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REVIEW

Endometriosis, polycystic ovary syndrome, and the thyroid: a review

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Abstract

Endometriosis and polycystic ovary syndrome (PCOS) are common gynecological disorders that constitute a significant burden of disease in women of fertile age. The disorders share a link to female reproduction and infertility; however, divergent effects on menstrual cycle, related hormones, and body composition have been proposed. Disorders of the thyroid gland including abnormal thyroid dysfunction (hyperthyroidism or hypothyroidism) and/or markers of thyroid autoimmunity similarly show a female predominance and onset in younger age groups. We reviewed the literature on the association between endometriosis, PCOS, and thyroid disease up until July 1, 2023, and identified 8 original studies on endometriosis and thyroid disease and 30 original studies on PCOS and thyroid disease. The studies were observational and heterogeneous regarding the design, sample size, and definitions of exposure and outcome; however, a tendency was seen toward an association between hyperthyroidism and endometriosis. Especially an association between endometriosis and slightly elevated levels of thyroid-stimulating hormone receptor antibodies has been found and corroborated in studies from different populations. On the other hand, the literature review turned a focus toward an association between hypothyroidism and PCOS, however, with uncertainties as to whether the association is caused by hypothyroidism per se and/or the thyroid autoantibodies (thyroid peroxidase and thyroglobulin antibodies). More evidence is needed to substantiate an association between endometriosis, PCOS, and thyroid disease, and to differentiate between the role of thyroid function and thyroid autoimmunity. Furthermore, studies are warranted to extend knowledge on the different disease characteristics and underlying mechanisms.

Keywords: hypothyroidism; hyperthyroidism; gynecology; autoimmunity; pregnancy

Introduction

Thyroid disorders are common endocrine disorders with a female predominance. In the reproductive age span, the disorders are mainly of autoimmune origin with hyperthyroidism being part of Graves' disease (GD) (1), and hypothyroidism seen as part of Hashimoto's thyroiditis (HT) (2). In GD, antibodies against the thyroid-stimulating hormone (TSH) receptor (TRAb) stimulate the thyroid gland to an increased production of thyroid hormone that causes the biochemical hyperthyroidism. In contrast, thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) are the main markers of thyroid autoimmunity in HT. From the pathogenesis it appears that abnormal thyroid function as well as thyroid autoimmunity are characteristics of the disorders, and possible mechanisms involved regarding disease outcomes. Thus, in nonpregnant as well as pregnant individuals the exact underlying mechanisms regarding adverse outcomes of thyroid disease are

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debated (3). Another characteristic of autoimmune thyroid disease as well as other autoimmune disorders is the multifactorial origin and the link to genetic as well as environmental factors (4). From this line of thought it follows that patient characteristics such as for example body mass index (BMI), smoking habits, and alcohol intake influence the occurrence of disease and the role of these nonthyroidal factors is an essential part of the debate.

The management of thyroid disease in women of reproductive age includes the possibility of a current or future pregnancy or the patient's desire to become pregnant. The role of thyroid hormones in reproductive health has long been brought into clinical and scientific consideration (5). It is well-characterized that thyroid hormones are important developmental factors and that thyroid hormone receptors are abundantly expressed in human organs. Specifically, thyroid hormone receptors are present in the female reproductive organs and in the placenta during a pregnancy (6, 7). Thus, the role of thyroid hormones in female reproduction is biologically plausible and a focus of clinical care. A link between thyroid disease and infertility as well as early pregnancy complications has been established; however, uncertainties prevail regarding the underlying mechanisms for the associations observed and as to whether thyroid function and/or autoimmunity is the key determinant (8, 9, 10, 11).

Endometriosis and polycystic ovary syndrome (PCOS) are common gynecological disorders that affect women of reproductive age (12, 13, 14). Both disorders have been linked to female reproduction and infertility and constitute a significant burden of disease. Thus, efforts to prevent and ensure proper diagnosis, management, and treatment are important. The etiology of the disorders is not completely clear, and different hypotheses have been brought forward. Furthermore, it has been considered whether the disorders are related to each other; however, in more recent years it was suggested that endometriosis and PCOS are diametric disorders, meaning that patient characteristics, symptoms, and biochemical findings point in opposite directions (15).

