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REVIEW

Hyperthyroidism in pregnancy: evidence and hypothesis in fetal programming and development

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Abstract

The management of hyperthyroidism in pregnant patients has been a topic of raised clinical awareness for decades. It is a strong recommendation that overt hyperthyroidism of Graves' disease in pregnant women should be treated to prevent complications. The consequences of hyperthyroidism in pregnancy are less studied than hypothyroidism, and a literature review illustrates that the main burden of evidence to support current clinical guidance emerges from early observations of severe complications in Graves' disease patients suffering from untreated hyperthyroidism in the pregnancy. On the other hand, the more long-term consequences in children born to mothers with hyperthyroidism are less clear. A hypothesis of fetal programming by maternal hyperthyroidism implies that excessive levels of maternal thyroid hormones impair fetal growth and development. Evidence from experimental studies provides clues on such mechanisms and report adverse developmental abnormalities in the fetal brain and other organs. Only few human studies addressed developmental outcomes in children born to mothers with hyperthyroidism and did not consistently support an association. In contrast, large observational human studies performed within the last decade substantiate a risk of teratogenic side effects to the use of antithyroid drugs in early pregnancy. Thus, scientific and clinical practice are challenged by the distinct role of the various exposures associated with Graves' disease including the hyperthyroidism *per se*, the treatment, and thyroid autoimmunity. More basic and clinical studies are needed to extend knowledge on the effects of each exposure, on the potential interaction between exposures and with other determinants, and on the underlying mechanisms.

Key Words

- ▶ pregnancy
- ▶ hyperthyroidism
- ▶ Graves' disease
- ▶ antithyroid drugs
- ▶ autoimmunity

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Introduction

Hyperthyroidism is the clinical state that results from an excessive production of thyroid hormones in the thyroid gland (1, 2). It is a signature of the disease that the incidence of the different subtypes of hyperthyroidism varies with age (3). While toxic nodular goiter is the predominant cause of hyperthyroidism after the age of 50 years, the predominant cause of hyperthyroidism in patients younger than 50 years of age is Graves' disease (GD) (3).

Since GD predominantly occurs in female patients and in the reproductive time span, the management of the disease should consider the patient's reproductive history and the possibility of a current or future pregnancy (1, 2).

GD is an autoimmune disease caused by alterations in the immune system, and a key pathophysiological mechanism is the production of TSH-receptor autoantibodies (TRAb) (4). The disease was first described in

the 19th century, and considerations on the management in pregnant women, specifically, can be ascertained from the beginning of the 20th century with a main concern about adverse pregnancy outcomes in women suffering from severe, untreated hyperthyroidism (5).

The use of antithyroid drugs (ATDs) for the treatment of hyperthyroidism was introduced in clinical practice in the 1940s and is currently the recommended treatment for the hyperthyroidism of GD in pregnant women (6). Clinical guidelines indisputably state that overt hyperthyroidism caused by GD in pregnant women should be treated to prevent maternal and fetal complications, however, the management is challenged by the potential risk of severe side effects associated with the treatment (1, 2). Furthermore, a pertinent question is on the role of thyroid autoimmunity. Thus, the determination of causal factors for outcome of a pregnancy and offspring development in women suffering from the hyperthyroidism of GD is complex and hitherto not clarified in detail.

In this review, we explore outcomes of hyperthyroidism in pregnancy with a focus on the underlying mechanisms and different exposures associated with the disease (hyperthyroidism *per se*, antithyroid drug treatment, and thyroid autoimmunity). We describe the hypothesis of fetal programming by maternal hyperthyroidism and supporting evidence from experimental and human studies, and we discuss methodological aspects and implications for scientific and clinical practice.

