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Antithyroid drug therapy in pregnancy and risk of congenital anomalies: Systematic review and meta-analysis

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Abstract

Objectives: The risk of congenital anomalies following in utero exposure to thionamide antithyroid drugs (ATDs) is unresolved. Observational studies are contradictory and existing meta-analyses predate and preclude more recent studies. We undertook an updated meta-analysis of congenital anomaly risk in women exposed to carbimazole or methimazole (CMZ/MMI), propylthiouracil (PTU), or untreated hyperthyroidism in pregnancy.

Methods: We searched Medline, Embase, and the Cochrane database for articles published up till August 2021. We pooled separate crude and adjusted risk estimates using random effects models and subgroup analyses to address heterogeneity.

Results: We identified 16 cohort studies comprising 5957, 15,785, and 15,666 exposures to CMZ/MMI, PTU, and untreated hyperthyroidism, respectively. Compared to non-disease controls, adjusted risk ratio (RR) and 95% confidence intervals (95% CIs) for congenital anomalies was increased for CMZ/MMI (RR, 1.28; 95% CI, 1.06–1.54) and PTU (RR, 1.16; 95% CI, 1.08–1.25). Crude risk for CMZ/MMI was increased relative to PTU (RR, 1.20; 95% CI, 1.01–1.43). Increased risk was also seen with exposure to both CMZ/MMI and PTU, that is, women who switched ATDs in pregnancy (RR, 1.51; 95% CI, 1.14–1.99). However, the timing of ATD switch was highly variable and included pre-pregnancy switches in some studies. The excess number of anomalies per 1000 live births was 17.2 for patients exposed to CMZ/MMI, 9.8, for PTU exposure, and 31.4 for exposure to both CMZ/MMI and PTU. Risk in the untreated group did not differ from control or ATD groups. The untreated group was however highly heterogeneous in terms of thyroid status. Subgroup analysis showed more positive associations in studies with >500 exposures and up to 1-year follow-up.

Conclusions: ATD therapy carries a small risk of congenital anomalies which is higher for CMZ/MMI than for PTU and does not appear to be reduced by switching ATDs in pregnancy. Due to key limitations in the available data, further studies will be required to clarify the risks associated with untreated hyperthyroidism and with switching ATDs in pregnancy.

KEYWORDS
carbimazole, hyperthyroidism congenital anomalies, methimazole, pregnancy antithyroid drugs, propylthiouracil

1 | INTRODUCTION

Hyperthyroidism is common in women of reproductive age and affects about 0.1%–0.5% of pregnant women.[1] Uncontrolled hyperthyroidism has adverse effects on pregnancy outcomes including an increased risk of pre-eclampsia, preterm delivery, and low birth weight.[2–4] The thionamide antithyroid drugs (ATD), namely methimazole (MMI), its prodrug derivative, carbimazole (CMZ), and propylthiouracil (PTU), are effective in the treatment of hyperthyroidism.[5] CMZ/MMI is the recommended ATD in the nonpregnant population while PTU is reserved as second line due to the potentially serious adverse effect of hepatotoxicity.[5] One drawback of CMZ/MMI however is the risk of offspring congenital anomalies when administered in early pregnancy, that is, during the critical phase of organogenesis.[6,7] CMZ/MMI has been linked with a broad range of defects including the so called CMZ/MMI embryopathy, a cluster of anomalies comprising aplasia cutis, choanal atresia, trachea-oesophageal fistula, and dysmorphic facial features.[8]

Accordingly, international guidelines recommend that PTU is used instead of CMZ/MMI in early gestation or in the preconception period.[9–11] Guidelines also suggest that ATDs can be discontinued altogether in women with mild disease in pregnancy.[9–11] However, the benefits of these approaches remain uncertain. Congenital anomaly risk is well established for CMZ/MMI but increased anomaly risk has also been reported in PTU treated women including those who switch from CMZ/MMI to PTU on conception.[12,13] To compound matters, some studies have suggested that hyperthyroidism by itself has teratogenic potential independent of ATD exposure.[14] Randomised controlled trials are now unlikely to be conducted given the potential ethical dilemmas that such trials will entail. Thus, a meta-analysis of observational studies represents the next best level of evidence for evaluating the safety of ATDs in pregnancy.