Efforts to improve the health of women of reproductive age are encouraged considering the young age and the future possibility of a pregnancy. Investigation of underlying disease mechanisms as well as potential interaction between common disorders in young female patients may contribute to preventive efforts. Endometriosis, PCOS, and thyroid disease are all common disorders in women of fertile age, and the underlying mechanisms regarding disease etiology and impact of the disorders on reproduction are not completely clear. The endocrine system has been brought forward across the diseases (4, 15), and a role of TRAb as a new biomarker in endometriosis was recently proposed (16).

This led us to describe the existing literature on the association between endometriosis, PCOS, and thyroid disease. In more detail, we speculated whether thyroid dysfunction and thyroid autoimmunity associate with the gynecological disorders. Considering the opposite biochemical findings in hyperthyroidism and hypothyroidism, we hypothesized that the disorders may show different associations with endometriosis and PCOS. We identified and reviewed original studies on the association between endometriosis, PCOS, and thyroid disease up until July 1, 2023 (Fig. 1). In addition, we evaluated the associations in a Danish cohort which included stored blood samples from early pregnant women. Finally, we considered and discussed potential underlying mechanisms for the associations observed.

Endometriosis and the thyroid

Endometriosis is a benign gynecological disease that affects 5–10% of menstruating women (12, 13). The disease is characterized by severe pelvic pain, often during menstruation, defecation, and coitus, and associated with infertility. Endometriosis occurs when functional endometrium is located outside the uterine

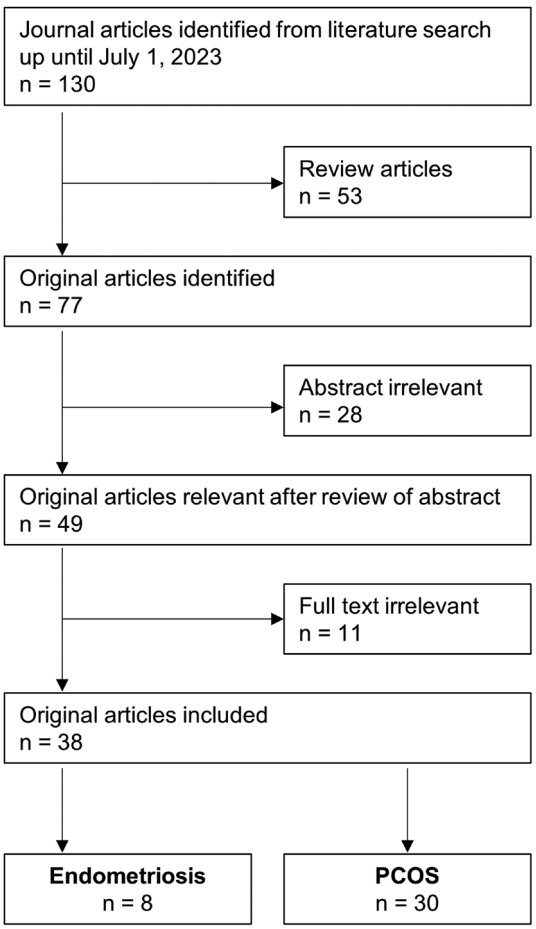

Figure 1

Flowchart of the literature search performed on the association between endometriosis, polycystic ovary syndrome (PCOS), and thyroid disease.

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cavity, mostly affecting the ovaries, uterine ligaments, the rectovaginal septum, and peritoneum (12). During menstruation, rejected endometrium induces an inflammatory cascade, resulting in severe pain, fibrosis, and the formation of adhesions in the peritoneal cavity (12). Several theories have been proposed regarding the pathogenesis of endometriosis, with Sampson's theory being the most described (12, 13). This theory refers to the presence of endometriomas resulting from retrograde menstruation through the salpinges into the peritoneal space (12, 13). In more recent years, increasing attention to the manifestations of endometriosis outside the pelvis has evolved (13). In this approach, endometriosis is considered a chronic systemic disease with systemic inflammation and altered metabolism in the liver and adipose tissue as well as altered gene expression in the brain (13). These effects may in turn explain the clinical findings of for example lower BMI and neurological and psychiatric manifestations in endometriosis patients. Research into the causes of endometriosis and development of pelvic as well as nonpelvic disease manifestations has considered many aspects including genetic and environmental risk factors (13, 15). As part of this assessment, alterations within the immune system have also been considered and described; however, no uniform theory of disease development has been substantiated. Efforts to identify risk factors and/or diagnostic markers are important, considering the severity of the disease and the difficulties in early diagnosis.

