NEONATAL OUTCOMES OF PREGNANCIES COMPLICATED BY MATERNAL HYPERTHYROIDISM

DR. ADLINA AWANIS BINTI MAMAT @ ABDULLAH

DISSERTATION SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER IN MEDICINE

(PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2021

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Acknowledgement

I thank GOD ALMIGHTY for all the opportunities, trials and strength that have been showered on me to finish writing the thesis. First and foremost, I would like to sincerely thanks my supervisor A/P Dr. Noraida Ramli, for her expertise, assistance, guidance and most importantly, she has provided positive encouragement and a warm spirit to finish this thesis. I also would like to thank to my co supervisor, Dr Suhaimi Hussain and Dr Najib Majdi for their advice and contribution for this thesis. My utmost appreciation to my fellow lecturers, colleagues, staff members of Hospital Universiti Sains Malaysia, family and friends for the encouragement and supports along the walks. May this work benefit others.

LIST OF TABLES AND FIGURES

LIST OF ABBREBIATION AND NOMENCLATURE

Hospital USM	: Hospital Universiti Sains Malaysia
NICU	: Neonatal Intensive Care Unit
TFT	: Thyroid function test
TSH	: Thyroid stimulating hormone
TRH	: Thyrotropin-releasing hormone
T4	: Thyroxine
T3	: Triiodothyronine
TRAb	: Thyroid receptor antibody
Anti-TPO	: anti thyroid peroxidase
Anti-TG	: anti thyroglobulin
GD	: Graves' disease
ATD	: anti thyroid drugs
BW	: birth weight
COH	: circumference of head
SGA	: small for gestational age
AGA	: appropriate for gestational age

CI : Confidence Interval

OR : Odd Ratio

HR : Hazard Ratio

SD : Standard deviation

IQR : Interquartile range

PTU : Prophylthiouracil

CBMZ : Carbimazole

MMI : Methimazole

ABSTRAK

Objektif: Mengkaji kadar bayi yang dilahirkan oleh ibu yang mempunyai masalah hyperthyroidism, status klinikal mereka, status hormon, masa median normalisasi tahap dan faktor-faktor yang mempengaruhi normalisasi free T4(fT4) dan TSH turut dikaji.

Kaedah: Kajian keratan rentas merekrut 186 bayi yang dimasukkan ke unit rawatan rapi neonatal (NICU), Hospital Universiti Sains Malaysia (Hospital USM) dari Januari 2013 hingga Disember 2018. Kami telah menganalisa data demografik dan ciri-ciri klinikal bayi, rawatan ibu, tahap autoantibodi tiroid ibu dan fungsi tiroid ibu. Akhirnya, kami menganalisa fungsi tiroid dan autoantibodi tiroid bayi. Fungsi tiroid yang tidak normal dikategorikan mengikut European Society of Paediatric Endocrinology (ESPE) untuk bayi. Analisis Kaplan Meier digunakan untuk menentukan masa normalisasi median untuk fT4, TSH dan model regresi logistik berganda digunakan untuk mengkaji perkaitan antara pemboleh-ubah berisiko mempengaruhi normalisasi fT4, TSH untuk bayi-bayi ini.

Keputusan: Kadar bayi yang dilahirkan oleh ibu yang mempunyai masalah hyperthyroidism adalah seramai 0.92 % (186/ 20198). Hanya 170 bayi

dimasukkan di dalam kajian. Dari 102(60%) bayi yang mempunyai fungsi tiroid yang tidak normal, 7(4.1%) mendapat overt hyperthyroidism dengan 4 (2.4%) mengalami krisis tiroid. Hanya 54 daripada 170 ibu (31.7%) diperiksa untuk antibodi tiroid. Median masa untuk normalisasi TFT adalah 30 hari (95% CI): (27.1, 32.8). Cox Proportional Hazard menunjukkan TFT normal pada hari 3-5, crude HR: 95% CI: 4.918 (2.11, 11.44) dan TFT pada hari 15: 3.496 (1.61, 7.58) adalah pemboleh ubah penting yang mempengaruhi masa normalisasi TFT.

