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Maternal-fetal Morbidity and Mortality in the pregnant population with thyroid dysfunction in Catalonia

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Abstract

Background

Thyroid dysfunction (TD) during pregnancy has been associated with adverse maternal and perinatal outcomes, although evidence remains inconsistent. The physiological changes of gestation and variability in laboratory reference ranges complicate diagnosis and management. This study aimed to determine the prevalence of maternal–fetal morbidity and mortality associated with TD in Catalonia and to evaluate whether first-trimester TSH monitoring influences these outcomes.

Methods

A population-based descriptive study was conducted using the SIDIAP database, including 111,811 pregnancies between 2014 and 2016. TD was classified as hyperthyroidism, untreated hypothyroidism, treated hypothyroidism, or no TD. Outcomes included miscarriage, preeclampsia, prematurity, cesarean section, low birth weight, APGAR < 7, and perinatal mortality. First-trimester TSH values were categorized as ≤ 0.1, 0.1–2.5, 2.5–4, > 4 mIU/L, or not measured. Multivariable logistic regression assessed miscarriage risk adjusting for age, obesity, and TD.

Results

TD prevalence was 5.6%. Treated hypothyroidism was associated with higher rates of preeclampsia (5.7%), cesarean section (24.8%), and prematurity (6.8%). Untreated hypothyroidism showed increased preeclampsia (6.1%). Miscarriage risk increased progressively with rising TSH values, independently of TD diagnosis. Hyperthyroidism remained associated with miscarriage independently of TSH values. Lack of first-trimester TSH testing was consistently associated with higher miscarriage rates in all TD groups (treated: 11.4%; untreated: 8.2%). Among women without TD, miscarriage increased with rising TSH values, suggesting undiagnosed dysfunction. No significant differences were observed in perinatal mortality or low birth weight.

Conclusions

TD during pregnancy increases the risk of preeclampsia, prematurity, and cesarean section. Miscarriage risk is primarily driven by inadequate TSH control rather than TD diagnosis itself. The absence of first-trimester TSH testing is associated with worse outcomes. More than 6% of women without known TD had TSH > 4 mIU/L, supporting consideration of universal thyroid screening during pregnancy.

BACKGROUND

Thyroid hormones are essential for the proper fetal development, so it is important to ensure a correct thyroid gland function during pregnancy ([1]Glinoer 1997). It is now well known that thyroid dysfunction (TD) has harmful effects on the mother, the fetus and the newborn ([2]Chen2014, [3]Chen 2017, [4]Karakosta2012, [5]Männistö 2009, [6]Sahu2010, [7]Wilson2012). Maternal hypothyroidism has been associated with an increased risk of related pregnancy hypertension, [8]Nazarpour2015 [2]Chen2014, [7]Wilson2012) anemia, postpartum hemorrhage, spontaneous abortion, prematurity and stillbirth ([8]Nazarpour2015, [9]Nazarpour2015, [10]Arbib2016; [4]Karakosta2012;[11] Knøsgaard 2023; [12]Korevaar2019;). Miscarriage rate is increased in pregnant women with hypothyroidism, even among those under levothyroxine treatment, according to Taylor's work ([13]Taylor 2014).

Primary hypothyroidism rises preeclampsia probability up to 1.5 times during pregnancy. Premature delivery probability is also increased by 1.3 times due to primary hypothyroidism. Iatrogenic hypothyroidism is related to non-cephalic presentations (OR: 2.09), preeclampsia (OR: 3.64) and premature delivery (OR: 1.78) ([14]Männistö). Hyperthyroidism increases premature delivery probability by 1.8, according to Männistö et al. work ([14]Männistö) Männistö et al. study admits not having information about pregnant women thyroid treatment. Consequently, they cannot conclude if the complications observed are due to an inadequate control of the thyroid illness during pregnancy, or due to the thyroid illness itself ([14]Männistö).

Uncontrolled hyperthyroidism is associated with preeclampsia, antenatal death, spontaneous abortion, premature delivery, maternal heart failure, intrauterine growth retardation and placental abruption ([14]Männistö 2013; [15]Alexander 2017 [16] Andersen [17]Yim).

Nevertheless, there is controversy about the adverse effects on some thyroid disorders. After a complete review of different papers based on hypothyroxinemia and subclinical hypothyroidism, ATA (American Thyroid Association) 2017 and 2026 ([15]Alexander 2017 Korevaar 2026 [18]), concludes that both alterations are associated with some adverse perinatal outcomes in several studies, but not in all of them. Therefore, ATA 2017 and 2026 Korevaar 2026 [18] does not recommend systematical treatment with levothyroxine in these cases.

However, SEEN-SEGO (Sociedad Española de Endocrinología y Nutrición-Sociedad Española de Ginecología y Obstetricia) recommend levothyroxine treatment to pregnant women with TSH values > 4 mIU/L ([19]Velasco 2023). A recent meta-analysis supports this decision ([20]Sankoda2024). Nonetheless, screening all pregnant women to detect subclinical thyroid diseases and treating them remains controversial (Korevaar 2026 [18] ([19]Velasco 2023).

To this debate, another difficulty must be added since we do not know what the best way is to properly diagnose the thyroid disease during pregnancy, both for the thyroid physiological changes during pregnancy and the different techniques used to evaluate thyroid hormones.

These physiological changes in gestation make that the thyroid hormonal general population reference values are not the same in case of pregnancy. [21]Tingi2016, [15]Alexander). On the other hand, the different techniques used to evaluate thyroid hormones can vary depending on the laboratory. ([22]Valdés2017, [23]Taylor2018).

The TSH cut-off point, which implies higher risk for the maternal-fetal mortality and morbidity, is also controversial. Since 2011, ATA([24]Stagnado-Green2011) recommends each laboratory had its own reference values for every gestation trimestre. In this document, ATA 2011 stated that if no TSH own values are available, the TSH cut-off point should be 2.5 mIU/L as an upper limit in the first trimester. Such decision implied subclinical hypothyroidism overdiagnosis ([25]Korevaar 2015) [26] Yamamoto.