Findings from observational studies have been conflicting and challenging to synthesize due to methodological discrepancies across studies.[15] Initial meta-analyses were marked by disparities in comparison groups and the use of crude risk estimates that failed to account for potential confounders.[16–18] Furthermore, earlier meta-analyses were published over four years ago and do not include a number of relevant studies that have subsequently emerged in the literature.[12,13,19–21] A recent meta-analysis by Morales et al.[22] showed an increase in adjusted anomaly risk in the children of women exposed to CMZ/MMI, PTU, as well as those exposed to untreated hyperthyroidism. In contrast however, three recently published studies, not included in the Morales meta-analyses, reported no excess anomaly risk in association with PTU or untreated hyperthyroidism.[19–21] Thus, the risk of congenital anomalies with ATD therapy, particularly with respect to the PTU and untreated disease groups, remains unresolved. Our objective was therefore to present an updated meta-analysis of all available studies to date. To optimise the use of available data, we have pooled separate crude and adjusted risk estimates using random effects models and subgroup analyses to address heterogeneity.

2 | METHODS

2.1 | Search strategy

We searched Medline, Embase, and the Cochrane database, for English language articles in humans published between database inception and August 2021 using a combination of the key words: pregnancy, hyperthyroidism, ATDs, thionamides, MMI, CMZ, thiamazole, PTU, and congenital anomaly. The search strategy is detailed in appendix 1. Additional publications were obtained from references cited in individual articles. Relevant articles were selected after initial reading of titles and abstracts and full texts were accessed when the title or abstract did not provide enough information to exclude the study. The search was conducted by two authors (M. A. and O. E. O.) with discrepancies resolved by consensus. The study was reported according to the PRISMA system (Preferred Reporting Items for Systematic Reviews) and was registered on the International prospective register of systematic reviews, PROSPERO (Registration No.: CRD42021226637).

2.2 | Study selection and data extraction

We selected prospective or retrospective cohort studies in women treated with ATDs in pregnancy. Studies were eligible if they included adequate information to allow comparisons of effect estimates between any two of the following groups: (1) a group exposed to either CMZ/MMI, PTU, or both drugs (exposure group); (2) a control group of women without hyperthyroidism or ATD exposure in pregnancy (control group); and (3) women with hyperthyroidism who did not receive ATD treatment in pregnancy (untreated disease group). We also included studies with frequency data to allow comparisons between ATD treatment groups. Outcome was the risk of offspring congenital anomalies including studies that reported outcomes as crude or adjusted risk estimates or studies that provided frequency tables from which crude risk estimates could be calculated. Information on study characteristics, exposures, and outcomes was extracted using predesigned questionnaires.

2.3 | Study quality

We assessed the methodological quality of studies using the Newcastle Ottawa Scale (NOS) for the assessment of observational studies.[23] The

NOS assesses patient selection, comparability of cases and controls, and the assessment of the outcomes. Domains scored for this study included how well the study sample represented a pregnant hyperthyroid population, control for confounders, and the adequacy and duration of follow up for ascertainment of congenital anomalies.

2.4 | Data analysis

Effect estimates are presented as risk ratios and 95% confidence intervals (CIs) using a random effects model with inverse variance method. Risk ratios were compared in children of exposure versus control groups, in untreated versus control groups, as well as in untreated versus exposure groups. Adjusted risk ratios were taken as the primary analysis, but pooled crude risk ratios were also independently determined from studies without adjusted risk estimates. Heterogeneity was assessed using I^2 statistics with values of <25%, 25%–50%, and >50%, representing low, moderate, and high heterogeneity, respectively. A funnel plot with Harbord test was used to assess publication bias.[24] Sensitivity analysis was undertaken to evaluate the impact of sample size, the duration of follow-up in children, and the ascertainment of outcomes.

The excess number of anomalies per 1000 live births was computed from the absolute risk (AR) difference between the exposed and unexposed population using the formula, $1000 \times (AR_e - AR_u)$, where AR_e and AR_u represent ARs in the exposed and unexposed groups respectively. AR_u was computed from the proportion of anomalies/exposures in the unexposed disease-free population while AR_e was derived from the product of AR_u and the adjusted relative risks obtained from the pooled analysis.[25] A p-value of less than 0.05 was considered significant. The analysis was undertaken using the Revman (Review Manager, version 5.4.1, the Cochrane Collaboration, 2020) and Stata software packages (Stata; version 15.1; StataCorp).