Kesimpulan: Kadar bayi yang dilahirkan oleh ibu yang mempunyai masalah hyperthyroidism adalah seramai 0.92 %. Kebanyakan bayi yang dilahirkan oleh ibu dengan masalah hyperthyroidism adalah tidak terlalu bahaya, dengan median masa untuk normalisasi TFT adalah 30 hari. TFT tidak normal hari 3-5, TFT tidak normal hari 15, ibu menerima rawatan tiroid dan ibu mempunyai autoantibodi tiroid adalah factor peramal penting yang mempengaruhi normalisasi fT4, TSH untuk bayi-bayi ini.

Kata Kunci: Bayi dengan ibu mempunyai masalah hyperthyroidism, Ibu mempunyal masalah hyperthyroidism, Graves disease (GD), ujian fungsi thyroid

ABSTRACT

Objective: We aim to study the proportion of infants born to maternal hyperthyroidism, their clinical, hormonal status, median time and factors affecting time for serum free T4 (fT4) and TSH normalization.

Methodology: A cross-sectional study recruited 186 inborns admitted to Neonatal Intensive Care Unit (NICU), Hospital Universiti Sains Malaysia (Hospital USM) from January 2013 until December 2018. We analyzed newborn's demographic and clinical characteristic, maternal treatment, maternal thyroid autoantibodies level and thyroid function. Finally, we analyzed the newborn's thyroid function and thyroid autoantibodies. Abnormal thyroid function was categorised according to European Society of Paediatric Endocrinology (ESPE) for newborn. Kaplan Meier analysis were used to determine median time of fT4, TSH normalization and multiple logistic regression model were used to examine the associations between risk variables affecting fT4, TSH normalization in these newborns.

Results: The proportion of newborns with maternal hyperthyroidism were 0.92% (186/ 20198). Only 170 newborns were included in the study. Out of 102 (60%) newborns with an abnormal TFT, 7 (4.1%) developed overt hyperthyroidism with 4 (2.4%) were complicated by thyroid storm. Only 54 out 170 mothers (31.7%) were checked for presence of thyroid autoantibodies. The overall median time for TFT normalization was 30 days (95% CI): (27.1, 32.8). Cox Proportional Hazard revealed normal TFT on day

3-5, crude HR: 95% CI: 4.918 (2.11, 11.44) and day 15: 3.496 (1.61, 7.58) were significant variables affecting time of normalization.

Conclusion: The proportion of newborns with maternal hyperthyroidism were 0.92%. Most infants with maternal hyperthyroidism had a self-limiting course with median TFT normalization time of 30 days. Abnormal TFT at day 3-5, abnormal TFT at day 15, maternal received thyroid treatment and maternal presence of thyroid autoantibodies were significant predictors affecting fT4, TSH normalization for these newborns.

Keywords: Infant of mother with maternal hyperthyroidism, maternal hyperthyroidism, Graves' disease (GD), thyroid function test

CHAPTER II

THE TEXT

2.1 Section A:

Introduction

Introduction

Newborn screening for congenital hypothyroidism has become routine in most developed countries since pilot screening program was started in 1975, in Quebec and Pittsburgh[1]. In October 1998, Malaysia embarked on the same program[2].

However, the consensus to identify neonatal who are at risk for hyperthyroidism are still lacking. Neonates born to hyperthyroid mothers particularly Graves' disease are at risk for significant morbidity and mortality. Peter Lauberg et al. and Hatice Dulak et al. reported prevalence of maternal hyperthyroidism to be 0.7% and 2.8% respectively[3-4]. In Malaysia, studies have shown that the incidence of hyperthyroidism in pregnancy is 0.9 per 1000 deliveries[5]. Graves' disease (GD) was the most common cause. Other etiologies contributing of hyperthyroidism in pregnancy are single toxic adenoma, multinodular toxic goiter, thyroiditis, gestational hyperthyroidism and mutations in the thyroid stimulating hormone (TSH) receptor.

