of Newborns From Mothers With Grave's Disease: A Case Study

Abstract

Introduction

Maternal Graves' disease may be responsible for neonatal complications as well as neonatal hyperthyroidism. The aim was to determine the characteristics and course of neonates born to mothers with Graves' disease.

Materials and methods :

This was a descriptive retrospective cohort study conducted jointly by the Internal Medicine and Pediatrics departments of the Abass Ndao Hospital in Dakar. It involved patient records registered from 2006 to 2021.

Results:

One hundred and thirty-seven (137) mothers with their newborns were included. The mean age was 29 years with +/- 6.93. The diagnosis of Graves' disease was known prior to pregnancy in 119 of our patients (86.8%). The majority of mothers (59.22%) were on imidazole alone prior to pregnancy.

Birth weights ranged from 1,200 g to 7,000 g, with an average of 2,775.6 g. Most newborns were eutrophic (61.32%). Forty-seven newborns (34.3%) presented complications, including 16 cases of neonatal death. Two-thirds (22/33) of infants were euthyroid. 56.20% of mothers practiced exclusive breast-feeding, mostly with therapeutic abstention or readjustment of synthetic antithyroid drugs doses. Only 33 (24%) newborns had a thyroid check-up. During the first three months of life, there were 9 cases (27.7%) of hyperthyroidism and 2 cases of hypothyroidism. At 6 months, 3 cases of persistent hyperthyroidism. One had associated bilateral exophthalmos.

Conclusion:

Thyroid disorders affect one-third of children born to basedowian mothers. However, they are transient in the majority of cases. It is also worth noting the low rate of systematic thyroid work-up, which may bias the interpretation of the results obtained.

Key words: Grave's disease, newborns, Senegal, Hyperthyroidism.

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1 Introduction :

Clinical hyperthyroidism affects 0.1 to 0.4% of pregnancies. Gestational thyrotoxicosis is due to the structural homology of TSH and HCG. It constitutes a form of transient and spontaneously regressive hyperthyroidism during the first trimester of pregnancy. Graves' disease is the most common cause of clinically significant hyperthyroidism. In Senegal, there is not much data on the prevalence of this condition but it is estimated at 72% of the causes of hyperthyroidism in a study carried out at the Le Dantec University Hospital [1].

Graves' disease can cause thyroid dysfunction in the newborn. Neonatal hyperthyroidism is most often the consequence of transplacental passage of maternal thyroid-stimulating antibodies of the IgG type (TRAK : thyrotropin-receptor antibodies) in the context of maternal Graves' disease [2]. Poor control of hyperthyroidism can be responsible for intrauterine growth retardation, goiter, cardiac and neurological complications and perinatal mortality among others [3]. Neonatal hypothyroidism can be iatrogenic, a consequence of inappropriate doses of synthetic antithyroid drugs in the mother or linked to the transplacental passage of blocking anti-TSH receptor antibodies. Finally, the possibility of congenital central hypothyroidism by negative feedback of excess thyroid hormones on fetal TSH has been described [4].

Diagnostic efforts should be made in the fetal period to avoid neonatal complications [5]. It is in this context that we initiated this work whose main objective was to determine the characteristics of thyroid disorders in newborns born to mothers with Graves' disease and their short-term evolution.

2. Materials and methods

This was a descriptive retrospective cohort study jointly between the Internal Medicine and Pediatrics departments of the Abass Ndao Hospital Center in Dakar. It involved the files of patients followed for Graves' disease discovered before or during pregnancy in the Internal Medicine department from 2006 to 2021.

Inclusion criteria

Children of mothers being monitored for Graves' disease in the internal medicine department of Abass Ndao hospital in Dakar.

Non-inclusion criteria

We have not included:

- Incomplete and/or unusable files;
- Files with invalid telephone numbers;
- Files of mothers lost to follow-up during pregnancy.

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Data collection

The sources that made this study possible were:

- the files of mothers followed up in the internal medicine department;
- additional information to mothers by telephone call.

The data were collected on the basis of a pre-established survey form validated by the two departments of Pediatrics and Internal Medicine.