ATA 2017 changed TSH cut-off point from 2.5 to 4 mIU/L for hypothyroidism diagnose. However, TSH < 2.5 mU/L should be the goal in case of pregnant women under treatment with levothyroxine. (Korevaar 2026 [18])

Some studies report a maternal-fetal morbidity increase when TSH > 2.5 mIU/L ([10]Arbib 2016; [4]Karakosta 2012, [27] Hernández, López and Soldevila), but such higher risk is not homogeneous ([28]Nazarpour 2018; [13]Taylor 2014). Therefore, the controversy regarding the TSH risk cut-off point remains unresolved.

A research conducted in Lleida (Catalonia) reported that TSH values > 2.5 mU/L during the first trimestre of pregnancy were associated with a higher risk of adverse obsterical results ([27] Hernández, López and Soldevila). In spite of that, another population-based study in the same area did not observe a maternal-fetal morbidity increase in 1127 women with hypothyroidism. Although hypothyroidism was associated with a higher presence of diabetes, hypertension and dyslipidemia in this report([29]Siscart 2023).

The objectives of this study are to know the maternal-fetal morbidity and mortality prevalence related to TD and to analyze whether TD control, during the first trimester of pregnancy, is associated with some changes in the maternal-fetal morbidity and mortality.

METHODOLOGY

A descriptive study of pregnancies occurred in Catalonia, between 2014 and 2016 was performed. It was based on secondary data from the computerized register of the Primary Health Care Research Information and Development System (SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) (www.sidiap.org).

SIDIAP generates a comprehensive amount of medical data providing access to reliable information for primary healthcare research. The data originate mainly from ICS (Institut Català de la Salut) electronic health records and other sources. ICS is the governmental institution that manages the public health system in Catalonia. SIDIAP database covers about 80% of the Catalan population with over 7 million inhabitants during the studied period.

The analytical results come from 33 laboratories which provide service to primary health centers in Catalonia. During the studied period, three laboratories out of the 33 had reference values adjusted for pregnant people.

The population under study included pregnancies that started between 2014 and 2016 in women who had at least one follow-up visit to the Sexual and Reproductive Health Program at the primary healthcare. This program is responsible for antenatal care in Catalonia. Multiple pregnancies or pregnancies in women younger than 16 or older than 49 years of age were excluded.

The population on which the various statistical analyses were performed is shown in Fig. 1

Sample size and sample procedures

The goals of the present study are to assess mother and fetal morbidity and mortality associated with TD and to analyze whether TD control is associated with differences in maternal and fetal morbidity and mortality.

To calculate the sample size it is necessary to attain the aim that requires a larger sample size, which is the one with the prevalence closer to 50% in the smallest subpopulation. This context will be the cesarean section rate estimated in hyperthyroid women.

Hyperthyroidism prevalence among young Spanish women is around 0.6% (0.5-1% [22]Valdés2017, 0.54% [30] Torrejón). It was observed a 9.5% of cesarean section rate among hyperthyroid pregnant women ([5]Männistö 2009). Assuming that 10% of cesarean section is expected to be identified with a precision of 2.5% (interval width of 5%) 554 hyperthyroid pregnant women are needed. Considering that this figure represents a 0.6% from the total pregnant women, 92333 pregnancies need to be studied.

SIDIAP database has 134860 pregnancies in the same period, so this figure covers the required sample size widely. For the purpose of the present study, all the records in the SIDIAP database fulfilling the inclusion criteria will be analyzed.

Variable definition

Exposure Variables

The principal exposure variable was TD, describing four groups according to active register at last menstrual period date (LMP) for prescription of thyroid hormones or diagnose codes in ECAP (Estación Clínica informatizada de Atención Primaria; Electronics records in Primary Health Care): without TD, hyperthyroidism, untreated hypothyroidism and treated hypothyroidism.

Hyperthyroidism was defined if there was an active prescription of antithyroid drugs (ATC (*Anatomical, Therapeutic, Chemical classification System) code* H03B) or the International Classification Disease (ICD) diagnose code E05 (Thyrotoxicosis).

Untreated hypothyroidism was defined in the presence of any of the following diagnose codes (ICD-10: E02, E03, E89.0) without an active prescription register of thyroid hormones (ATC code H03AA -levothyroxine-).

Treated hypothyroidism was defined if there was an active prescription of thyroid hormones (ATC code H03AA -levothyroxine-).

The following study independent variables were evaluated on the date of the LMP as they are very important health risk factors, especially during pregnancy: age, hypertension (I10, I15), diabetes (E11, E12, E13; E14), obesity (E66, E66.0, E66.1, E66.2, E66.9), Morbid obesity (E66.8), and ischemic heart disease (I20, I21, I22, I23, I24, I25).

TSH evaluation was defined as having a record of TSH during the first trimester. The value of this TSH record is categorized according to the following levels: (0.1–2.5), [2.5-4], > 4 (TSH level).

Outcomes

Miscarriage, considering pregnancy episodes classified as: “Miscarriage”, "Ectopic pregnancy” or “Molar pregnancy”.

Perinatal mortality, considering pregnancy episodes classified as “Stillbirth”.

Newborns under 10th percentile of their sex and gestational age were considered having low birth weight (LBW) ([31]normes catalanes 1997–2001).

5-minute Apgar score was categorized as being above or below 7.

Preeclampsia was defined as having systolic blood pressure > 140 and/or diastolic blood pressure > 90 during the third trimester of pregnancy.

Cesarean section, considering pregnancy episodes classified as “Cesarean section”.

Prematurity was considered for deliveries with gestational age between 22 and 36(+ 6d) weeks.

Statistical analysis

Study variables were described using absolute and relative frequencies (and mean and standard deviation for age as continuous). Chi-square test was used to compare frequencies of maternal-fetal morbidity and mortality outcomes according to TD groups, according to TSH evaluation, and according to TSH level (overall and stratified by TD groups); in cases where any subgroup contained fewer than five observations, Fisher’s exact test was applied instead. Post-hoc comparisons were performed when appropriate.

To assess the association between miscarriage and the other variables three models were explored: a full model including all covariates and interaction terms among TSH categories and thyroid dysfunction status, a full model excluding interaction terms and a reduced model obtained through backward variable selection based on Akaike Information Criterion, starting from the full interaction model. Adjusted odds ratios with 95% confidence intervals were calculated. Statistical significance was defined as a two-sided p-value < 0.05

The R-4.0.3 statistical package for Windows was used.