3 | RESULTS

3.1 | Study selection and characteristics

The study selection flow chart is shown in Figure 1. The search identified 1393 unique articles of which 1324 were excluded after title or abstract screening. A further 53 papers were excluded after full text review, resulting in a final 16 papers in the review.[12–14,19–21,26–35] Papers excluded on full text review are listed in appendix 2 while the characteristics of the selected studies are shown in Table 1. Publication years ranged from 1984 to 2021 and included studies from Denmark,[12,27] Sweden,[26] Japan,[14,20,33] Taiwan,[28] United States,[30–32] Israel,[34] South Korea,[13] Italy,[29] Norway,[21] France,[35] and Finland.[19] All studies were cohort studies including one study with a matched case control design.[28] The studies varied with respect to exposure windows, duration of follow-up in children, and ascertainment of outcomes and included data on 5957, 15,785, and 15,666 exposures to CMZ/MMI, PTU, and untreated hyperthyroidism, respectively. All 16 studies presented frequency tables from which crude risk ratios (RR) and 95% CIs could be computed. In addition, nine studies also presented adjusted risk ratios which corrected for various factors including maternal age, smoking, diabetes, and hypertension

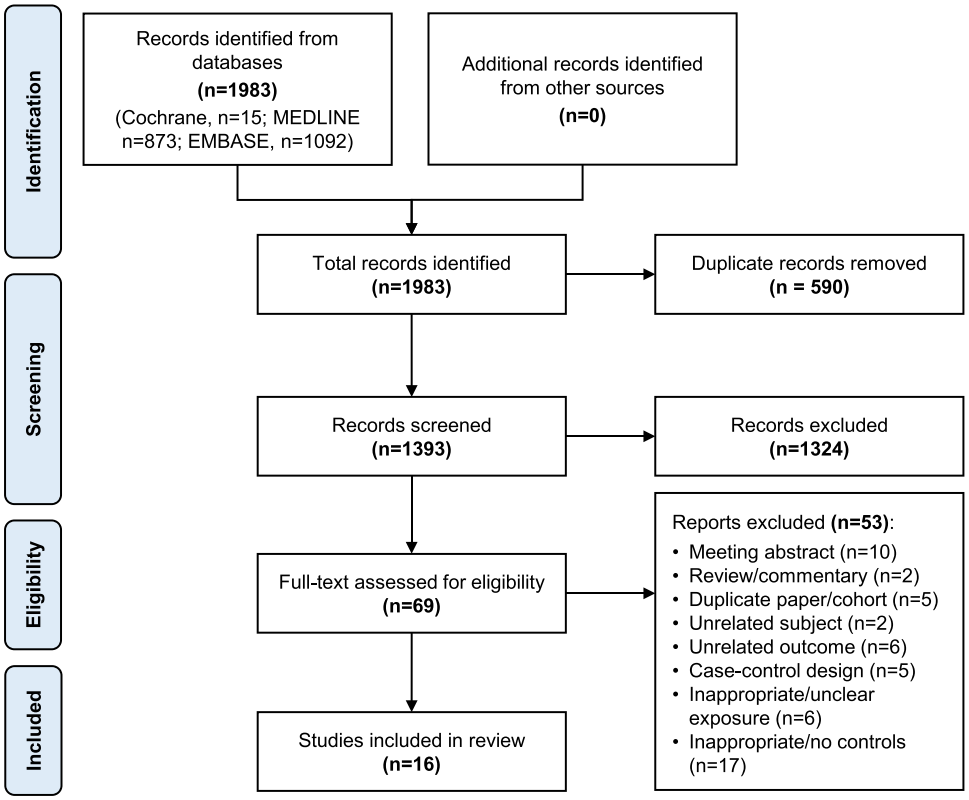

FIGURE 1 Study selection flow chart

TABLE 1 Study characteristics

Author, year	Country, period	Study design	CMZ/MMI cases/total	PTU cases/ total	Untreated cases/total	Controls cases/total	Variables adjusted for	Exposure time	Child follow-up	Type of anomalies
Andersen, 2013	Denmark, 1996–2008	Retrospective Cohort study	100/1097	45/564	190/3543	45,982/ 811,730	Birth-year, gender, multiple birth, maternal age, cohabitation, income, birthplace, residence	6 months pre- to 10 weeks gestation	Up to 2 years	All anomalies
Andersen, 2017	Sweden, 2006–2012	Retrospective Cohort study	11/162	14/218	136/1551	54,827/ 682,343	Birth-year, maternal age, parity, BMI, smoking, origin, multiple birth	6 months pre- to 11 weeks gestation	Up to 2 years	All anomalies
Andersen, 2019	Denmark, 1997–2016	Retrospective Cohort study	151/1574	74/889	–	777,91/ 1,159,181	Multiple birth, maternal age, parity, smoking, origin, DM	6 months pre- to 10 weeks gestation	Up to 2 years	All anomalies
Chen, 2011	Taiwan, 2005	Retrospective Cohort with matched controls	0/73	5/630	15/2127	92/14,150	Mother's education, anaemia, dyslipidaemia, DM, hypertension, hyperemesis, gender, birth order	Therapy >30 days during pregnancy	At Birth	Major anomalies[a]
Di Gianantonio, 2001	Europe, Unclear	Prospective Cohort study	8/241	–	–	23/1089	None	Pregestation to 1st trimester	3–12 months	Major anomalies[b]
El Khalil, 2021	Norway, 2008–2018	Retrospective Cohort study	5/200	10/285	46/945	–	Birth year, maternal age, marital status, parity, smoking, previous pregnancy loss, folic acid, and multivitamin use	Week 1–12 gestation	At Birth	All anomalies, and cardiac anomalies
Hawken, 2016	France, 2005–2012	Retrospective Cohort study	4/19	0/13	–	–	None	First trimester	At birth	All anomalies
Korelitz, 2013	USA, 2005–2009	Retrospective Cohort study	6/108	66/915	205/3236	37,351/ 634,858	Mother's age	6 months pregestation to delivery	Up to 1 year	All anomalies
Lo, 2015	USA, 1996–2010	Retrospective Cohort study	1/30	15/507	52/1171	–	None	2 months pre- to delivery	At Birth	All anomalies