The causative antibodies in GD i.e., TSH receptor autoantibodies (TRAb), belongs to the immunoglobulin G class and freely cross the placenta, particularly during the second half of pregnancy. There are 2 types; either stimulating antibodies or blocking antibodies. TRAb stimulating antibodies binds to the TSH-receptor on thyroid follicular cells and lead to autonomous thyroid hormone production. TRAb blocking antibodies binds to the TSH-receptor but does not initiate intracellular signaling. Transfer of these TRAb to the fetus especially during second and third trimesters will result in utero and/or postnatal thyroid function abnormality[6].

There are 3 thyroid function abnormality associated with neonates born with maternal hyperthyroidism, which are; 1) neonatal hyperthyroidism, due to

transplacental passage of TRAb stimulating antibodies; 2) primary hypothyroidism, transient due to transplacental passage of TRAb blocking antibodies or transplacental passage of maternal Anti thyroid drugs (ATD) during pregnancy; 3) hypothalamic-pituitary hypothyroidism due to increased transplacental passage of thyroid hormone to the foetus during first trimester which interferes with the maturation of the thyroid-pituitary regulatory mechanism.

Foetal hyperthyroidism is most commonly seen during the third trimester. In a newborn, signs and symptoms of hyperthyroidism are nonspecific and could also be attributed to sepsis or illicit drug withdrawal, thus can be overlooked. Ogilvy-Stuart et al.[7] in 2002 reported up to 20 % mortality.

The objective of this study is to determine the prevalence of clinical, biochemical and other complications during admission for babies born to maternal hyperthyroidism. We also aim to estimate the median time to normalization of serum T4 & TSH and determine the associated factors affecting its normalization.

SECTION B:
Study Protocol

2.2.1 Documents submitted for ethical approval

Dissertation proposal

School of Medical Science
Universiti Sains Malaysia
Prepared in partial requirement fulfillment
For the Degree of Master of Medicine (Paediatric)
2017/2021

NEONATAL OUTCOMES OF PREGNANCIES COMPLICATED BY MATERNAL HYPERTHYROIDISM

Dr Adlina Awanis binti Mamat @ Abdullah
PUM 0087

Supervisors:
Assoc.Prof. Dr. Noraida Ramli
Dr Suhaimi Hussain

Research title: Neonatal Outcomes of Pregnancies Complicated by Maternal hyperthyroidism

Principal investigator: Dr. Adlina Awanis binti Mamat@ Abdullah (MPM 62468)

Co-researchers:

Prof (Madya) Dr Noraida Ramli, Consultant Paediatrician and Neonatologist, Senior Lecturer, Paediatric Department, Hospital Universiti Sains Malaysia (MPM 32514)

Dr Shuhaimi Hussain, Consultant Paediatrician and Endocrinologist, Senior Lecturer, Paediatric Department, Hospital Universiti Sains Malaysia (MPM 33606)

Dr Najib Majdi bin Yaacob, Lecturer, Department of Biostatistics and Research Methodology, Hospital Universiti Sains Malaysia (MPM 41754)

Introduction

Thyroid functions in the foetus and newborn carry importance in terms of the baby's health and development of the central nervous system. Maternal iodine deficiency, exposure to iodine, thyroid diseases (Hashimoto thyroiditis, Graves') and drugs used by the mother affect thyroid functions in the fetus. Reflections of these effects are observed immediately after delivery. Investigation of the mother in terms of thyroid diseases during pregnancy, recognition and appropriate assessment of the required conditions, screening of all newborns in the first days of life in terms of congenital hypothyroidism, timely and appropriate evaluation of the screening results, early diagnosis and appropriate treatment of cases of congenital hypothyroidism, assessment and management of cases of transient thyroid hormone disorders and close monitoring of the thyroid functions and development of patients in whom treatment has been initiated with a diagnosis of hypothyroidism are crucial in terms of developmental outcomes of the babies who have thyroid function disorders or hypothyroidism.