The association between thyroid disease and endometriosis has been studied, and in our literature search we identified eight original studies (16, 17, 18, 19, 20, 21, 22, 23) (Fig. 1) that were published from 2002 and onward (Table 1). The studies were all observational and mainly cross-sectional or case–control designs. The methods used for assessment of thyroid disease varied considerably, and three studied relied on registered diagnosis of thyroid disease rather than actual biochemical measurements. Among studies with biochemical assessment, it varied whether thyroid function and/or thyroid autoantibodies were considered. Regarding thyroid function and endometriosis, no clear association with either hyperthyroidism or hypothyroidism or both thyroid function abnormalities appeared; however, the number of studies was small, since only five of the eight studies identified evaluated the association with thyroid function and in three of these five studies no association was seen (Table 1). Furthermore, the statistical handling of data (e.g. the nonnormal distribution of TSH) varied between studies, which may have influenced the findings. Regarding thyroid autoimmunity, six of the eight studies evaluated this exposure, with two studies finding no association, two studies reporting an association with TPO-Ab or the outcome of autoimmune thyroiditis, and two studies suggesting an association between TRAb and endometriosis. It should be emphasized that not all studies investigated all types of thyroid autoantibodies which may influence the summary of the findings. In total, four studies measured TPO-Ab and/or Tg-Ab and a single study found an association with TPO-Ab. This was the case–control study by Poppe *et al.* (18) including 438 female patients with infertility of various causes and 100 age-matched controls. Endometriosis was the cause of infertility in 21 patients, and 29% of these patients were positive for TPO-Ab as compared to 8% of controls. On the other hand, median TSH was similar among women with endometriosis and controls, which led the authors to highlight the role thyroid autoimmunity in endometriosis; however, the association was observed among infertile patients specifically.

Altogether three of the studies identified included a measure of TRAb and in two of these studies an association with endometriosis was seen (Table 1). In these studies from Sweden (16, 21) the authors measured TRAb using an in-house ELISA assay among 172 women with surgically confirmed endometriosis and among controls. They found that TRAb were more commonly detected in endometriosis patients and most

Table 1 Overview of studies on the association between endometriosis and thyroid function as well as thyroid autoantibodies up until July 1, 2023. Plus (+) indicates significant association and minus (−) indicates no significant association.

Year	Author	Design	Cases (*n*)	Controls (*n*)	Thyroid assessment	Thyroid function	Thyroid autoantibodies
2002	Sinaii	Cross-sectional	3,680	NR	Diagnosis	+ Hypothyroidism	NA
2002	Poppe	Case–control	438	100	TSH, T4, TPO-Ab	–	+ TPO-Ab
2007	Petta	Cross-sectional	148	158	TSH, T3, T4, TPO-Ab, Tg-Ab	–	–
2016	Yuk	Cross-sectional	5,615	22,460	Diagnosis	+ Hyperthyroidism	NA
2018	Ek	Case cohort	172	117	TRAb, TPO-Ab	NA	+ TRAb
2020	Porpora	Case–control	148	150	Diagnosis	NA	+ Autoimmune thyroiditis
2022	Svensson	Cross-sectional	172	164	TSH, TRAb	NA	+ TRAb
2023	Serifoglu	Cross-sectional	51	51	TSH, T4, TPO-Ab, TRAb	–	–

NA; not assessed; NR, not reported; T3, triiodothyronine; T4, thyroxine; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