RESULTS

Pregnancies which met all the inclusion criteria were 111811.The average age of pregnant women was 31.08 years (standard deviation 5.75) and 23.5% of them were 35 years or older at the LMP date. Their prevalence of hypertension, diabetes mellitus, obesity, morbid obesity and heart disease was 0.9, 0.5, 8.7, 0.3 and 0.02%, respectively. The women participating in the study, 0.63% suffered from hyperthyroidism, 2.69% had hypothyroidism without treatment and 2.29% were treated for hypothyroidism.TD rate increased significantly with age (Table 1). Characteristics on women with pre and full-term pregnancies and their prevalence of TD were very similar to the above mentioned (Table 1).

Miscarriage rate in the total studied population was 7.1%. No significant statistical differences were observed depending on whether TD was present (Table 2). Differences in perinatal death, low birth weight (LBW), Apgar score < 7 at 5 minutes were not observed either, depending on whether TD was present.

Preeclampsia rate in the total studied population was 4.0%. Higher ratios were observed in treated or untreated hypothyroid women, 5.7% and 6.1%, respectively ($p < 0.001$) (Table 2).

Cesarean section rate in the total studied population was 19.8%. Higher values were observed in treated hypothyroid population (24.8%) ($p < 0.001$).

Prematurity rate was also higher in treated hypothyroid population (6.8%) compared with the total studied population (5.2%) ($p = 0.022$), without confirmation in the posthoc analysis (Table 2).

Table 3 shows the results of hypothyroid population whether they have a TSH test in the gestation first trimester. No TSH test was carried out in the first trimester in 43.3% of women diagnosed with hypothyroidism. Miscarriage rate in women suffering from hypothyroidism was significantly superior in the ones with no TSH test in the first trimester (9.3% vs 5.5%; $p < 0.001$).

Women suffering from hypothyroidism with a TSH test during the first trimester had an Apgar test < 7 at five minutes in a percentage of 0.6%. However, this percentage was 0.1% ($p = 0.038$) for those without a TSH test.

Table 4 shows the results of untreated hypothyroid population whether they have a TSH test done and its values. Miscarriage rate was significantly superior in women with no TSH evidence with regard to the ones with TSH values < 4 mIU/L ($p < 0.001$). The Apgar score < 7 was significantly different ($p = 0.038$), but no significance was observed in the post hoc analysis. A similar result was observed for the cesarean section rate ($p = 0.017$) in the untreated hypothyroid group.

Table 5 shows the results of treated hypothyroid population depending on whether they had a TSH test done and its values. Spontaneous abortion rate is significantly superior in women without a TSH test ($p < 0.001$). Cesarean section rate is higher in women with treated hypothyroidism without a TSH test, as well as in the ones with TSH values between 0.1 to 2.5 mIU/L ($p = 0.012$), although the post hoc analysis does not establish any significance.

Table 6 shows the results of the population without TD depending on whether they had a TSH test done and its values. Among the ones with a TSH test done (18.79%), 6.7% had a TSH value superior to 4 mIU/L. Women without TD, but with a TSH determination during the first trimester, had higher rates of obesity, morbid obesity, diabetes and hypertension (Table S1 in supplementary material).

The observed spontaneous abortion rate based on TSH levels in Table 6 was statistically significant. When the TSH value was below 0.1mIU/L, the miscarriage rate was lower compared to other groups. The spontaneous abortion rate increases as TSH levels rise.

Prevalence rates of obesity, morbid obesity, diabetes and hypertension were similar in these groups with or without TSH determination and in those women with hyperthyroidism, as well as in women with untreated hypothyroidism (Tables S2 and S3 in supplementary material).

Women with treated hypothyroidism had statistically superior prevalence rates for morbid obesity, diabetes and hypertension (Table S4 in supplementary material).

In multivariable analyses (Table S5), maternal age, obesity and TSH categories were independently associated with miscarriage risk. After adjustment for these variables, TD categories (treated or untreated hypothyroidism) were no longer independently associated with miscarriage. Conversely, TSH levels showed a graded association with miscarriage risk, with lower TSH values associated with lower risk and progressively higher TSH values associated with increased risk. Hyperthyroidism remained associated with miscarriage, independently of TSH levels (Table 7).

Table 1
Thyroid Dysfunction Prevalence according to age and medical conditions in global pregnancies and in Pre and Full-term pregnancies.

Global Pregnancies		**n analyzed**	**Missing**	**Global**	**No (n = 105530)**	**HyperT (n = 707)**	**HypoT 0 (n = 3012)**	**HypoT 1 (n = 2562)**	**p value**	**posthocs**
Age at LMP		111811	0						< 0.001	bcdij
	< 35			85486 (76.5%)	81154 (94.9%)	502 (0.6%)	2209 (2.6%)	1621 (1.9%)		
	35–39			22134 (19.8%)	20575 (93.0%)	164 (0.7%)	663 (3.0%)	732 (3.3%)		
	>=40			4191 (3.7%)	3801 (90.7%)	41 (1.0%)	140 (3.3%)	209 (5.0%)		
Obesity		111811	0	9744 (8.7%)	8862 (8.4%)	70 (9.9%)	447 (14.8%)	365 (14.2%)	< 0.001	cdhi
Morbid obesity		111811	0	349 (0.3%)	308 (0.3%)	1 (0.1%)	20 (0.7%)	20 (0.8%)	< 0.001	cd
Hypertension		111811	0	961 (0.9%)	856 (0.8%)	9 (1.3%)	41 (1.4%)	55 (2.1%)	< 0.001	cd
Diabetes		111811	0	515 (0.5%)	425 (0.4%)	12 (1.7%)	25 (0.8%)	53 (2.1%)	< 0.001	bcdj
heart disease		111811	0	18 (0.0%)	15 (0.0%)	2 (0.3%)	1 (0.0%)	0 (0.0%)	0.011	
Pre and Full-term Pregnancies		**n analyzed**	**Missing**	**Global**	**No (n = 68362)**	**HyperT (n = 439)**	**HypoT 0 (n = 1933)**	**HypoT 1 (n = 1590)**	**p value**	**posthocs**
Age at LMP		72324	0						< 0.001	bcdj
	< 35			57150 (79.0%)	54277 (95.0%)	321 (0.6%)	1483 (2.6%)	1069 (1.9%)		
	35–39			13180 (18.2%)	12278 (93.2%)	96 (0.7%)	377 (2.9%)	429 (3.3%)		
	>=40			1994 (2.8%)	1807 (90.6%)	22 (1.1%)	73 (3.7%)	92 (4.6%)		
Obesity		72324	0	6304 (8.7%)	5752 (8.4%)	41 (9.3%)	282 (14.6%)	229 (14.4%)	< 0.001	cdh
Morbid obesity		72324	0	205 (0.3%)	185 (0.3%)	0 (0.0%)	9 (0.5%)	11 (0.7%)	0.009	
Hypertension		72324	0	539 (0.7%)	481 (0.7%)	6 (1.4%)	20 (1.0%)	32 (2.0%)	< 0.001	d
Diabetes		72324	0	279 (0.4%)	226 (0.3%)	8 (1.8%)	13 (0.7%)	32 (2.0%)	< 0.001	bdj
heart disease		72324	0	10 (0.0%)	9 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0.428	