Maternal hyperthyroidism occurs in 0.1 – 0.4% of all pregnancies. Graves' disease is the most common85%. Other causes are single toxic adenoma, multinodular toxic goiter, thyroiditis, gestational hyperthyroidism and mutations in the TSH receptor (rare). Women with Graves' disease have thyroid receptor autoantibodies (TRAbs) that can stimulate or inhibit the fetal thyroid.

Inhibitory TRAbs may occasionally cause transient neonatal hypothyroidism in neonates of mothers with Graves'.

Many studies have been done to determine the outcomes, follow up of infant with maternal hyperthyroid disease in international levels, but currently there is no specific studies or guideline in managing this newborn in Malaysia. Thus, this study plan to know the prevalence and the outcomes of infant with maternal hyperthyroid disease, to provide guide lines for our centre in managing of infant with hyperthyroid mothers.

Problem statement & Study rationale

Maternal hyperthyroidism is observed in 0.4-4% of pregnancies. Graves' disease constitutes 85-92% of the cases. More rarely, toxic adenoma, subacute thyroiditis or thyroxine intake may be the cause. Gestational thyrotoxicosis is manifested as multiple pregnancy, hyperemesis gravidarum, nausea, vomiting, and hydatiform mole. Maternal hyperthyroid disease significantly affect newborn out comes biochemically and clinically.

Thus, this study will be conducted to determine the outcome of newborn with pregnancies complicated by maternal hyperthyroidism.

Research Question

Does the newborn born with maternal hyperthyroid diseases will be clinically or biochemically affected?

Objective

General: To study the prevalence of newborn born with maternal hyperthyroid disease and to determine the outcomes of newborn of maternal with hyperthyroid disease

Specific:

1.To determine prevalence of clinical, biochemical problems and other complication during admission for newborn with maternal with hyperthyroid disease

2. To estimate the median time to normalization of serum T4 & TSH of newborn with maternal hyperthyroid disease

3. To determine factors affecting time for serum T4 & TSH to normalize in newborn with maternal hyperthyroid disease

Literature review

Tuija Mannisto et. al conducted a study regarding neonatal outcomes which was complicated by maternal thyroid disease. This study aimed to determine the effect of maternal thyroid

diseases on birth weight and neonatal morbidity and mortality for 223,512 singleton pregnancies in US from 2002-2008. This retrospective cohort study reveals that 0.2 % of mother had hyperthyroidism, 1.4 % has primary hypothyroidism, 0.1 % has iatrogenic hypothyroidism and 1.3 % had other/unspecified thyroid disorder. Newborn with maternal hyperthyroidism were more likely to require neonatal resuscitation and had 1.6-2.0 folds risk to get respiratory distress, transient tachypnoea and sepsis as compared to other newborn. On the other hand, newborn with mother diagnosed to have primary hypothyroidism and iatrogenic hypothyroidism respectively, they also have 1.3-1.4fold of increased odds for neonatal sepsis, respiratory distress syndrome, transient tachypnoea in newborn and apnoea. Hence, the authors concluded that maternal thyroid disorder significantly affect newborn outcome during early and postnatal event.

Another study conducted by Rosanna Rovelli et al. This study aims to evaluate thyroid function of newborn with maternally diagnosed autoimmune thyroiditis and associated maternal factor (presence of thyroid peroxidase antibody thyroid medication) affecting newborn thyroid function. This prospective study was done in April 2003 to March 2006, whereby 129 newborns were included in this study. Thyroid function (T4 and TSH) on 3rd day, 15th day and at one month of life was collected. Regular monitoring of thyroid function were performed periodically until 6 months of life if newborn thyroid antibody were documented positive. Out of 129 newborn, 28% neonates showed abnormal thyroid function at the different determinations and majority of them has spontaneous normalization within the first month life. 3 newborns were started on L-thyroxine replacement therapy. Maternal

factor including presence of maternal thyroid antibody and medication therapy were not related with newborn thyroid function in this population.