Data processing

Data entry was done using Sphinx Declic 2 software and analysis using SPSS 24.0 software. Tables and graphs were made using Microsoft Office Excel and Google Sheets software.

3. RESULTS

3.1 Maternal data

The mean age was 29 years with a standard deviation of 6.93. More than a third (35%) of the patients had a specific medical history.

Two-thirds of the women had at most 3 pregnancies (65.18%). The mean parity was 2.82 with a standard deviation of 12.32, and 29.23% were multiparous. 16.57% of the mothers had a history of abortion.

Familial thyroid disorder was found in 19 mothers. Diabetes was the most frequently found medical history (in 14 cases), followed by hypertension (13 cases). Only one patient had a mother followed in dermatology for lupus. (fig. 1)

The diagnosis of Graves' disease was known before pregnancy for 119 of our patients (77.27%). Height patients (8) were in remission. The time between diagnosis and the onset of pregnancy varied between 1 month and 13 years with an average of 184 weeks, or approximately 3 and a half years.

In 10 patients, the diagnosis of Graves' disease was made during pregnancy (6.49%). Most patients (78.3%) had progressive Graves' disease before pregnancy. (Fig. 2)

The majority of mothers (59.22%) were on imidazole alone. The number of antenatal consultations (ANC) ranged from 1 to 5. The median class was 3 ANC (40.70%).

Assessment during pregnancy (Tab 1)

***** For the 1st quarter :**

- Thyroid assessment

  TSH (N=43) was low in 33 reported results (76.74%)

  Free T4 (N=90) was increased in 37 cases (41.11%).

  TRAKs were above normal in 2 of the 3 assays performed.

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- Thyroid ultrasound (N=31): A goiter was found in 30 ultrasounds (96.77%). It was most often diffuse moderate hypervascularized homogeneous.
- ATS treatment (N=101): 89.11% of mothers were on imidazole, 6.93% on thiouracil and 3.96% on monitoring alone.

***** For the 2nd quarter :**

- Thyroid assessment

  TSH (N=24) was low in 15 reported results (62.5%).

  Free T4 (N=88) was increased in 25 cases (28.41%).

  TRAKs are higher than normal in 7 of the 8 assays performed.
- ATS treatment (N=96)

➢ 88 mothers were on imidazole (91.66%) and 4 on thiouracil

➢ 4 were under surveillance alone (4.17%).

***** For the 3rd quarter:**

- Thyroid assessment

  TSH (N=15) was low in 9 reported results (60%).

  Free T4 (N=69) was increased in 25 cases (36.23%).

  TRAKs were normal in both assays performed.
- ATS treatment (N=74)

➢ 69 were put on imidazole (93.24%), 4 were on thiouracil

➢ 2 were under surveillance only (2.70%).

Seventeen (17) pregnancies ended in abortion (11.04%) with a minimum gestational age of 6 weeks and a maximum of 27 weeks, or an average of 16 weeks and 3 days.
Delivery was at term in 83.13% of cases. The simple vaginal route is the most frequently found mode of delivery (in 114 cases) against 23 cesarean sections for different indications.

3.2 Neonatal data

Both sexes were found in equal parts: 63 boys (45.99%) and 63 girls (45.99%), for a total of 126 newborns. The weight varied from 1200 g to 7000 g, or an average of 2775.64 g.
Most of the newborns were eutrophic (61.32%) and 21.9% had low birth weight.

Neonatal complications (N=137) (fig. 3)

We recorded 47 complications (34.31%) in newborns including 16 cases of neonatal death

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(11.68% of births).

Neonatal thyroid assessment (N=33) (fig. 4)

The assessment was carried out at different times. Two-thirds of the infants were euthyroid.

More than half of the mothers (56.20%) practiced exclusive breastfeeding, most of the time with therapeutic abstention or readjustment of ATS doses.

The evolution of newborns (=137)

During the first three months of life, there were:

- 47 cases of complications (34.31%) including 9 cases of hyperthyroidism which subsequently improved after reduction of ATS doses in the mother and 2 cases of transient hypothyroidism.
- The rest of the newborns (79 cases or 57.66%) were asymptomatic.