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pronounced when considering results above the assay detection limit, thus suggesting that TRAb titers were slightly elevated in the patients. Ek *et al.* found that TRAb only had a statistically significant association when titers were in a range of 1.2–1.7 IE/L (international units per liter), considered the gray zone, whereas a positive TRAb value above 1.7 IE/L was considered positive, but was not significantly associated with endometriosis (21). Similarly, Svensson *et al.* found almost identical findings when using 1 IE/L as a positive cutoff value and 0.3–1 IE/L as the gray zone. They found that 29.1% of patients with endometriosis had positive TRAb values compared to 2.6% of controls, while 94.5% of patients had a gray zone level of TRAb compared to 7.9% of controls (16). These findings led the authors to suggest that TRAb may have the potential to support the diagnosis of endometriosis. In contrast to these reports, the study by Serifoglu *et al.* found no association between TRAb and endometriosis (23). This was a cross-sectional study of 102 women who underwent surgery for benign gynecological disease, and in half of these cases endometriosis was the cause of surgery. Thus, the study did not include a healthy control group, but controls suffered from other types of benign gynecological disease treated by surgery and differed from cases regarding for example maternal age and parity. The specific biochemical method used for assessment of TRAb was not described, and TRAb values were considered by the mean concentration rather than from the classification of TRAb positivity using a method-specific cutoff. No significant difference in mean TRAb was observed among cases and controls, and TRAb levels did not differ according to the stage of endometriosis or the location (unilateral/bilateral). Thus, some methodological aspects are to be considered in the interpretation of the findings from this study (23). In general, the comparison of studies on the association with TRAb and the conclusion is challenged by the different assays used and the lack of assay-specific information including parameters to support the validity of the assay.

In conclusion, only few studies examined the association between thyroid function, thyroid autoimmunity, and endometriosis. The studies were heterogeneous in design with limited sample size and some studies were register based with no direct biochemical assessment which challenges the interpretation and summary of the findings. A trend was seen toward an association between slightly elevated levels of TRAb and endometriosis, but further large studies are needed to extend the findings.

PCOS and the thyroid

PCOS is defined as an endocrine disease that affects up to 20% of women in the reproductive age (14). PCOS has been defined by the Rotterdam criteria since 2003, which require two of the three following criteria to be present: Oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, or at least one polycystic ovary. These clinical features are due to hyperinsulinemia and hypersecretion of luteinizing hormone (LH), which stimulate the production of androgens in the ovary (14). However, the remaining peripheral tissue has been found to be insulin-resistant, thus inducing obesity in most PCOS patients. From the pathogenesis it appears that PCOS is a heterogeneous disorder associated with metabolic manifestations, and a link toward metabolic syndrome has been brought forward.

The association between thyroid disease and PCOS has been studied, and in our literature search we identified 30 original studies (24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53) (Fig. 1) that were published from 2004 and onward (Table 2). Hence, the association between thyroid disease and PCOS has been more extensively studied than what was found for endometriosis. All studies were observational in design, but the subtype of study design varied as did the size of the study population and the assessment of thyroid function and/or thyroid autoimmunity (Table 2). Among the 30 studies identified, a total of nine studies found no association with thyroid function and/or thyroid autoimmunity, whereas in 21 studies an association was seen between PCOS and hypothyroidism and/or thyroid autoimmunity (TPO-Ab and/or Tg-Ab). Thus, even if the studies and the findings were diverse, a trend was seen toward a dominant association with hypothyroidism, and none of the studies found an association with hyperthyroidism. This contrasts with the findings observed for endometriosis; however, none of the studies reporting the outcome of PCOS included a measure of TRAb and thereby any association between this thyroid autoantibody and PCOS cannot be evaluated from the existing literature.

One of the considerations when studying outcome of thyroid disease is on the differential role of thyroid dysfunction as opposed to thyroid autoimmunity, and this consideration is especially relevant when studying outcome of disease and associated disorders in women of fertile age because in this age span autoimmunity is the predominant cause of thyroid disease. Following this line of thought one may speculate on the underlying mechanisms for an association observed between hypothyroidism and PCOS. Considering the ten studies that found an association with hypothyroidism, TPO-Ab and/or Tg-Ab levels were assessed in nine of these studies, and in seven studies an association was also seen between thyroid autoantibodies and PCOS (Table 2). From this summary statistic, it is difficult to draw solid conclusions regarding the role of hypothyroidism and thyroid autoimmunity, respectively, and in most studies each exposure was evaluated among all cases, whereas stratified analyses on for example the role of hypothyroidism in TPO-Ab-positive and TPO-Ab-negative women, respectively, were not performed. Janssen *et al.* (24) studied 175 patients with PCOS and 168 age-matched controls and found that 26.9% of PCOS patients and 8.3% of controls were positive for TPO-Ab and/or Tg-Ab. Among

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Table 2 Overview of studies on the association between polycystic ovary syndrome and thyroid function as well as thyroid autoantibodies up until July 1, 2023. Plus (+) indicates significant association and minus (−) indicates no significant association.