M. Phoojaroenchanachai et al. conducted a study on effect of maternal hyperthyroidism during late pregnancy on the risk of neonatal low birth weight on 2001.This retrospective study was done at Siriraj Hospital, Bangkok, Thailand between 1982 till 1996. Among 188 pregnancies in 181 mothers, the newborns were divided into two group based on maternal thyroid function status: euthyroid state and hyperthyroid state. Maternal thyroid function test was periodically evaluated before and during third trimester of pregnancy and for newborns, thyroid function test and birth weights were assessed. The study reveals that maternal hyperthyroidism during the third trimester of pregnancy independently increase the risk of low birth weight by 4.1 fold .

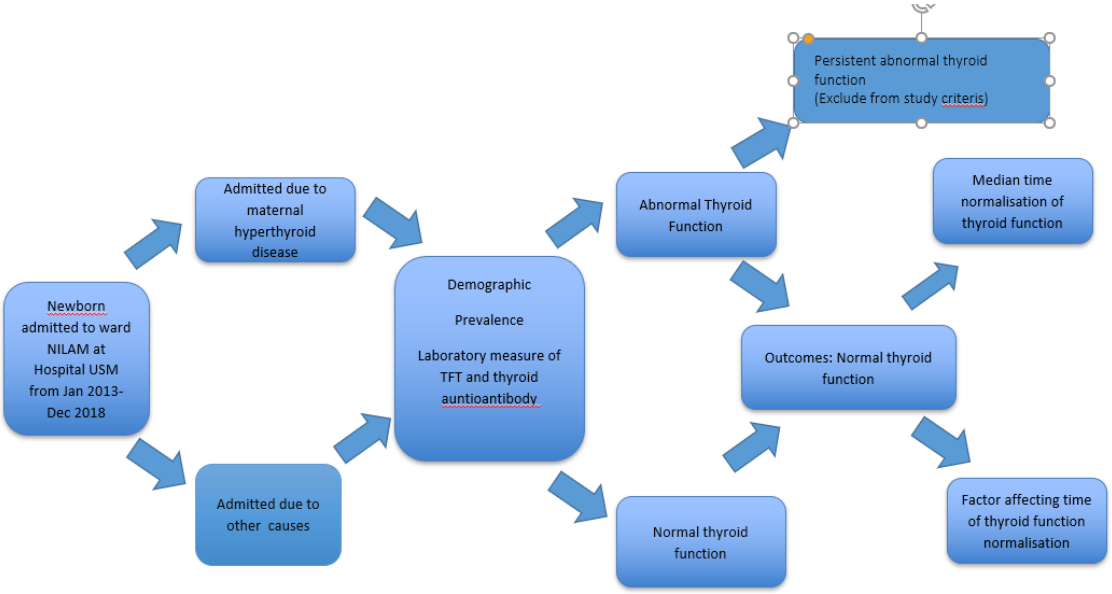
Conceptual framework

Quoting Rovelli et al, ''Newborn of mothers affected with autoimmune thyroiditis: the importance of thyroid function monitoring in the first months of life".

Admission of newborn with maternal hyperthyroid disease to ward NILAM (neonatal ward), Hospital USM, then further classified based on the demographic, clinical and laboratory measures. Subsequently, outcomes of this newborn will be studied.

Research design

This is cross sectional cohort study for objective 1 and retrospective cohort study for objective 2 and 3.



Study area

Hospital Universiti Sains Malaysia (Hospital USM) , Kubang Kerian, Kelantan

Study population

Reference Population	All newborn with maternal hyperthyroidism admitted to Hospital USM
Source population	All newborn with maternal hyperthyroidism in Hospital USM from January 2013-December 2018
Sampling frame	Data collected using Proforma Medical record-endocrine lab, record unit, admission to NICU

Subject criteria

Inclusion criteria

Newborns who were admitted to neonatal unit Hospital USM with the diagnosis of 'maternal hyperthyroidism' from 1st January 2013 until 31st December 2018. Newborn who need treament for persistent abnormal thyroid function (beyond 1 year old).

Records with inadequate “crucial data”. Crucial data include the date of diagnosis, lack of three or more sociodemographic variables of interest and lack of follow-up records.