The hypothesis of fetal programming

Fetal programming is a concept within reproductive epidemiology that links exposures during fetal life with the later development of disease in the offspring. It has been described in relation to different maternal diseases and different mechanisms have been proposed, however, the overall hypothesis is analogous irrespective of the specific exposure and outcome (7). The concept is also known as ‘fetal origin of adult diseases’ (8), and the basic idea is that disturbances during fetal life can cause permanent alterations in the offspring that at a later point in time might predispose to the development of adverse outcomes. Many aspects are yet to be clarified considering the mechanisms, but growing evidence is linking the concept to epigenetic alterations (9). Different study designs are used to investigate the hypothesis. Experimental evidence is a classic determinant of causality as brought forward by Bradford Hill in the 1960s (10). In addition to such results, the main burden of evidence develops from observational human studies.

The determination of causality in observational studies is a difficult task, and it is a challenge to distinguish the exposure of interest from other prenatal exposures and from the role of postnatal exposures during development (7).

Considering fetal programming by maternal thyroid disease, the role of thyroid hormones during fetal development is a key mechanism (7). Thyroid hormones are important developmental factors (11). The fetal thyroid gland is increasingly able to synthesize thyroid hormones in the second half of a pregnancy, which emphasizes the importance of maternal thyroid hormones in the early pregnancy. Furthermore, the importance of maternal thyroid hormones in later pregnancy after the onset of fetal thyroid hormone production is evident from the measurement of thyroxine (T4) in cord blood from newborns with a defect in thyroid hormone synthesis (12). Thus, maternal thyroid function remains important to the fetus throughout the pregnancy. The transport of thyroid hormones from the mother to the fetus during a pregnancy and physiological alterations affecting maternal thyroid function should be considered. In the early pregnancy, the pregnancy hormone human chorionic gonadotropin (hCG) stimulates the maternal thyroid gland to an increased production of thyroid hormone, potentially balancing the extra need of thyroid hormones to supply both the mother and the fetus (13). Yet, another mechanism in the early pregnancy that tends to balance the effect of hCG is the type 3 deiodinase (DIO3) in placenta (13). This enzyme inactivates thyroid hormones by catalyzing the conversion of T4 to reverse T3 (rT3) and T3 to T2. Activity of DIO3 in placenta is apparent from the early pregnancy weeks in rats and in humans and is evident from the high rT3/T3 ratio seen in pregnant women (13). The activity of DIO3 is considered part of the reason why athyreotic women need a 50% increase in their Levothyroxine dose by the time they become pregnant (14). Thus, the activity of DIO3 is likely to explain the higher maternal TSH in the early pregnancy prior to the hCG-peak (13, 15). In line with this thought, patients with DIO3 containing hemangiomas present with consumptive hypothyroidism and a high rT3/T3-ratio (16). These findings suggest a delicate balance under strict hormonal control and propose clinically important impact of slight imbalance.

Considering outcomes of maternal thyroid disease in pregnancy, the focus has especially been turned to hypothyroidism. The hypothesis of fetal programming by maternal hypothyroidism is biological plausible from experimental evidence and from the description of cretinism with profound mental and physical deficits in

children born to mothers with severe hypothyroidism caused by iodine deficiency (7). Consequently, clinical guidelines unanimously state that overt hypothyroidism in pregnant women should be treated, whereas the management of smaller abnormalities in thyroid function such as subclinical hypothyroidism, and the entity of isolated low T4 (hypothyroxinemia) is unclarified (1, 17). Turning from lack of maternal thyroid hormone to excess, it is similarly a strong and consistent recommendation that overt hyperthyroidism caused by GD should be treated in pregnant women (1, 2). However, the hypothesis of fetal programming by maternal hyperthyroidism (Fig. 1) has gained less attention (1). It is likely that the association between thyroid activity and adverse outcomes of pregnancy and child development is u-shaped. Such dependency is seen for other prenatal exposures for example, maternal hemoglobin concentration in pregnancy and outcomes of pregnancy as well as environmental factors for example, iodine and iron intake (18). This offers a path to follow for describing the influence of maternal thyroid dysfunction on pregnancy outcomes.