Hypothyroidism 0: without treatment. Hypothyroidism 1: with treatment

Post-hoc contrasts applied to statistically significant differences

b = No vs Hyperthyroidism; c = No vs Hypothyroidism 0; d = No vs Hypothyroidism 1;

h = Hyperthyroidism vs Hypothyroidism 0; i = Hyperthyroidism vs Hypothyroidism 1;

j = Hypothyroidism 0 vs Hypothyroidism 1

Table 2
Complications depending on the presence or absence of Thyroid Dysfunction

Global Pregnancies	n analyzed	Missing	Global	No (n = 105530)	Hyperthyroidism (n = 707)	Hypothyroidism 0 (n = 3012)	Hypothyroidism 1 (n = 2562)	p value	posthocs
Miscarriage	111811	0	7884 (7.1%)	7426 (7.0%)	60 (8.5%)	197 (6.5%)	201 (7.8%)	0.117	
Perinatal mortality	111811	0	238 (0.2%)	226 (0.2%)	1 (0.1%)	7 (0.2%)	4 (0.2%)	0.950	
Pre and Full-term Pregnancies	**n analyzed**	**Missing**	**Global**	**No (n = 68362)**	**Hyperthyroidism (n = 439)**	**Hypothyroidism 0 (n = 1933)**	**Hypothyroidism 1 (n = 1590)**	**p value**	**posthocs**
Preeclampsia	66844	5480	2699 (4.0%)	2501 (3.9%)	14 (3.6%)	106 (6.1%)	78 (5.7%)	< 0.001	cd
Caesarean section	72324	0	14298 (19.8%)	13409 (19.6%)	81 (18.5%)	414 (21.4%)	394 (24.8%)	< 0.001	d
Prematurity	72324	0	3779 (5.2%)	3537 (5.2%)	28 (6.4%)	106 (5.5%)	108 (6.8%)	0.022	
Low birth weight	70712	1612	5512 (7.8%)	5211 (7.8%)	28 (6.5%)	156 (8.3%)	117 (7.5%)	0.642	
Apgar score at 5 minutes < 7	63382	8942	223 (0.4%)	210 (0.4%)	1 (0.3%)	8 (0.5%)	4 (0.3%)	0.796	

Hypothyroidism 0: without treatment. Hypothyroidism 1: with treatment

c = No vs Hypothyroidism 0 ; d = No vs Hypothyroidism 1

Table 3
Complications in Patients with Hypothyroidism (treated or untreated) depending on whether a TSH test is done in the 1st trimester.

Global Pregnancies	n analyzed	Missing	Global	No TSH (n = 2416)	TSH (n = 3158)	p value
Miscarriage	5574	0	398 (7.1%)	224 (9.3%)	174 (5.5%)	< 0.001
Perinatal mortality	5574	0	11 (0.2%)	5 (0.2%)	6 (0.2%)	1.000
Pre and Full-term Pregnancies	**n analyzed**	**Missing**	**Global**	**No TSH (n = 1323)**	**TSH (n = 2200)**	**p value**
Preeclampsia	3105	418	184 (5.9%)	69 (6.1%)	115 (5.8%)	0.813
Caesarean section	3523	0	808 (22.9%)	319 (24.1%)	489 (22.2%)	0.200
Prematurity	3523	0	214 (6.1%)	75 (5.7%)	139 (6.3%)	0.467
Low birth weight	3448	75	273 (7.9%)	106 (8.2%)	167 (7.8%)	0.649
Apgar score at 5 minutes < 7	3041	482	12 (0.4%)	1 (0.1%)	11 (0.6%)	0.038

Table 4
Complications in Patients with Untreated Hypothyroidism

Global Pregnancies	**n analyzed**	**Missing**	**Global**	**TSH < = 0.1 (n = 8)**	**TSH(0.1, 2.5] (n = 470)**	**TSH(2.5, 4] (n = 475)**	**TSH > 4 (n = 468)**	**No TSH (n = 1591)**	**p value**	**posthocs**
Miscarriage	3012	0	197 (6.5%)	0 (0.0%)	19 (4.0%)	19 (4.0%)	29 (6.2%)	130 (8.2%)	< 0.001	gi
Perinatal mortality	3012	0	7 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	4 (0.3%)	0.155	
Pre and Full-term Pregnancies	**n analyzed**	**Missing**	**Global**	**<=0.1 (n = 6)**	**(0.1, 2.5] (n = 344)**	**(2.5, 4] (n = 354)**	**> 4 (n = 330)**	**No TSH (n = 899)**	**p value**	**posthocs**
Preeclampsia	1747	186	106 (6.1%)	0 (0.0%)	24 (7.4%)	22 (6.8%)	14 (4.7%)	46 (5.8%)	0.086	
Caesarean section	1933	0	414 (21.4%)	0 (0.0%)	70 (20.3%)	73 (20.6%)	70 (21.2%)	201 (22.4%)	0.017	
Prematurity	1933	0	106 (5.5%)	0 (0.0%)	20 (5.8%)	16 (4.5%)	21 (6.4%)	49 (5.5%)	0.839	
Low birth weight	1884	49	156 (8.3%)	0 (0.0%)	27 (8.2%)	25 (7.1%)	33 (10.3%)	71 (8.1%)	0.168	
Apgar score at 5 minutes < 7	1662	271	8 (0.5%)	0 (0.0%)	3 (1.0%)	3 (1.0%)	1 (0.4%)	1 (0.1%)	0.038	