Sample size estimation

For **first objective**, we identified the prevalence of newborn admitted to NILAM Hospital USM due to maternal hyperthyroid from January 2013 until December 2018. It will be calculated by identifying total number of newborns admitted to NILAM Hospital USM due to maternal hyperthyroid from January 2013 until December 2018, then dividing with the total number of newborns admitted to NILAM Hospital from January 2013 until December 2018, as denominator.

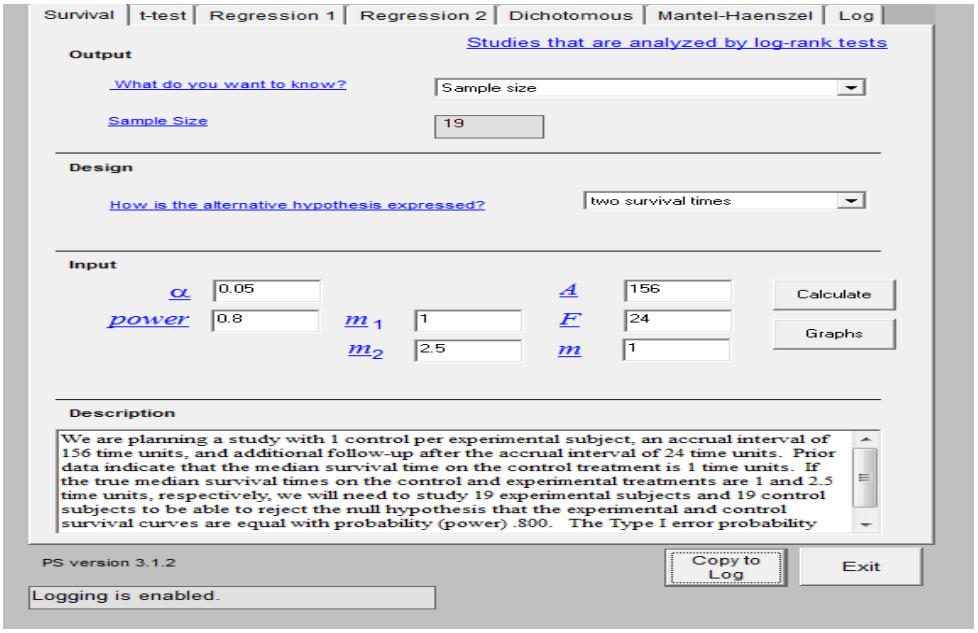
Prevalence =

Number of newborns admitted to NILAM HUSM due to maternal hyperthyroid from January 2013-December 2018

Number of newborns admitted to NILAM HUSM from January 2013-December 2018

For **second objective**, we estimate median time to normalization, which is a descriptive process and do not need sample size calculation.

For **third objective**, we want to determine factors affecting time for T4/TSH to normalize in newborns with maternal hyperthyroid disease, we use PS software to derive sample size.



Total sample sizes required are as per summarized in the table, according to the factor associated with T4/TSH normalization.

Newborn/Maternal factor	**M1**	**M2**	**M (ratio M1:M2)**	**N1 (total)**	**N2 (corrected)**	**Total size calculated *anticipate 10 % dropout**
Newborn: Gestational age Preterm <37 w Term >37-40 w	4	12	0.3	28	8	40
Newborn: Weight <2.5 kg Weight >2.5 kg	4	8	0.5	49	25	82
Newborn: Started treatment/no treatment						
Newborn: Clinical presentation at birth (Presence of thyroid symptom)						
Maternal: Presence of thyroid antibodies	4	8	0.5	49	25	82
Maternal: On treatment/no treatment						
Maternal : Thyroid status during delivery Euthyroid/Hyperthyroid						

Sampling method and subject recruitment

Subject will be recruited all through newborn admission list from Nilam ward, Hospital Universiti Sains Malaysia from January 2013-December 2018. Newborns with maternal hyperthyroid disease will be identified.