Hyperthyroidism and fetal brain development

Thyroid hormones regulate numerous processes during early brain development including neuronal proliferation, migration, differentiation, synaptogenesis, and myelination (19). In addition to the development of brain structures, they also play a role in the regulation of the neurochemical environment. It sounds reasonable that the lack of thyroid hormones might disturb these processes, whereas it is less clear how an excessive production of thyroid hormones associated with hyperthyroidism could affect fetal development. We searched the PubMed database for original, experimental studies on fetal outcomes of maternal hyperthyroidism in pregnancy up until October 1, 2020, and this search identified 52 publications. By contrast, a search for hypothyroidism identified 247 publication, which illustrates the predominant focus on this entity.

After review of the search results, we identified nine studies (20, 21, 22, 23, 24, 25, 26, 27, 28) that investigated the impact of maternal hyperthyroidism on fetal brain development in experimental animals (Table 1). Notably, all the studies reported one or more abnormal findings in the offspring after exposure to maternal hyperthyroidism. However, the findings were diverse. All studies used T4 for the induction of maternal hyperthyroidism, but the method of T4 administration differed between the studies and the timing of outcome assessment in the offspring ranged from gestational day 21 up until the third postnatal month (Table 1). It is beyond the scope of this review to describe and discuss details regarding the design and methodology of studies in experimental animals. However, some considerations seem important to highlight when interpreting and including evidence from experimental studies in a clinical context. First, the age of an experimental animal and the duration of a pregnancy are not interchangeable with humans (29, 30). Whereas the human pregnancy is on average 40 weeks, the length of a pregnancy is 22 days in rats and 19 days in mice (29). Furthermore, disparities exist regarding the postnatal age as compared to humans and among experimental animals, for example, rats and mice. Thus, the lifespan of laboratory rat is about 3 years, whereas it is about 2 years for laboratory mice (30). Considering these life spans in relation to human age, an age of 1/3/6 months in rats approximate 9/15/18 years of age in humans and an age of 1/3/6 months in a mice approximate 14/23/34 years of age in humans (30). Secondly, the timing and duration of the various neurodevelopmental stages are not completely synchronous in humans and in experimental animals (29). Furthermore, the structural and functional properties of different brain regions and organs are not identical. For example, the placentas of humans and rats show anatomical similarities with a discoid shape and hemochorial type of fetal-maternal interface, however, disparities exist regarding the histological structure and the function of the yolk sac (31). Finally, important considerations are on the assessment of brain development in humans and in experimental animals, respectively (32).

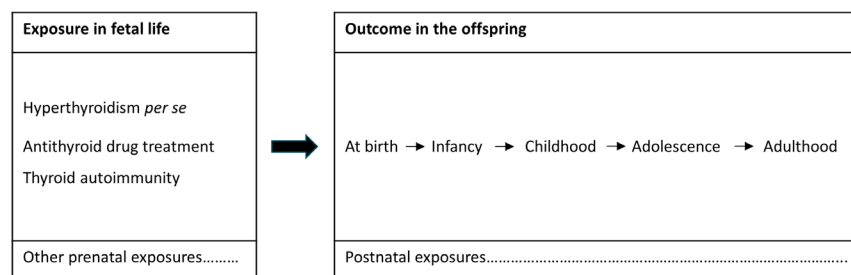


Figure 1
The hypothesis of fetal programming by maternal hyperthyroidism.

Table 1 Experimental studies on maternal hyperthyroidism in pregnancy and brain development in the offspring.