At 6 months:

- 97.52% of newborns (118 cases) had a favorable outcome.
- 3 cases (2.48%) of persistent hyperthyroidism in infants. One of them had associated bilateral exophthalmos.

Discussion

The majority of women (62%) in our cohort did not have any paid activity. In a previous work in Senegal, Diop Dia et al [6] also found 61% of women to be housewives. The socio-economic level poses the problem of adequate care. Thus, mothers are often confronted with good therapeutic compliance, compliance with paraclinical assessments and follow-up appointments. We noted 16.88% of mothers who had an abortion. Our results are consistent with data from the literature. Indeed, women with untreated or poorly controlled Graves' disease often undergo multiple abortions with severe fetal hyperthyroidism. Several series suggest fetal mortality rates of up to 20% [7].

Most patients (78.3%) had progressive Graves' disease before pregnancy. Pregnancy can cause a relapse of the disease (in 75 % of cases) [8], accompanied by an increase in TRAK levels, particularly during the first trimester and after delivery.

The diagnosis of Graves' disease was known before pregnancy in 77.27% of our patients. The delay between diagnosis and the onset of pregnancy varied between 1 month and 13 years with an average of 184 weeks, or approximately 3 and a half years. Luz IR et al [9] also found an average delay of 3 and a half years in Portugal.

The median ANC class was 3. WHO recommends at least 4 antenatal consultations for a normal pregnancy. For an association of Graves' disease type on pregnancy, given the frequency and

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severity of complications that can be life-threatening, pregnancies were not adequately monitored.

During pregnancy, TSH was low in 2/3 of cases and free T4 was increased in at least ¼ of cases, indicating progressive hyperthyroidism. TRAK, when measured, was positive in 66.67% of cases in the 1st trimester, 87.5% in the 2nd trimester and 100% in the 3rd trimester. We deplore the low rate of performance of this examination, which is so essential during pregnancy for the prevention and early management of neonatal thyroid disorder. Indeed, out of a total sample of 154 mothers, only 3 were able to bring back the results in the 1st trimester, 8 in the 2nd trimester and 2 in the 3rd trimester. This is linked to the common unavailability and cost of the examination (20,000 CFA).

From a therapeutic point of view, all mothers had received medical treatment with synthetic anthyroid. Radioactive iodine is formally contraindicated during pregnancy and there was no indication for thyroidectomy in our series. The vast majority of our pregnant women were therefore on imidazoles during pregnancy. In the literature, PTU is the reference molecule in the first trimester because imidazoles can have teratogenic effects on the fetus such as localized scalp aplasia with methimazole , but also and above all malformation syndromes: esophageal atresia, diaphragmatic hypoplasia, imperforate choanae [10]. However, PTU is not available in Senegal and Benzylthiouracil is only prescribed in the event of a shortage of Carbimazole in pharmacies.

Obstetric ultrasound did not show fetal goiter in any of our cases. The study by M. Polak and al had shown the importance of having the fetal thyroid examined by an ultrasound specialist and working as a team with obstetricians and pediatric endocrinologists in pregnant women with Graves' disease. This had allowed them to accurately determine the status of the fetal thyroid and successfully adapt treatment in mothers during pregnancy [11]. In case of maternal thyroid disorder, it is therefore recommended to perform obstetric ultrasounds in expert centers where the fetal thyroid will be well examined and the ossification points sought.

Furthermore, 11.04% of the pregnancies in our cohort ended in abortion or fetal death, with a minimum gestational age of 6 weeks and a maximum of 27 weeks, or an average of 16 weeks and 3 days. Similarly, M. Uenaka and al. [12], in his study conducted in Kobe, Japan on 35 pregnancies associated with Basedow, had 11.4% of abortions between 5 and 18 weeks.

Preterm delivery accounted for 10.22% of cases with a gestational age ranging from 28 weeks to 36 weeks and 6 days.