Data will be traced through record unit, endocrine lab and patient's folder during admission. It is retrospective study and does not need consent from participant.

Research tool

Performa

Operational definition

1. Thyroid disease

-medical condition that affect the functions of thyroid gland

2. Hyperthyroidism

- Form of thyrotoxicosis due to high synthesis and secretion of thyroid hormone by thyroid gland

3. Thyrotoxicosis

- Clinical state that results from any condition leading to high thyroid hormone in tissues

4. Maternal hyperthyroidism

-medical condition that affect the functions of thyroid gland relating to a mother, especially during pregnancy or shortly after childbirth

Data collection method

Duration of study

January 2013-December 2018 (312 weeks)

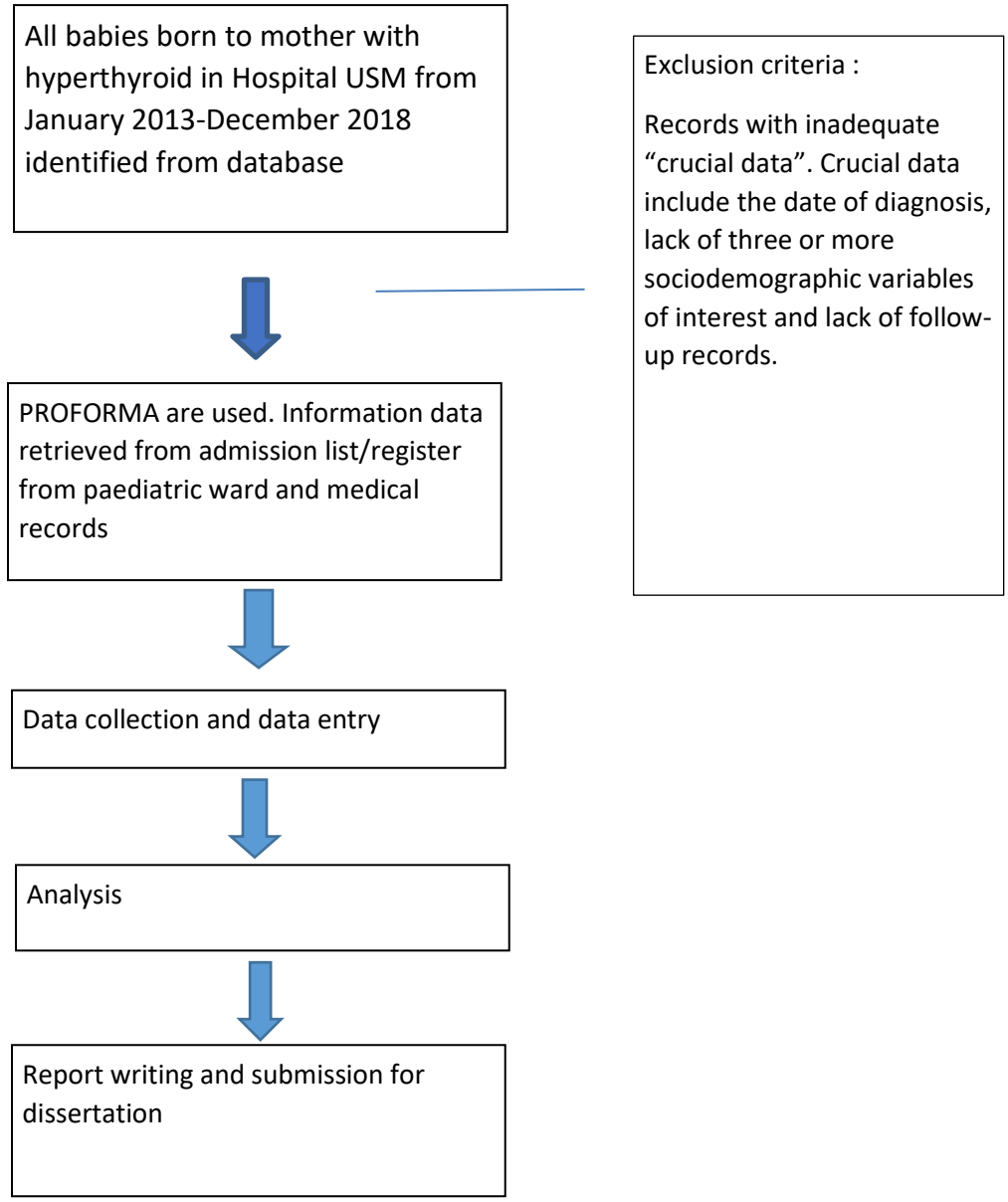
Follow up study:

January 2019-December 2019 (52 weeks)

Study design

Objective 1 is a cross sectional cohort study, whereby objective 2 and 3 is retrospective cohort study.

Study flowchart



Data analysis

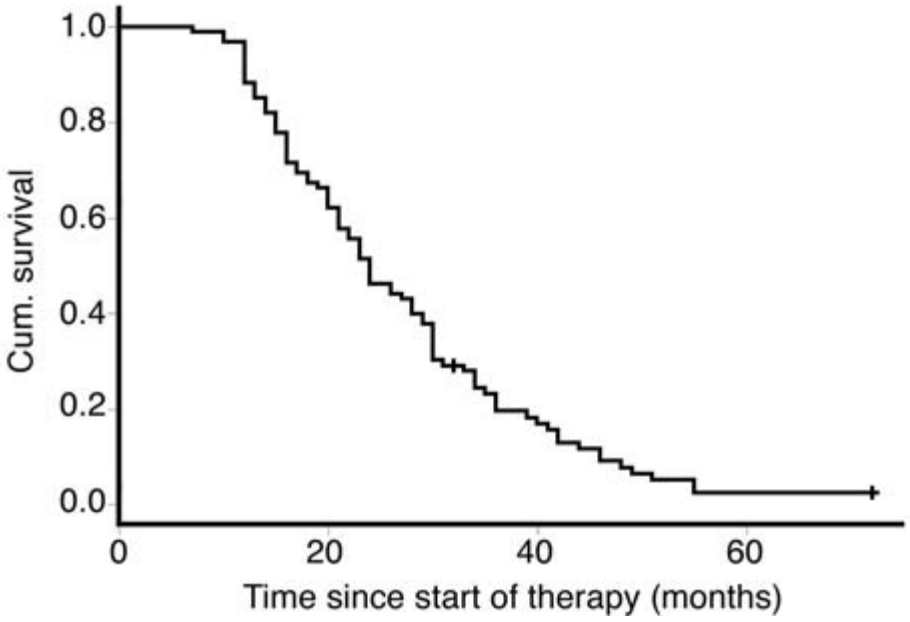
For **first objective**, we identified the prevalence of newborn admitted to NILAM Hospital USM due to maternal hyperthyroidism from January 2013 until December 2018. It will be calculated by identifying total number of newborn admitted to NILAM Hospital USM due to maternal hyperthyroidism from January 2013 until December 2018, then dividing with the total number of newborn admitted to NILAM Hospital from January 2013 until December 2018, as denominator. Results will be presented as percentage.

Prevalence =

Number of newborns admitted to NILAM HUSM due to maternal hyperthyroidism from January 2013-December 2018

Number of newborns admitted to NILAM HUSM from January 2013-December 2018

As for **second objective**, we use Kaplan-Meier survival analysis to get median time of normalization of T4, TSH of newborn with maternal hyperthyroidism. Result will be presented the median time and 95 % confidence interval (CI).



For **third objective**, we use simple and multiple cox regression analysis to determine associated factor for normalization of T4/TSH in newborn with maternal hyperthyroid mother.

Expected result(s)

Demography of Newborn with Maternal Hyperthyroidism admitted to Nilam HUSM (from Jan 2013-Dec 2018)

Demography	Newborn (N) =
Gestational age at delivery: <38 week 38-40 week	
Birth weight : <2500g ≥2500g	
Sex: Male Female	
Mode of delivery: Spontaneous vaginal delivery (SVD) Caesarean section	