Author	Year	Animal	Induction of hyperthyroidism	Outcome assessment	Findings in the offspring
Evans <i>et al.</i> (20)	2002	Rats	s.c. infusion (T4)	Gestational day 21	Increased expression of different neuronal cytoskeletal proteins in the brain
Zhang <i>et al.</i> (21)	2008	Rats	s.c. infusion (T4)	Postnatal months 1–3	Altered morphology of hippocampal neurons and impaired ability to cope with stress
Zhang <i>et al.</i> (22)	2010	Rats	s.c. infusion (T4)	Postnatal months 1–3	Aberrant organization of hypothalamic stress related regions in the brain
El-Bakry <i>et al.</i> (23)	2010	Rats	Intragastric administration (T4)	Postnatal weeks 1–3	Histopathological effects in different brain regions and accelerated skeletal features
Ahmed <i>et al.</i> (24)	2010	Rats	Intragastric administration (T4)	Postnatal weeks 1–3	Increased excitability and synaptic transmissions in cerebrum, cerebellum and medulla oblongata
Ahmed <i>et al.</i> (25)	2012	Rats	Intragastric administration (T4)	Postnatal weeks 1–3	Impaired development of neurons in different brain regions and excess oxidative stress
Strobl <i>et al.</i> (26)	2017	Mice	Intraperitoneal administration (T4)	Postnatal day 18	Abnormal axons and synapses in thalamocortical neurons and in visual cortex
Laureano-Melo <i>et al.</i> (27)	2019	Mice	s.c. infusion (T4)	Postnatal day 70	Alterations in hippocampal serotonergic and GABAergic systems and increased anxiolysis
Salami <i>et al.</i> (28)	2019	Rats	Added to drinking water (T4)	Postnatal days 5, 10, 20	Increased expression of hippocampal apolipoprotein D and increased oxidative stress

T4, thyroxine.

A commonly used marker in humans is the intelligence quotient (IQ). It is a standardized measure based on a subset of tests (33). Alternative markers of brain development in humans include structural abnormalities in the brain assessed using for example brain scans of the child at a certain age (34). Furthermore, information on diagnosis of neurodevelopmental diseases in the child can be used as a proxy for impaired brain development (7). As opposed to this, the assessment of brain development in experimental animals such as rats and mice commonly relies on histopathological examination and evaluation of gene expression and in addition to these markers, the performance of the animal in different test (e.g. maze) can be evaluated (Table 1). However, no measure of brain development in an experimental animal directly translates to IQ in humans (32). Furthermore, it is important to notice that many methodological considerations exist when the role of maternal thyroid disease in relation to fetal brain development is assessed in humans and in an experimental design. In humans, the risk of confounding is a particular concern in observational designs (7), and in experimental animals it has recently been discussed that the currently available models may not be sensitive

enough to detect the neurodevelopmental abnormalities associated with different degrees of abnormal maternal thyroid function (32).

Although the findings are diverse, evidence suggests that maternal hyperthyroidism in pregnancy may impair fetal brain development in experimental animals (Table 1) via alterations in the development and organization of neurons, in the neurochemical environment, and altered expression of different proteins in the brain. However, the human brain is more complex and slight developmental skewness may cause disturbances that are detectable in humans only.

So, what do we know from human studies about brain development in children born to mothers with hyperthyroidism? Few studies addressed outcomes of brain development in the child in relation to maternal hyperthyroidism. In contrast, the number of studies that addressed the association between insufficient levels of maternal thyroid hormones and child brain development is considerable (1, 17). A recent systematic review and meta-analysis identified nine observational studies on the association between maternal hyperthyroidism in pregnancy and neurodevelopmental diseases in

the offspring including attention deficit hyperactivity disorder, autism spectrum disorder, epilepsy, and schizophrenia (35). Most of these studies were register-based studies, which are typically large, but are hampered by the fact that the assessment of exposure in pregnancy is indirectly performed from hospital diagnoses and/or redeemed prescriptions of drugs. For each of the different outcomes, only two individual studies were included in a meta-analysis, and the combined measures showed a significant association between maternal hyperthyroidism and ADHD and epilepsy in the child (35). In another study (36), using a case-cohort design, the assessment of maternal hyperthyroidism was made from the measurement of thyroid function parameters in stored blood samples from the early pregnancy. In this study, a risk of epilepsy in the child was corroborated, but no association between maternal hyperthyroidism and ADHD in the child was seen (36). Notably, high circulating levels of thyroid hormones in patients with generalized resistance to thyroid hormone (mutation in the thyroid receptor β -gene) have been associated with a high occurrence of ADHD (37), providing a clue toward an association between hyperthyroidism and brain development. Furthermore, parallel observations in human and in rats have shown that fetal exposure to high maternal thyroid hormone levels is associated with persistent central resistance to thyroid hormones in adulthood, likely mediated via increased expression of the DIO3 in the brain (38). Hence, mechanisms of fetal programming may include offspring alterations in the hypothalamic-pituitary-thyroid hormone axis.