g = (0.1, 2.5] vs No TSH; i = (2.5, 4] vs No TSH

Table 5
Complications in Patients with Treated Hypothyroidism

Global Pregnancies	**n analyzed**	**Missing**	**Global**	**TSH < = 0.1 (n = 45)**	**TSH(0.1, 2.5] (n = 676)**	**TSH(2.5, 4] (n = 462)**	**TSH > 4 (n = 554)**	**No TSH (n = 825)**	**p value**	**posthocs**
Miscarriage	2562	0	201 (7.8%)	1 (2.2%)	41 (6.1%)	30 (6.5%)	35 (6.3%)	94 (11.4%)	< 0.001	gij
Perinatal mortality	2562	0	4 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.5%)	1 (0.1%)	0.164	
Pre and Full-term Pregnancies	**n analyzed**	**Missing**	**Global**	**<=0.1 (n = 20)**	**(0.1, 2.5] (n = 464)**	**(2.5, 4] (n = 311)**	**> 4 (n = 371)**	**No TSH (n = 424)**	**p value**	**posthocs**
Preeclampsia	1358	232	78 (5.7%)	2 (13.3%)	15 (3.7%)	21 (7.6%)	17 (5.3%)	23 (6.8%)	0.085	
Caesarean section	1590	0	394 (24.8%)	3 (15.0%)	132 (28.4%)	65 (20.9%)	76 (20.5%)	118 (27.8%)	0.012	
Prematurity	1590	0	108 (6.8%)	2 (10.0%)	30 (6.5%)	23 (7.4%)	27 (7.3%)	26 (6.1%)	0.818	
Low birth weight	1564	26	117 (7.5%)	4 (20.0%)	29 (6.4%)	19 (6.3%)	30 (8.2%)	35 (8.4%)	0.168	
Apgar score at 5 minutes < 7	1379	211	4 (0.3%)	1 (5.3%)	2 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0.038	

g = (0.1, 2.5] vs No TSH ; i = (2.5, 4] vs No TSH ; j = > 4 vs No TSH

Table 6
Complications in the total population without Thyroid Dysfunction

Global Pregnancies	**n analyzed**	**Missing**	**Global**	**TSH < = 0.1 (n = 626)**	**TSH(0.1, 2.5] (n = 14376)**	**TSH(2.5, 4] (n = 3498)**	**TSH > 4 (n = 1329)**	**No TSH (n = 85701)**	**p value**	**posthocs**
Miscarriage	105530	0	7426 (7.0%)	14 (2.2%)	691 (4.8%)	208 (5.9%)	95 (7.1%)	6418 (7.5%)	< 0.001	abcdfgi
Perinatal mortality	105530	0	226 (0.2%)	2 (0.3%)	44 (0.3%)	6 (0.2%)	4 (0.3%)	170 (0.2%)	0.068	
Pre and Full-term Pregnancies	**n analyzed**	**Missing**	**Global**	**<=0.1 (n = 465)**	**(0.1, 2.5] (n = 10640)**	**(2.5, 4] (n = 2531)**	**> 4 (n = 914)**	**No TSH (n = 53812)**	**p value**	**posthocs**
Preeclampsia	63353	5009	2501 (3.9%)	14 (3.3%)	434 (4.4%)	95 (4.1%)	40 (4.7%)	1918 (3.8%)	0.042	
Caesarean section	68362	0	13409 (19.6%)	82 (17.6%)	1996 (18.8%)	501 (19.8%)	173 (18.9%)	10657 (19.8%)	0.114	
Prematurity	68362	0	3537 (5.2%)	15 (3.2%)	595 (5.6%)	141 (5.6%)	41 (4.5%)	2745 (5.1%)	0.051	
Low birth weight	66836	1526	5211 (7.8%)	36 (7.9%)	809 (7.7%)	201 (8.1%)	70 (7.8%)	4095 (7.8%)	0.979	
Apgar score at 5 minutes < 7	59955	8407	210 (0.4%)	0 (0.0%)	25 (0.3%)	17 (0.8%)	3 (0.4%)	165 (0.4%)	0.023	e

a = <=0.1 vs (0.1, 2.5] ; b = <=0.1 vs (2.5, 4] ; c = <=0.1 vs > 4 ; d = <=0.1 vs No TSH ; e = (0.1, 2.5] vs (2.5, 4] ; f = (0.1, 2.5] vs > 4 ; g = (0.1, 2.5] vs No TSH ; i = (2.5, 4] vs No TSH

Table 7
Multivariate logistic regression predicting miscarriage. Reduced model resulting from a stepwise backwards selection process based on Akaike Information Criteria starting from the full model with interaction.

		Reduced model	
		OR (95%CI)	**p-value**
(Intercept)		0.04 (0.04, 0.04)	< 0.001
TSH	*<=0.1*	0.57 (0.36, 0.86)	0.013
	(0.1, 2.5]	(ref.)	
	(2.5, 4]	1.26 (1.08, 1.45)	0.002
	> 4	1.44 (1.20, 1.72)	< 0.001
	Not measured	1.66 (1.54, 1.79)	< 0.001
Thyroid dysfunction	*No TD*	(ref.)	
	HyperT	1.34 (1.01, 1.74)	0.033
	Untreated HypoT	0.94 (0.80, 1.09)	0.391
	Treated HypoT	1.11 (0.95, 1.29)	0.181
Age at LMP	*< 35*	(ref.)	
	[35, 40)	2.01 (1.91, 2.12)	< 0.001
	>=40	3.38 (3.10, 3.69)	< 0.001
Obesity		1.16 (1.08, 1.25)	< 0.001

DISCUSSION

The present study analyses the impact that TD has on the maternal-fetal morbidity and mortality in Catalonia and shows how the control of the different thyroid disorders has an effect in the obstetrical and perinatal results.

Prematurity, cesarean section and preeclampsia rates are significantly higher in the population with treated hypothyroidism. Preeclampsia rate is also significantly higher in the population with untreated hypothyroidism.

Miscarriage rate is significantly higher when a TSH test is not performed in the first trimester of gestation in women with treated or untreated hypothyroidism and in women without TD.

It is observed that as TSH values increase, miscarriage rate increases, too. Hyperthyroidism is associated with more spontaneous abortions, independently of TSH levels, age or obesity.