Year	Author	Design	Cases (*n*)	Controls (*n*)	Thyroid assessment	Thyroid function	Thyroid autoantibodies
2004	Janssen	Case cohort	175	168	TSH, T4, TPO-Ab, Tg-Ab	+ Hypothyroidism	+ TPO-Ab, Tg-Ab
2011	Anaforoglu	Case–control	84	81	TSH, T3, T4, TPO-Ab, Tg-Ab	−	−
2012	Kachuei	Case–control	78	350	TSH, TPO-Ab, Tg-Ab	−	+ TPO-Ab
2013	Garelli	Case–control	113	100	TSH, T3, T4, TPO-Ab, Tg-Ab	+ Hypothyroidism	+ Autoimmune thyroiditis
2013	Sinha	Cross-sectional	80	80	TSH, T3, T4, TPO-Ab	+ Hypothyroidism	+ TPO-Ab
2014	Al-Saab	Case–control	56	30	TSH, T4, TPO-Ab, Tg-Ab	−	+ TPO-Ab
2015	Arduc	Cross-sectional	86	60	TSH, T4, T3, TPO-Ab, Tg-Ab	+ Hypothyroidism	+ TPO-Ab, Tg-Ab
2015	Duran	Cohort study	73	60	TSH, T4, TPO-Ab, Tg-Ab	−	−
2015	Novais	Cross-sectional	65	65	TSH, T4, T3, TPO-Ab, Tg-Ab	+ Hypothyroidism	−
2015	Petrikova	Cohort study	64	68	TSH, T4, T3, TPO-Ab, Tg-Ab	−	−
2016	Arora	Case–control	55	51	TSH, T4, T3, TPO-Ab, Tg-Ab	−	+ Tg-Ab
2016	Polat	Case–control	70	84	TSH, T4, TPO-Ab	−	−
2016	Tehrani	Cross-sectional	74	417	TSH, T4, TPO-Ab	−	−
2016	Yasar	Case–control	217	131	TSH, T4, T3, TPO-Ab, Tg-Ab	+ Hypothyroidism	+ Autoimmune thyroiditis
2016	Yu	Case–control	100	100	TSH, T4, T3, TPO-Ab	+ Hypothyroidism	+ TPO-Ab
2017	Karaköse	Case–control	97	71	TSH, T4, T3, TPO-Ab, Tg-Ab	−	+ TPO-Ab
2017	Menon	Case–control	9	9	TSH, T4. TPO-Ab	−	+ TPO-Ab
2018	Hepsen	Case–control	184	106	TSH, T4, TPO-Ab, Tg-Ab	−	+ TPO-Ab, Tg-Ab
2018	Wang	Cohort	121	408	TPO-Ab, Tg-Ab	NA	+ TPO-Ab
2019	Cai	Cross-sectional	600	200	TSH, TPO-Ab, Tg-Ab	+ Hypothyroidism	−
2020	Adamska	Cross-sectional	141	88	TSH, T3, T4, TPO-Ab	−	−
2020	Ho	Cohort	4,931	26,924	Diagnosis	NA	+ Autoimmune thyroid disease
2021	Raj	Case–control	200	200	TSH, T4, T3	+ Hypothyroidism	NA
2021	Skrzynska	Case–control	80	64	TSH, T4, TPO-Ab, Tg-Ab	−	−
2022	Altuntas	Case–control	178	92	TSH, T4, T3, TPO-Ab, Tg-Ab	−	+ TPO-Ab
2022	Gawron	Cohort	367	None	TSH, T4, T3, TPO-Ab, Tg-Ab	−	−
2022	Kim	Case–control	210	343	TSH, T4, TPO-Ab	−	−
2022	Sharma	Case–control	33	32	TSH, T4, T3, TPO-Ab	−	+ TPO-Ab
2023	Bonakdaran	Cross-sectional	41	41	TS, T4, T3, TPO-Ab	+ Hypothyroidism	+ TPO-Ab
2023	Heidarpour	Cross-sectional	76	66	TPO-Ab	NA	+ TPO-Ab

NA; not assessed; T3, triiodothyronine; T4, thyroxine; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

patients with PCOS they found no significant difference in mean TSH and free T4 when stratified by whether the women were thyroid autoantibody positive or negative. This finding would to some extent point toward a predominant role of thyroid autoimmunity as opposed to thyroid dysfunction regarding the association with PCOS; however, more studies are needed to substantiate the findings.