Most of the newborns were eutrophic (61.32%), low birth weight accounted for 21.9%. Fetal hypotrophy can be a consequence of maternal Graves' disease as well as other maternal factors

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such as young age, size, high blood pressure, anemia and poor nutritional status among other factors described by Moyambe and al [13].

polymalformative syndromes (clubfoot and cleft palate) and congenital heart disease were found. Neonatal mortality was 11.68%, the cause was rarely specified, mothers were often seen again months later for a follow-up appointment and most of the time without the pregnancy monitoring booklet. This is problematic since the data concerning the delivery and the newborn's parameters were poorly reported.

From a biological point of view, thyroid assessments were rarely performed. In our study: two-thirds of infants were euthyroid, 27% were hyperthyroid for assessments performed between 1 and 6 months. Only 6% had transient hypothyroidism, which regressed after reduction of maternal doses or weaning. Smaller proportions have been reported in the literature. Indeed, for Uenaka and al [12]: nine mothers had neonatal thyroid dysfunction (25.71%) involving five newborns with hyperthyroidism (14.29%), three with transient hyperthyroidism (8.57%), one hypothyroidism (2.86%) and one central hypothyroidism (2.86%). Similarly, Polak and al, reported transient hyperthyroidism in 6 of 69 newborns (8.70%), and the mean age at diagnosis was 4.7 days [11]. The difference in age at diagnosis between our studies is enormous. This discrepancy could result from the fact that in developed countries, fetal ultrasound and TRAK assay allow for early diagnosis.

Regarding the type of feeding, 56.20% of mothers practiced exclusive breastfeeding, most of the time with therapeutic abstention or reduction of ATS doses. Antithyroid drugs are transferred from the mother's blood to the milk. However, with a small dose of antithyroid drugs (less than 20 mg of Neomercazole ®, 450 mg of Proracyl ®), it is possible to authorize breastfeeding [10]. Ideally, it is recommended to space out feedings by 4 hours after taking the medication. However, 4 cases of complete agalactia were noted, requiring artificial breastfeeding. According to Marasco [14], it seems that the main problem is at the level of the ejection reflex, and not at that of milk synthesis, whether in the case of hyperthyroidism or hypothyroidism. Taking galactogogues will only be effective if the thyroid status is correct, they can help, but should not be considered as the first line treatment.

Conclusion

Thyroid disorder affects one in three children born to a Graves' mother in our context.

However, they are transient in the majority of cases.

Thyroid testing is not systematically performed and is sometimes done late, which constitutes a risk of under-diagnosis.

To improve the prognosis, it is important to support women before and during pregnancy and

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then to provide pediatric care for all newborns regardless of the risk for at least the first 6 months of life.

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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Figures and tables