WOMEN SUFFERING FROM A KNOWN THYROID DISFUNCTION

Hypothyroidism per se has been related to a higher rate of miscarriages in some publications (Zhang 2017[32], Shinohara 2018 [33]), but in the present study, as well as in Siscart et al. (Siscart 2023[29]), this relation has not been found.

Post-hoc analysis did not reveal significant differences in miscarriage rates according to TSH levels among women with both treated or untreated hypothyroidism (Tables 4 and 5). In fact, the rates were very similar when TSH is > 4mIU/L (6.3% for treated women and 6.2% for the untreated ones). Besides, multivariable analysis assessing factors associated with miscarriage risk showed that hypothyroidism diagnose was not associated with an increased risk of miscarriage. By contrast, miscarriage risk increased progressively as TSH levels rose, regardless of hypothyroidism diagnosis. This finding suggests that miscarriage risk is more closely related to TSH levels than to the presence of hypothyroidism itself, a relationship that has also been reported by different authors (Benhadi 2009 [34]; Negro 2010 [35]; Taylor 2014 [36]). In the present study, multivariable analysis show that hyperthyroidism diagnosis is independently associated with an increased risk of miscarriage, regardless of maternal TSH levels. Consistent with our findings, Turunen et al. [37]reported a higher incidence of adverse perinatal outcomes and a greater prevalence of previous spontaneous miscarriages among women with hyperthyroidism. Likewise, the meta-analysis by Alves et al. [38] confirmed that treated hyperthyroidism was associated with an increased risk of spontaneous abortion and other obstetric complications, although information on the maternal thyrotoxicosis control was limited.

The mechanisms underlying this increased risk remain poorly understood. Factors related to the autoimmune disease, particularly persistent thyrotropin receptor antibodies (TRAb), have been proposed as potential contributors to adverse pregnancy outcomes (De Leo et al., 2017[39]).In contrast, Casey et al.[40]found no increase in adverse pregnancy outcomes among women with subclinical hyperthyroidism, compared with euthyroid women, suggesting that isolated TSH suppression in the absence of overt thyrotoxicosis is unlikely to increase the risk of miscarriage. Krassas et al.[41]concluded that the risk of maternal and fetal complications is closely related to the adequacy of maternal thyrotoxicosis control. Overall, these findings suggest that both thyroid autoimmunity and thyrotoxicosis control may contribute to adverse pregnancy outcomes, although further studies are needed to clarify their relative contribution.

There is some controversy over whether the risk of miscarriage is related to autoimmunity or whether it is caused by TSH levels. Studies such as Liu et al. 2014[42]show that the risk is greater when positive anti-thyroid peroxidase antibodies (TPOAb) are present and increases as TSH levels rise. Such results agree with those by [8]Nazarpour 2015 et al. Besides, the ATA 2026 guideline ([18]Korevaar 2026) informs that treating these cases with levothyroxine does not reduce the miscarriage risk. A view that is not supported by other authors. ([43]Thangaratinam). ATA 2026 notes that thyroid antibodies are likely to be an indicator of a more general autoimmune state that could increase the risk of co-complications during pregnancy.

Miscarriage rate is higher when a TSH test is not performed in both groups (treated or untreated hypothyroid women). The failure to determine TSH could be partly explained if these women had other gestational risks that would imply hospital assistance and monitoring. Data from hospitals are not available. However, the results show that over 95% of women without a TSH test did not have other registered risk factors but they have a higher miscarriage risk. It could be speculated that hypothyroid and pregnancy controls in this women were inadequate which would have increased miscarriage rate, as shown in other works Taylor 2014[13], Benhadi 2009[34].

Published data by [3]Chen et al. show a cesarean section percentage of 42.4% ($p<0.001$) in women with a TSH between 4.29-10mU/L before gestation. Results in the present study indicated a higher cesarean section rate among women with hypothyroidism, mainly those in treatment (24.8%) vs women without TD (19.5%). A higher cesarean section rate is not observed in cases with TSH>4 mU/L regardless they are or not treated for hypothyroidism. In the treated hypothyroid group (Table 5), cesarean section rate differs significantly ($p=0.012$) depending on the TSH levels and whether a TSH test was performed. Although, the post-hoc analysis showed no differences, a higher cesarean section rate was observed in the non-TSH group and in the group with TSH levels from 0.1–2.5 mIU/L. In order to explain these results it could be speculated that TSH values could be out of range in the non-TSH group. In spite of that, it is surprising the higher cesarean section rate in the treated hypothyroid women with TSH values between 0.1 to 2.5 mIU/L, reaching 28.4%. Cesarean section could be considered as an indicator of fetal distress. Consequently it can be assumed that these data are partly consistent with the ones published by [3]Chen et al, who describe an increase in labor dystocia when preconception TSH values rise, although they remain within the general population normal range. In fact, there is not a fully consistent explanation about it.[14]Männistö et al. ,who did not have data on the treatment, also report a greater risk for cesarean section in women with hypothyroidism, which is probably due to the obstetric complications such as hypertension, diabetes or prematurity.

Preeclampsia rate is significantly higher in hypothyroid population whether they are or not treated (p<0.001) (Table 2). This data were in agreement with the ones published by [2]Chen, [6]Sahu,[7]Wilson and [14]Männistö et al. However, the post-hoc analysis of these two groups (Tables 4 and 5) shows no significant changes in the preeclampsia rate based on TSH levels, despite the fact that a recent meta-analysis has found a significant increase in the risk of preeclampsia when TSH levels exceed 4 mIU/L (Han 2022[44]). Another systematic review has identified a U-shaped curve, suggesting that preeclampsia rates increase in both low and high TSH levels (Toloza 2022[45]), a finding that is not observed in the results of this study.

Prematurity rate was also significantly higher in the treated hypothyroid population compared to the same rate for the global studied population (p=0.02). However, the post-hoc analysis does not reveal any significant differences. Nevertheless, high rates are observed in the group of women with hyperthyroidism and in the group with treated hypothyroidism. Prematurity associated with thyroid disorders has been reported in various studies [11]Knøsgaard, [8]Nazarpour,[10]Arbib and [12]Korevaar et al. Nonetheless, results in the present study did not reveal a higher prematurity rate when TSH increased among hypothyroid treated or untreated women, unlike other related studies [10], Arbib [12]Korevaar et al. The risk of preterm delivery related to maternal thyroid function shows a conflictive association with some publications supporting this relation and most studies not demostrating an incresed risk for prematurity, like ([2] Chen2014, [5]Männistö 2009, [6]Sahu2010,[40]Cleary-Goldman et al.