Another challenge regarding the evaluation of the association between hypothyroidism and PCOS is the role of nonthyroidal characteristics in the associations observed. Some characteristics of women with PCOS and hypothyroidism overlap, e.g. BMI and diabetes mellitus; however, many studies adjusted for these maternal covariates and found similar associations.

In conclusion, the studies that investigated thyroid disease in relation to PCOS were heterogeneous and a rather small study population was examined in many of the studies; however, a predominant association with autoimmune hypothyroidism was seen.

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Thyroid function or autoimmunity?

The findings from the review of the literature led us to evaluate the interplay between thyroid disease, endometriosis, and PCOS in an established Danish cohort with biobank samples from early pregnant women. The North Denmark Region Pregnancy Cohort (NDRPC) is a large birth cohort established from 2011 to 2015 that includes biobank samples from 14,323 Danish pregnant women (54). The samples were drawn as part of prenatal screening for chromosomal anomalies which is offered to every pregnant woman in Denmark as part of routine clinical care. After ethical permission, serum residues of the samples were obtained for study purposes; thus, the samples were drawn for nonthyroidal reasons in a clinical setting. In retrospect, these samples have been used for biochemical measurement of maternal thyroid function parameters and thyroid autoantibodies. TRAb has been measured in a random subcohort of 606 women using an automatic immunoassay (KRYPTOR Compact, Thermo Fisher Diagnostics) and among these women TPO- and Tg-Ab were also measured in the same samples using an automatic immunoassay (ADVIA Centaur XPT, Siemens Healthineers) (55, 56). Information on endometriosis and PCOS in the NDRPC was obtained via linkage to the Danish nationwide health registers. Specifically, we assessed any hospital diagnosis classified according to the Tenth International Classification of Diseases (ICD-10) for endometriosis (ICD-10: N80.0-80.9) and PCOS (ICD-10: E28.2) from 1995 to 2018.

The 606 women studied (median 30 years of age) were consecutively included in the cohort in 2012 and had a blood sample drawn in median pregnancy week 10. Altogether 15 women (2.5%) had a diagnosis of endometriosis, 12 women had a diagnosis of PCOS (2.0%), and the remaining 579 had no diagnosis of these disorders and were considered controls (Fig. 2).

In each group of women, the frequency of having thyroid autoantibodies at or above the assay detection limit (TRAb: ≥0.27 IU/L, TPO-Ab: ≥28 U/mL, and Tg-Ab ≥15 U/mL) was evaluated. Notably, TRAb were more commonly detected among women with endometriosis as compared to controls, whereas no increased detection of TPO-Ab or Tg-Ab was seen in these patients (Fig. 2). No increased detection of either of the thyroid autoantibodies was observed for women diagnosed with PCOS, although a trend was seen toward more detectable TPO-Ab and Tg-Ab (Fig. 2). Among women with endometriosis, maternal TSH ranged from 0.2 to 3.5 mIU/L, and the median (1.02 mIU/L) did not differ from controls (1.07 mIU/L) or women with PCOS (1.12 mIU/L). It should be acknowledged that the number of cases was small in the cohort, and it is further a limitation that the identification of women with endometriosis and PCOS was predicated on the referral to hospital for management and treatment. Thus, milder cases that are managed in general practice alone would not be identified in our cohort. This creates a risk of referral bias; however, from the literature review, we identified that this is a general concern regarding the available literature that often cases are identified in a hospital setting and, in some situations, only when surgery is performed or infertility is managed. Nevertheless, our findings within a Danish birth cohort corroborate a link between subtle elevations of TRAb and endometriosis. On the other hand, no such link was seen for PCOS or for other subtypes of thyroid autoantibodies, and results did not suggest that abnormal maternal TSH was the causal link.