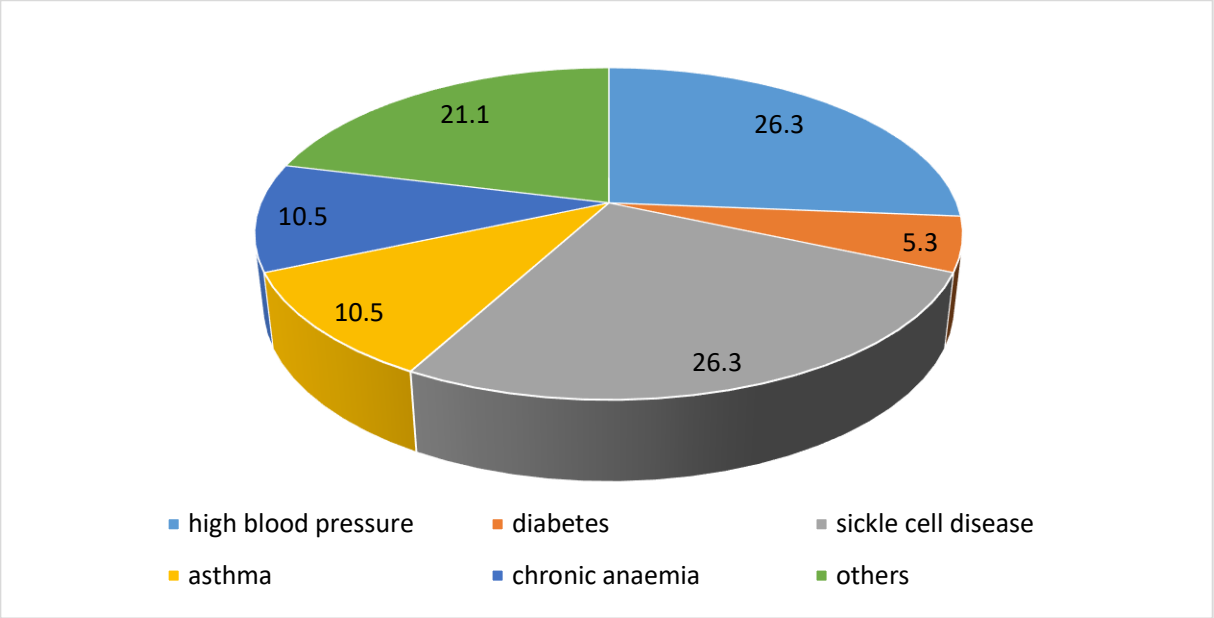

Figure 1: Mothers' personal medical history

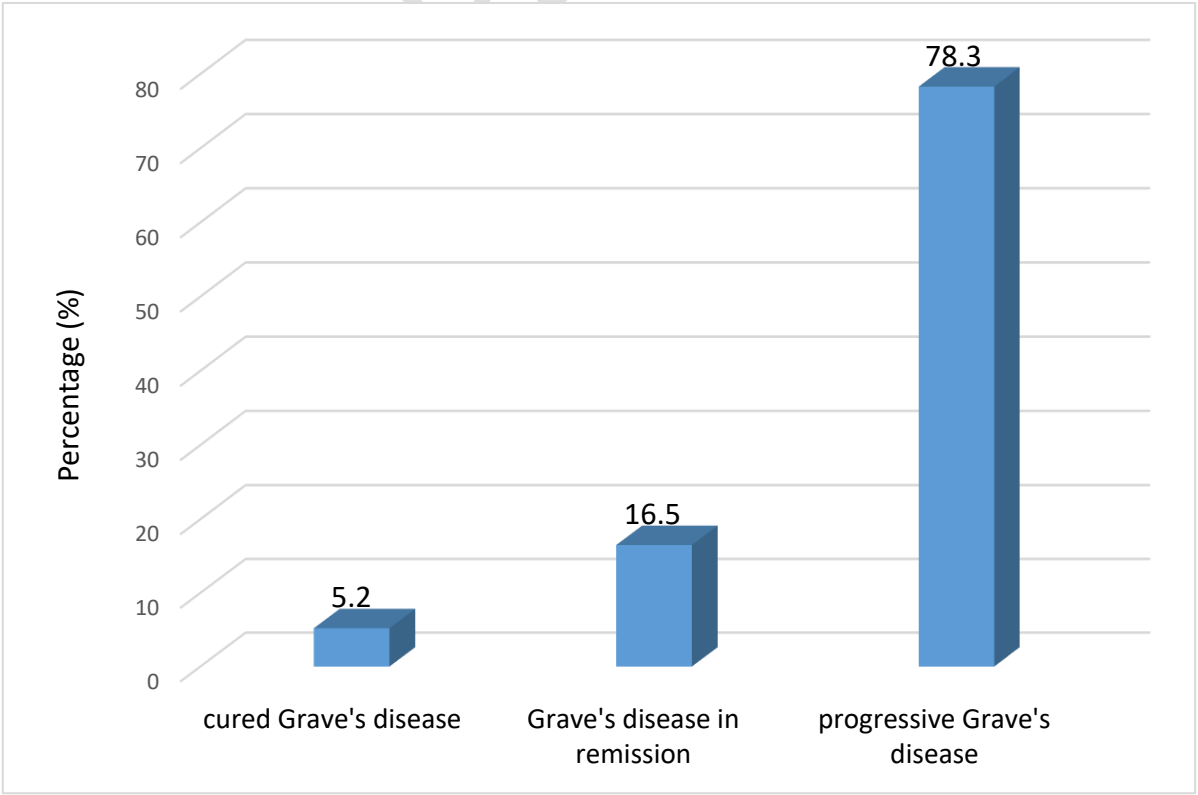

Figure 2 : Thyroid status of mothers before pregnancy

Table 1: Results of the thyroid assessment carried out during pregnancy

Thyroid balance		*Down*	*Normal*	*Elevated*
1 per quarter	**TSH (n= 43)**	76.74%	20.93 %	2.33 %