Different works show an increase rate in low birth weight (LBW) related to subclinical hyperthyroidism [10]Arbib2016 or higher thyroxine values; [46]León 2015 and also to overt and subclinical hypothyroidism([8]Nazarpour [47]Derakhshan 2017). Nevertheless, results in the present study did not show significant changes in the LBW rate, in line with those published by Khan [48], Allan [49] and Männistö et al. [5]. Such findings also concur with the ones reported by Cleary-Goldman[50]et al.

Derakhshan et al. [47]observe an increase rate in LBW in women treated with levothyroxine with a low TSH, suggesting that they may have been over-treated.

With regard to overtreatment, our study highlights that 20 % of women with hypothyroidism undergoing treatment and who had a TSH level below 0.1 mIU/L, gave birth to newborns with LBW. This figure is twice as high compared to the other groups with normal TSH values or TSH >4 mIU/L.

There is some disagreement in the literature regarding the effect of TD on birth weight. Derakhshan et al. [47]meta-analysis reported statistically significant inverse associations between maternal TSH, free thyroxine (FT4) values and birth weight. However, the magnitude of these effects is small (approximately 6 g lower birth weight per standard deviation increase in TSH and 21 g per standard deviation increase in FT4), suggesting that, although maternal thyroid function may influence fetal growth, its impact on absolute birth weight could be modest at the population level.

Concerning the Apgar test, pacients with a TSH during the first trimestre were more likely to show Apgar results <7 compared with the ones without a TSH. However, differencies based on TSH values were not detected in the current study (Table 3). Männistö et al. [5]reported 5-minute Apgar scores <7 in 11.1% of women with hypothyroidism, compared to 6.7% of women in the control group. Murillo-Llorente et al.[51]found an association between elevated first-trimester TSH levels and higher Apgar scores. Siscart et al.[29]do not observe a relationship between hypothyroidism and Apgar test results. The relationship between pregnancy complications and Apgar score are multifactorial and the effect of TD on Apgar test is unclear.

In the present study, no differencies among the TSH groups with regard to perinatal mortality were found, by contrast with other authors' findings ([8]Nazarpour2015, [6]Sahu2010). Neither have Cleary-Goldman et al [50]. found a relation between perinatal mortality and thyroid hypofunction. Männistö el al. [5] concluded that it is autoimmunity rather than TSH values which causes an increasing risk of perinatal mortality, probably related with prematurity. In the current study, the prematurity rate found was significantly higher in the treated hypothyroid population.

WOMEN WITHOUT KNOWN THYROID DISFUNCTION

Thyroid function universal screening before and during gestation is not recommended. Nowadays, it is only recommended for women who have a high risk for thyroid disturbances ([18]Korevaar 2026), although it is already known that at least one-third of the thyroid disturbances will not be detected ([52]Vaidya 2007, [53] Horacek 2010).

This study shows that 18.8% of women without TD had a TSH value recorded in the first trimester. Out of these with a TSH test, 1,329 (6.7%) had TSH values >4 mIU/L, consistent with hypothyroidism. Although the prevalence of certain comorbidities (obesity, diabetes, and hypertension) was higher in this population, we did not have information on other risk factors. Furthermore, among women without TD and a TSH test >4 mIU/L, the miscarriage rate was 7.1%. This rate is very similar to that of women without TD whose TSH was not measured (7.5%). These figures suggest that some of these women might have undetected dysfunctions that could cause miscarriages. As seen in the multivariate analysis, spontaneous abortion rates were related to increasing TSH levels, even in women without TD. Undetected dysfunctions could be diagnosed and treated if a universal thyroid screening was performed before or during gestation.

Furthermore, most of these miscarriages could be associated with undiagnosed thyroid autoimmunity, which also increases spontaneus abortion rate. As mentioned before, there is some controversy about whether miscarriage risk is related to autoimmunity or it is caused by TSH levels.

[8]Nazarpour2015, [43]Thangaratinam2011).

ATA 2026 (Korevaar 2026[18]) does not recommend universal thyroid function screening for pregnant population. However, based on our data, and in accordance with other authors ([19]SEEN-SEGO, [54]Vila 2013, [55] Stagnaro-Green 2020), screening for TD should be considered for all pregnant women in Catalonia.

Stagnaro-Green et al. (2020) [55]conclude that universal screening for overt thyroid disease should be the target and not searching for subclinical disease or thyroid autoimmunity, since treating overt thyroid disease has demonstrated a beneficial impact.

This study has some limitations. The data used come from

registers that are not intended for research. Complete information

on thyroid autoimmunity and free thyroxine were not available for the whole

population studied, consequently limiting the analysis of the

results. Some codes might not have been used properly due to human errors

or difficulties in selecting the proper ICD-10 code in some cases. In

addition, some codes could still be active after the illness resolution. It is highly likely that many women in the untreated hypothyroidism group did not have hypothyroidism when their pregnancy started. This is supported by the fact that 66.5% of these women had TSH levels between 0.1 and 4 mIU/L. Peeters et al. review [56]indicated that up to 46% of patients diagnosed with subclinical hypothyroidism may normalize TSH levels within two years following the diagnosis. ATA 2026 [18]inform in the same sense when the elevated TSH level is below 6 mIU/L.

ESCA (Enquesta de Salut de Catalunya) (Catalan Health Survey) reveals that 25.4% of Catalan women aged between 15 and 44 had private and public health care coverage in 2014. This figure increased up to 29% during 2015 and 2016. It is not possible to know if some participants had TSH tests in private healthcare.

The relevant strengths in this study are the large sample size and the database used, which covers more than 80% of the Catalan population with more than 7 million inhabitants during the studied period.

CONCLUSIONS

Thyroid dysfunction during pregnancy has a negative impact on prematurity, cesarean section and preeclampsia rates.

Neither treated nor untreated hypothyroidism has been independently associated with a higher rate of spontaneous abortion. The spontaneous abortion rate increases as TSH levels rise.

Hyperthyroidism remained associated with miscarriage independently of TSH levels.

The fact of not having a TSH monitoring in hypothyroid women and in women without TD during the first trimester implies a negative effect on miscarriage rate. It is necessary to raise awareness on women and health professionals about the importance of TD follow-up and monitoring before and during pregnancy.