Other outcomes of human fetal neurodevelopmental (child IQ and brain scans) are similarly rarely investigated in relation to maternal hyperthyroidism in pregnancy, but studies within different birth cohorts have evaluated the association between levels of TSH and free T4 in pregnancy and child IQ as well as child cortex and gray matter volume (33, 34). The findings are not consistent, and many determinants are to be considered, but results provide clues of a possible u-shaped association.

Hyperthyroidism and other outcomes of fetal development

The critical role of thyroid hormones during brain development is an important concern, but the consequences of a disturbance in maternal thyroid function in pregnancy may extend beyond fetal brain development. Thyroid hormones are developmental

factors and regulate numerous processes in many organs. Considering the hypothesis of fetal programming by maternal hyperthyroidism (Fig. 1), one may speculate on other outcomes of fetal development that are not related to the brain. From the literature search, we identified seven experimental studies (Table 2) that evaluated outcomes of maternal hyperthyroidism in pregnancy in relation to the development of other organ systems in the offspring not related to brain development (39, 40, 41, 42, 43, 44, 45). The studies were predominantly performed in rats, and the timing and type of outcome differed (Table 2). Thus, the studies assessed the development of genital organs, the cardiovascular system as well as bone and cartilage. Notably, all studies reported at least one abnormal finding, however, it appeared that some of the alterations were reversible for instance in the development of the bone (Table 2).

Considering human findings, only few studies investigated such other outcomes of fetal development. Studies from different birth cohorts have instigated blood pressure, BMI, total fat mass, and abdominal s.c. fat mass in children born to mothers with hyperthyroidism (46, 47, 48). Overall, results did not point toward associations except that lower maternal TSH levels associated with lower child BMI, fat mass, and diastolic blood pressure in one of the cohorts, in which no association with clinically diagnosed hyperthyroidism was seen (46). On the other hand, maternal hyperthyroidism as well as hypothyroidism has been associated with alterations in maternal body weight (48). Thus, it is a methodological challenge to distinguish the role of maternal thyroid disease from other BMI-related factors in the evaluation of fetal outcomes.

Hyperthyroidism and pregnancy complications

From the experimental and human studies reviewed previously that addressed the role of maternal hyperthyroidism in pregnancy in relation to fetal brain development and the development of other organ systems, it seems as if the strong and consistent clinical recommendation on treatment of overt hyperthyroidism caused by GD in pregnant women relies on other determinants. Thus, the main concern related to hyperthyroidism in pregnant women and the recommendation for treatment relate to the risk of complications during the pregnancy and/or at birth of the child and to a lesser extent on the evidence considering more long-term outcomes in the child.

It has been clinically recognized for more than a century that maternal hyperthyroidism can seriously complicate a pregnancy (5). The evidence in humans arises from clinical case studies, and the description of pregnancy complications in women referred to a hospital for the management of Graves' hyperthyroidism in pregnancy. These reports from 1929 and onwards have substantiated a focus on the adverse effects of untreated or insufficiently treated hyperthyroidism in pregnant women with GD (5, 49, 50, 51). Thus, it has been consistently shown that women who remained overtly hyperthyroid in pregnancy had a higher risk of pregnancy loss, preterm birth, low birth weight of the child, preeclampsia, and maternal heart failure. These early observations have later been corroborated in large observational studies including non-exposed controlled groups (52, 53, 54). On the other hand, subclinical hyperthyroidism has not been associated with a risk of pregnancy complications and no recommendation of treating this entity is proposed in clinical guidelines (55).

It remains a pertinent question how the thyroid autoimmunity itself, via the presence of TRAb in GD patients, potentially affects the outcome of a pregnancy. A main clinical focus regarding TRAb exists in the second half of pregnancy after the onset of fetal thyroid hormone production, which introduces the risk of fetal and neonatal hyperthyroidism caused by TRAb from the mother. However, the distinct roles of high maternal thyroid hormone levels as compared to high levels of TRAb remain to be elucidated concerning pregnancy complications and the hypothesis of fetal programming.