	Free T4 (n= 90)	12.22 %	46.66 %	41.11 %
	TRAK (n= 3)		33.33 %	66.66 %
2 nd quarter	**TSH (n= 24**	62.5%	33.33 %	4.16 %
	Free T4 (n=88)	15.91%	55.68%	28.41%
	TRAK (n=8)		12.5%	87.5%
3rd quarter	TSH (n=15)	60%	15%	26.67%
	Free T4 (n=69)	11.59%	52.17%	25%
	TRAK (n=2)		100%	

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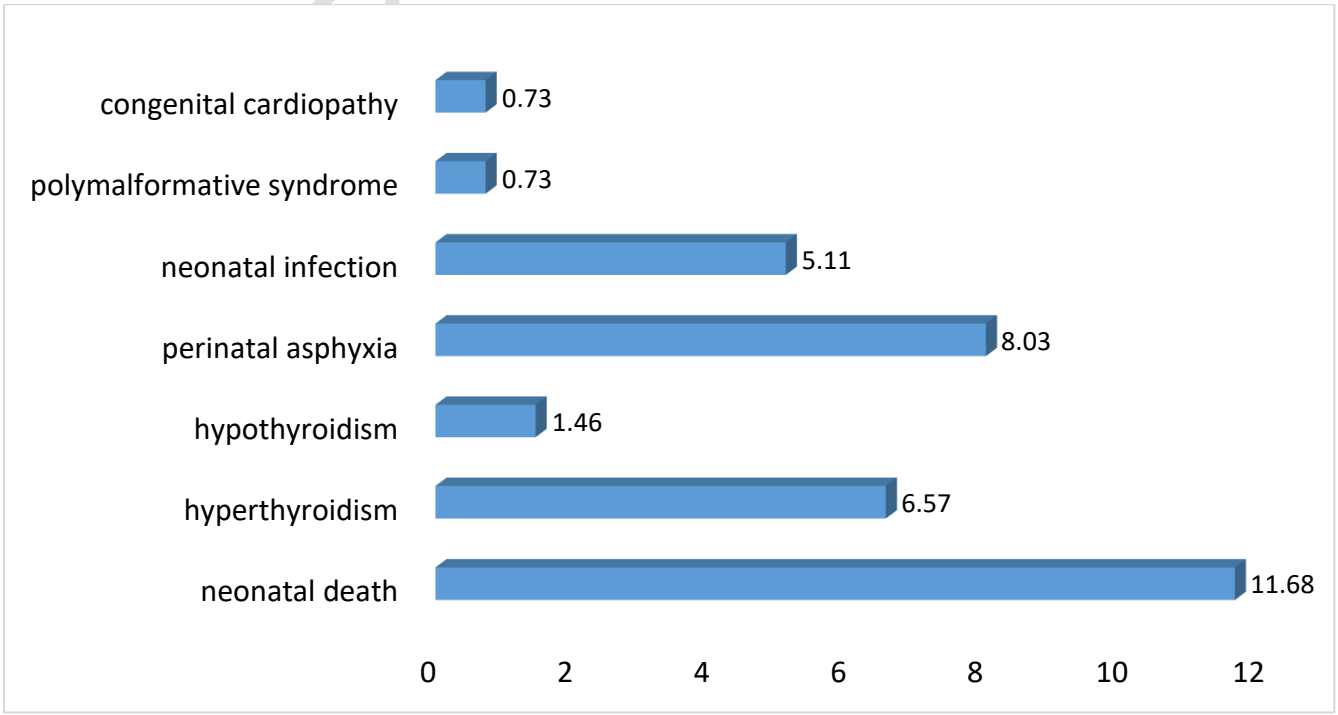