Endometriosis, PCOS, and the thyroid

Considering the findings from the literature review and in the Danish cohort, we speculated on the association

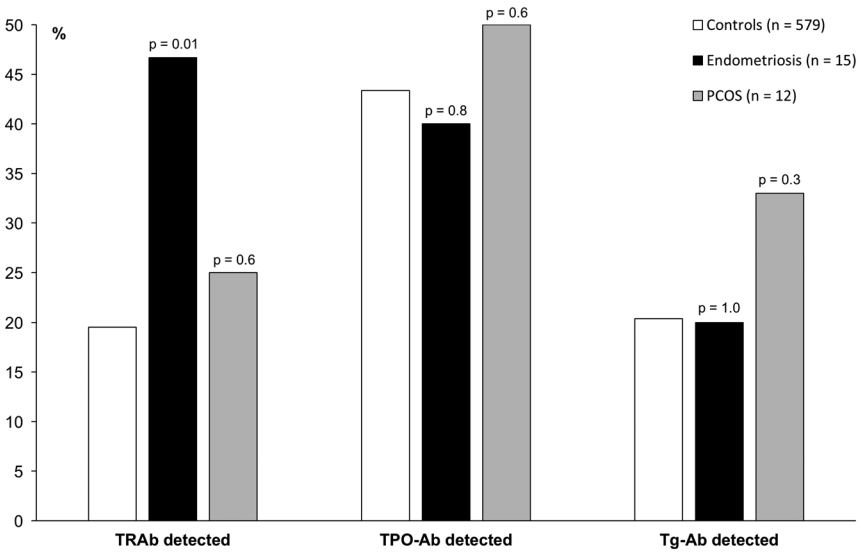

Figure 2

Frequency of thyroid autoantibodies in a random sample of 606 early pregnant women from the North Denmark Region Pregnancy Cohort split by controls, women with a diagnosis of endometriosis, and women with a diagnosis of polycystic ovary syndrome (PCOS). Thyroid-stimulating hormone receptor antibodies (TRAb) were considered detected when ≥0.27 IU/L, thyroid peroxidase antibodies (TPO-Ab) when ≥28 U/mL, and thyroglobulin antibodies (Tg-Ab) when ≥15 U/mL (assay detection limits). Reported *P*-values are the result of comparison with controls using the chi-square test.

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between maternal hyperthyroidism and endometriosis as well as hypothyroidism and PCOS. An autoimmune etiology is a characteristic of both types of thyroid dysfunction in women of fertile age; however, the dominant thyroid autoantibody and thereby the type of thyroid dysfunction and clinical presentation differ for hyperthyroidism and hypothyroidism. Endometriosis and PCOS are both benign gynecological disorders that occur in women of fertile age; however, it was recently described that the disorders differ diametrically on a series of clinical and biochemical parameters (Table 3) including menstrual cycle, levels of hormones, and body composition (15). Following this line of thought, we speculated how hyperthyroidism and hypothyroidism would influence these parameters (Table 3).

Opposite effects of endometriosis and PCOS have been described regarding menstrual cycle with earlier age at menarche and menopause in endometriosis combined with shorter length of the menstrual cycle, whereas among women with PCOS, later onset of menarche and menopause has been found as well as longer length of the menstrual cycle caused by amenorrhea or oligomenorrhea (15). Such clear and opposite pattern has not been described for hyperthyroidism and hypothyroidism (Table 3). Only few studies examined age at menarche and findings were diverse, however, with a trend toward later onset in hyperthyroidism and earlier in hypothyroidism (5). Turning to menopause, a study of 72 cases of subclinical hypothyroidism and controls found no difference in the age at menopause (57); however, other reports on hypothyroidism and hyperthyroidism are sparse. The opposite pattern observed for endometriosis and PCOS regarding the length of the menstrual cycle was not found for the disorders of thyroid dysfunction (Table 3). In these cases, menstrual disturbances such as amenorrhea and oligomenorrhea have been found consistent with a longer length of the menstrual cycle in hyperthyroidism as well as in hypothyroidism (5).

Opposing patterns were seen for endometriosis and PCOS as regards the levels of the hormones LH, follicle-stimulating hormone (FSH), estradiol, and testosterone (Table 3). Characteristics of endometriosis are lower levels of LH, higher levels of FSH, and thereby a reduced LH-to-FSH ratio, whereas in PCOS the findings are opposite with a higher LH-to-FSH ratio. Furthermore, a high estradiol-to-testosterone ratio is typically seen in endometriosis, whereas in PCOS this ratio is low because of high testosterone levels and mainly unaltered levels of estradiol (15). Evidence on alterations in these hormones is less consistent for disorders of thyroid dysfunction. Opposite findings have been described for hyperthyroidism and hypothyroidism but different than what were found for endometriosis and PCOS (Table 3). Hence, it has generally been found that hyperthyroidism associates with higher levels of these hormones, whereas for hypothyroidism unaltered levels of LH and FSH and lower levels of estradiol and testosterone have been reported (5). An important notion on the impact of thyroid dysfunction on levels of testosterone and estradiol should be considered. In hyperthyroidism and hypothyroidism, the level of sex hormone-binding globulin (SHBG) changes in opposite directions; thus, SHBG increases in hyperthyroidism and decreases in hypothyroidism (5). Thus, it leads to a speculation whether the alterations seen in the total levels of testosterone and estradiol are caused by concomitant alterations in SHBG, and data to extend the knowledge on the levels of free testosterone and free estradiol in females with hyperthyroidism or hypothyroidism are warranted (5).