More than 6% of women with an unknown TD have TSH values compatible with hypothyroidism during the first trimester. This fact is associated with a higher risk of miscarriage. Therefore, such figures should lead us to consider a TD screening in all pregnant women in Catalonia.

Abbreviations

ATA: American Thyroid Association

ATC: Anatomical, Therapeutic, Chemical classification System

CEIC: (Comité Ético de Investigación Clínica) Ethical Committee for Clinical Research

ECAP: (Estación Clínica informatizada de Atención Primaria) Electronics records in Primary Health Care)

ESCA (Enquesta de Salut de Catalunya) Catalan Health Survey

FT4: free thyroxine

ICD: International Classification Disease

ICS : (Institut Català de la Salut) Catalan Health Institution

IDIAP: (Institut Universitari d'Investigació en Atenció Primària) University Institute for Primary Care Research

LBW: low birth weight

LMP: Last menstrual period date

SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) Primary Health Care Research Information and Development System

TD: Thyroid dysfunction

TPOAb anti-thyroid peroxidase antibodies

TRAb: thyrotropin receptor antibodies

Declarations

Ethics approval and consent to participate

The Ethical Committee approved the study ethical protocol for Clinical Research (Comité Ético de Investigación Clínica CEIC) from IDIAP (Institut Universitari d'Investigació en Atenció Primària) Jordi Gol (P17/113). Confidentiality was ensured since all of the cases in the SIDIAP database are pseudo-anonymous and the established protocol was followed. Therefore, informed consent is not needed. The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable local legislation and institutional requirements.

Consent for publication

All the authors do their consent for publication. All the claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations.

Availability of data and materials

Publicly available datasets were analyzed in this study. The data that support the findings of this study are not publicly available on legal or ethical grounds, as they contain information that could compromise the privacy of research participants, but are available from Oriol Cunillera Puértolas upon reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

GTV: Wrote the main text of the manuscript.

OCP: Managed the data and conducted the formal analysis; wrote the methodology section and prepared Figure 1 and the tables.

MAR: Supervised and reviewed the text.

NPE: Wrote the methodology section, supervised and reviewed the text.

MIA: Reviewed the text.

GRP: Reviewed the text.

SPA: Reviewed the text.

MMP: Supervised and reviewed the text.

LV: Supervised and reviewed the text. Was responsible for the conceptualization.

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Figures

Figure 1

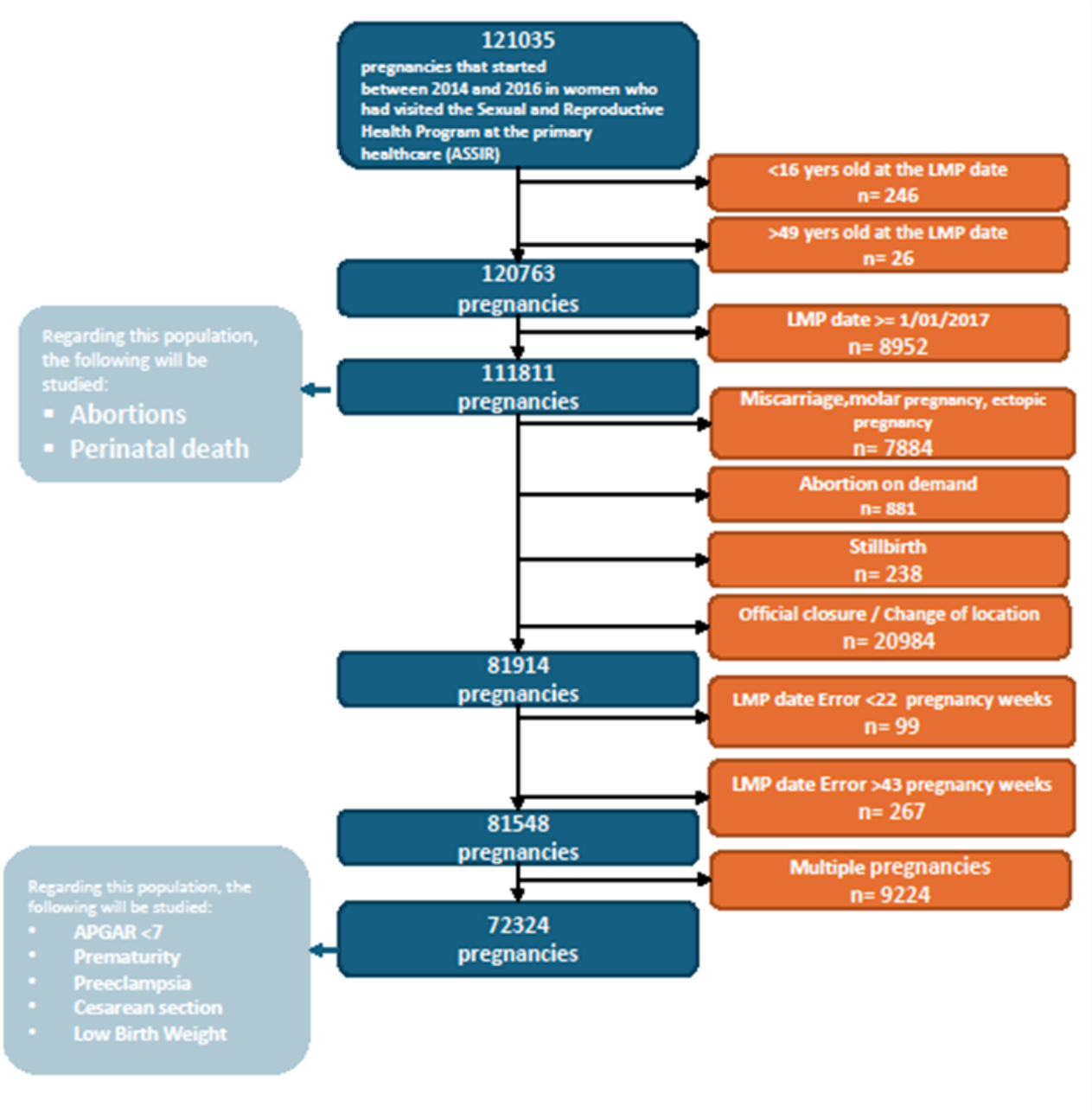


Figure 1

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