Antithyroid drug treatment

Another determinant considering outcomes of maternal hyperthyroidism in pregnancy is potential side effects to the treatment. As recently reviewed in detail, a major focus and concern is on the risk of teratogenic side effects with the use of ATDs in early pregnancy (56). This focus has emerged from a series of large, observational studies published in the 2010s that reported a risk of birth defects after early pregnancy exposure to Methimazole (MMI), and lately also after Propylthiouracil (PTU). However, the pattern and severity of malformations strikingly differed between MMI and PTU exposure with the most severe malformations observed after early pregnancy treatment MMI. Thus, the recommendation is to use PTU in early pregnancy and to shift from MMI to PTU already when pregnancy is planned or as soon as it is detected (1, 2).

Even when several large observational studies point toward an association, one may yet speculate on the underlying mechanisms and determinants of causality. Only few studies so far included data to evaluate the existence of a biological gradient from the dose of the drug, but a large study from Korea showed that a higher cumulative dose of MMI was associated with a higher risk of birth defects (57). Further clues to causal determinants may arise from experimental evidence (10). Thus, we searched for experimental studies that investigated the risk of malformations after prenatal exposure to ATDs. We identified four studies (Table 3)

Table 2 Experimental studies on hyperthyroidism in pregnancy and development of other organs in the offspring.

Author	Year	Animal	Induction of hyperthyroidism	Outcome assessment	Findings in the offspring
Ariyaratne <i>et al.</i> (39)	2000	Rats	s.c. injection (T3)	Postnatal days 7–21	Increased differentiation of adult Leydig cells in testis
Chattergoon <i>et al.</i> (40)	2012	Sheep	Added to growth media (T3)	Gestational day 100	Suppressed mitotic activity in cardiomyocytes
Lino <i>et al.</i> (41)	2014	Rats	Added to drinking water (T4)	Gestational days 18 and 20	Cardiac hypertrophy and altered expression of cardiac renin-angiotensin system components
Lino <i>et al.</i> (42)	2015	Rats	Added to drinking water (T4)	Postnatal day 90	Altered expression of cardiac renin-angiotensin system components and worse recovery after ischemic insult
Karaca <i>et al.</i> (43)	2015	Rats	s.c. injection (T4)	Gestational day 20	Higher expression of vascular endothelial growth factor and increased angiogenesis and apoptosis
Maia <i>et al.</i> (44)	2016	Rats	Orogastric administration (T4)	Postnatal days 0, 21, 42	Reversible reduced growth and reversible increased percentage of trabecular bone tissue
Ribeiro <i>et al.</i> (45)	2018	Rats	Orogastric administration (T4)	Postnatal days 0 and 20	Reduced endochondral bone growth and reduced proliferation rate in the cartilage

T3, triiodothyronine; T4, thyroxine.

Table 3 Experimental studies on antithyroid drug exposure in pregnancy and outcomes in the offspring.

Author	Year	Animal	Antithyroid drug	Outcome assessment	Findings in the offspring
Stanisstreet <i>et al.</i> (58)	1990	Rats	MMI	Gestational day 9.5	MMI was associated with abnormal development of rat embryos <i>in vitro</i> ; more severely at higher concentrations
Benavides <i>et al.</i> (59)	2012	Mice	MMI and PTU	Gestational day 10.5 and 18.5	PTU, but not MMI, was associated with neural tube and cardiac defects as well as fetal loss
Veenendaal <i>et al.</i> (60)	2013	Frogs	MMI and PTU	Nieuwkoop and Faber stage 45	PTU, but not MMI, was associated with cardiac and gut looping defects, abnormal ciliary function and abnormal expression of genes involved in left-right symmetry
Mallela <i>et al.</i> (61)	2014	Mice and rats	MMI and PTU	Gestational day 18 or 20	PTU and MMI were not associated with histopathological abnormalities or external gross malformations

MMI, methimazole; PTU, propylthiouracil.