Figure 3: Neonatal complications

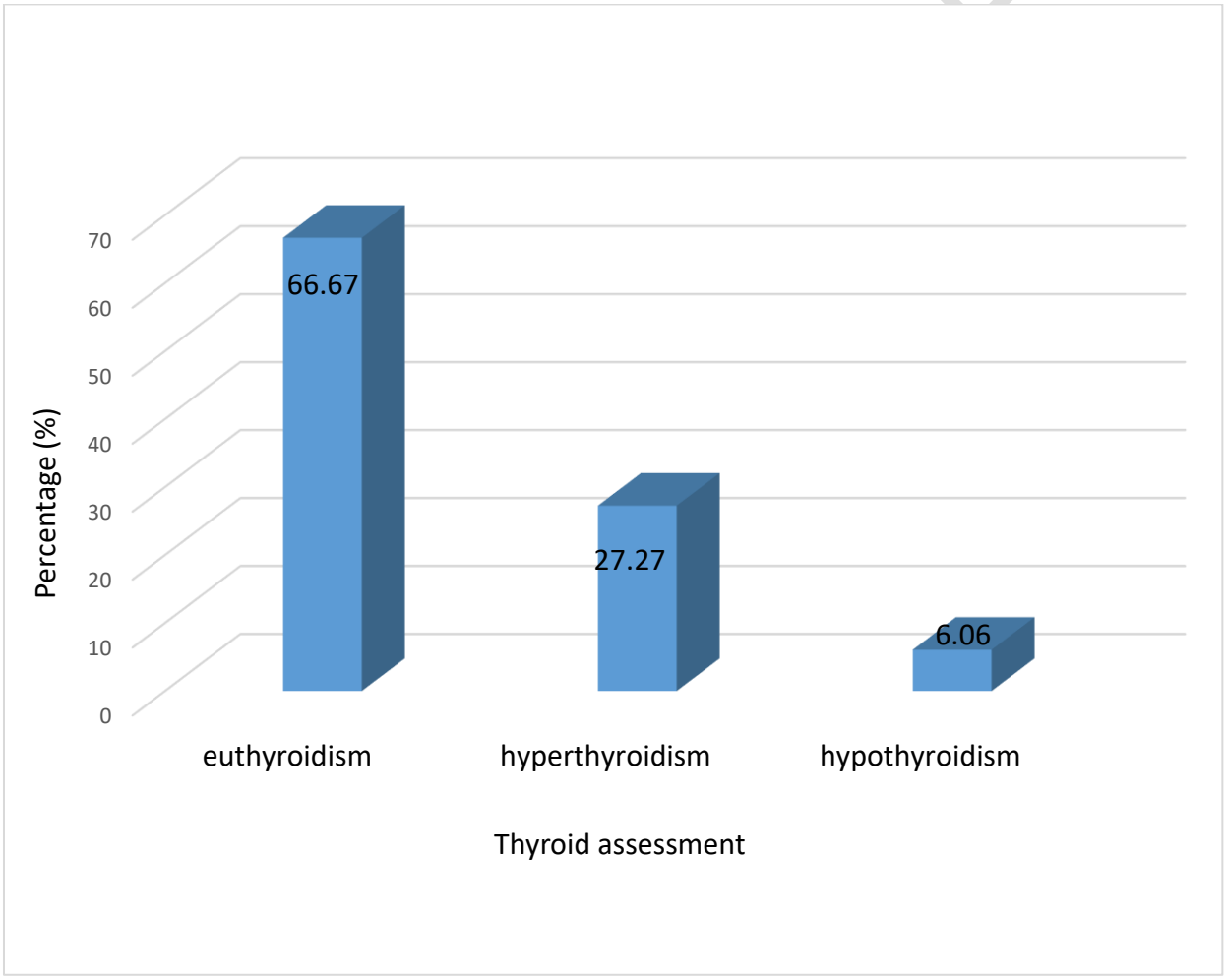

Figure 4: Neonatal thyroid assessment