Even if the alterations in menstrual cycle and hormone levels were not directly comparable for endometriosis and PCOS as opposed to hyperthyroidism and

Table 3 Characteristics of menstrual cycle, related hormones, and body composition described in endometriosis and polycystic ovary syndrome (PCOS) (15) as well as in hyperthyroidism and hypothyroidism. Dash (–) indicates that evidence is missing or inconclusive.

	Endometriosis	PCOS	Hyperthyroidism	Hypothyroidism
Menstrual cycle				
Menarche	Earlier	Later	Later	Earlier
Menopause	Earlier	Later	–	–
Menstrual cycle length	Shorter	Longer	Longer	Longer
Hormone levels				
LH	Decreased	Increased	Increased	Unaltered
FSH	Increased	Decreased	Increased	Unaltered
Estradiol	Increased	Unaltered	Increased	Decreased
Testosterone	Decreased	Increased	Increased	Decreased
Body composition				
Waist-to-hip ratio	Decreased	Increased	Decreased	Increased
Body mass index	Decreased	Increased	Decreased	Increased
Muscle mass	Decreased	Increased	Decreased	Increased

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

hypothyroidism, a notable pattern was seen regarding the measurements of body composition (Table 3). It has been found that waist-to-hip ratio, BMI, and muscle mass were lower in patients with endometriosis and higher in PCOS, and it has been proposed that these opposite effects emerge from the different estradiol-to-testosterone ratio (15). The body composition measures seen in hyperthyroidism and hypothyroidism mimic that of endometriosis and PCOS, respectively (Table 3). Substantial evidence supports an interaction between thyroid function and obesity, with a lower risk in hyperthyroidism and a higher risk in hypothyroidism (58). This is compatible with the alterations described in waist-to-hip ratio and BMI; however, the underlying mechanisms are debated and the alterations in muscle mass less substantiated. From observations along with the treatment of abnormal thyroid function in patients with hyperthyroidism or hypothyroidism, it has been found that the alterations in body weight after treatment do not relate to alterations in fat mass but rather to lean body mass including muscle mass (58). Thus, in patients with hyperthyroidism, the weight gain after therapy was caused by an increase in muscle mass (59), whereas in hypothyroidism, the weight loss in hypothyroidism was caused by a decrease in lean body mass along with an excess excretion of water accumulated during the hypothyroid phase (60). Thus, the underlying mechanisms of alterations in body composition, although in similar directions, may be different in endometriosis and PCOS as opposed to disorders of thyroid dysfunction.

Conclusion

The gynecological disorders, endometriosis and PCOS, and the thyroid disorders of hyperthyroidism and hypothyroidism constitute a significant burden of disease in women of fertile age. A link between the disorders is biologically plausible, considering the universal effect of thyroid hormones and the specific role in female reproduction. From a review of the existing literature, a clue toward an association between endometriosis and hyperthyroidism on the one hand and PCOS and hypothyroidism on the other has been traced. Whether thyroid dysfunction and/or thyroid autoimmunity are involved in the underlying mechanisms for the associations observed remains unresolved. A small sample size was a limitation in many studies along with heterogeneous designs and definitions of exposure and outcome. Nevertheless, the tendency observed and the rather robust findings across populations regarding subtypes of thyroid autoantibodies encourage further and large studies on the interplay between endometriosis, PCOS, and thyroid disease.

Declaration of interest

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

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Author contribution statement

Signe Kirkegaard, Nanna Maria Uldall Torp, and Stine Linding Andersen conceptualized the study, performed data analyses, and drafted the manuscript. Stig Andersen critically reviewed and discussed the manuscript.

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