that investigated this exposure and outcomes in rats, mice, and frogs (58, 59, 60, 61). Notably, the findings were diverse and in contrast to the findings in humans. Thus, in an experimental setting, MMI revealed adverse outcomes in the offspring in one of the four studies, whereas PTU associated with birth defects in the offspring in two of the three studies that examined this type of drug exposure (Table 3). We can only speculate on possible explanations for this disparity between experimental and human findings. Considering the types of malformations observed in humans after exposure to ATDs (56), it may be speculated that the less severe malformations seen after PTU exposure are not detectable in the rat (e.g. preauricular sinus) and similarly with some of the malformations observed after MMI exposure (e.g. aplasia cutis). Furthermore, the morphological differences between the human and the rat placenta mentioned previously may influence the evaluation of toxicological effects (31). Rate of organ development in different animals and in comparison with humans as well as dose dependency may differ and influence the risk of developmental defects. Finally, in human studies it is often difficult to distinguish between the role of hyperthyroidism *per se*, the treatment, and the thyroid autoimmunity. This may also be the case in experimental animals since the treatment with ATDs may induce hypothyroidism. The opposite may also be the case and could challenge experimental studies on the role of maternal hypothyroidism *per se*. Thus, maternal hypothyroidism in an experimental animal is typically induced from treatment with ATDs. Consequently, interpretation of the findings is a difficult task in an experimental design as much as in observational human studies.

Concluding remarks

It has long been recognized that overt hyperthyroidism of GD in pregnant women should be treated to prevent complications (Table 4). This review highlights that evidence on the adverse effects of untreated or insufficiently treated hyperthyroidism is predominantly obtained from early clinical observations. In these reports and subsequent larger observational studies, a higher risk of pregnancy complications has consistently been reported if the disease is left untreated. Thus, it is well-established and in line with current recommendations that the disease should be treated in pregnant women. On the other hand, it is noteworthy that the burden of evidence from experimental studies and from observational human studies on postpartum and long-term outcomes in the offspring is limited as compared to maternal hypothyroidism in pregnancy. The experimental evidence provides some clues on potential adverse effects in the fetus associated with maternal hyperthyroidism, indicating that perhaps the association between maternal thyroid hormone levels in pregnancy and fetal development is u-shaped. Still, many aspects remain unclarified regarding the underlying mechanisms. In experimental animals as well as in humans, difficulties exist on the distinction between the different exposures that constitute parts of the autoimmune entity of GD. Furthermore, methodological aspects on outcome assessment apply to both settings and adds to difficulties in the comparison of experimental and human findings. As discussed, this is apparent from the inconsistency between experimental and human findings considering teratogenic side effects to the use of ATDs. Nevertheless, to inform clinical practice it is crucial to encourage future studies, basic as well as clinical, to address the distinct role of hyperthyroidism *per se*, the treatment, and the

Table 4 Key points and implications for future studies.

Hyperthyroidism in pregnancy

- Graves' hyperthyroidism is an autoimmune disorder.
- Graves' hyperthyroidism should be treated in pregnant women.
- Untreated Graves' disease is associated with pregnancy complications.
- Hyperthyroidism in pregnancy is less studied than hypothyroidism.
- Experimental studies provide clues on a fetal programming effect.
- Human studies are sparse and provide no definite conclusions.
- The programming role of thyroid autoimmunity is unclarified.
- Teratogenic side effects to antithyroid drugs pose a challenge.

Implications for future studies

- enhance the understanding of underlying mechanisms
- address the role of hyperthyroidism, treatment, and autoimmunity
- assess different short- and long-term outcomes in the offspring
- consider mechanisms to support the development of new treatments

autoimmunity (Table 4). To move forward from here, it seems crucial to determine the underlying mechanisms by each exposure and potential interaction between and with other maternal characteristics. Such focus can at the same time provide important guidance on potential targets and possibilities for new treatments with less severe side effects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

Stine Linding Andersen conceptualized and drafted the manuscript. Stig Andersen critically reviewed and discussed the manuscript.

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