Momotani, 1984	Japan, 1965–1980	Retrospective Cohort study	2/243	–	3/50	1/350	None	1st trimester	At Birth	Major anomalies[c]
Rosenfield, 2009	Israel, 1994–2004	Prospective, Cohort study	–	1/80	–	34/1066	None	4–13 weeks gestation	Up to 6 years	Major anomalies[b]
Seo, 2018	Korea, 2008–2014	Retrospective Cohort study	91/1120	699/9930	–	170,716/ 2,872,109	Maternal age, birth year, multiple pregnancies, infant sex	First trimester	Up to 1 year	All anomalies
Turunen, 2020	Finland, 2004–2013	Retrospective Cohort study	–	–	76/1564	22,918/ 550,860	Maternal age, BMI, smoking, parity, socioeconomic status, birth year, DM, locality	3 months pre- to delivery	Up to 1 year	Major anomalies[d]

TABLE 1 (Continued)

Author, year	Country, period	Study design	CMZ/MMI cases/total	PTU cases/ total	Untreated cases/total	Controls cases/total	Variables adjusted for	Exposure time	Child follow-up	Type of anomalies
Wing, 1994	USA, 1974–1990	Retrospective Cohort study	1/36	3/99	1/43	-	None	During pregnancy	Unclear	Major anomalies[b]
Yoshihara, 2012	Japan, 1999–2010	Retrospective Cohort study	50/1231	26/1399	40/1906	-	Maternal age and thyroid status	First trimester	At Birth	Major anomalies[a]
Yoshihara, 2021	Japan, 2015–2019	Retrospective Cohort study	0/23	30/541	27/475	-	None	First trimester	1 year	Major anomalies[a]

Abbreviations: BMI, body mass index; CMZ/MMI, carbimazole/MMI; DM, diabetes mellitus; PTU, propylthiouracil.

[a]Major anomaly not specifically defined.

[b]Anomaly with surgical, medical, or cosmetic relevance.

[c]Major structural malformations of external organs readily detectable by surface examination.

[d]According to the European Congenital Anomaly guide which defined major anomalies as anomalies with surgical, medical, or cosmetic relevance.

(Table 1). Methodological quality scores of included studies ranged from 4 to 9 with 10 out of 15 studies awarded a score of 7 or more (Table S1).

3.2 | Risk of congenital anomalies in ATDs versus controls

Crude and adjusted RRs for congenital anomalies in the exposed versus control groups are presented in Figures 2 and 3, respectively. CMZ/MMI exposure was associated with increased crude and adjusted risks (Figures 2A and 3A). Anomaly risk was also increased after PTU exposure in both crude and adjusted analyses (Figures 2B and 3B). Risk ratios were also increased in children exposed to both drugs (CMZ/MMI + PTU) in the crude and adjusted estimates (Figures 2C and 3C). Moderate heterogeneity was seen with the estimates for the adjusted CMZ/MMI, adjusted CMZ/MMI + PTU, and the crude CMZ/MMI + PTU comparisons. Only one study specifically reported risk ratios in relation to the sequence of switching ATDs.[13] In this study, switching from MMI to PTU was not associated with reduced anomaly risk compared to continuing with MMI alone (odds ratio [OR] 1.06, 95% CI 0.79–1.42) while switching from PTU to MMI to was associated with increased risk compared to continued treatment with PTU (OR, 1.79; 95% CI, 1.08–2.97).[13]

3.3 | Risk of congenital anomalies in the untreated group

The risk of congenital anomaly in the untreated group was compared to the control as well as the drug exposed groups (Figures 4 and S1). Anomaly risk in the untreated group was not significantly different from controls whether in the crude or adjusted analysis (Figure S1A and 4A). There was no difference between the CMZ and untreated groups in both crude or adjusted analysis (Figures S1B and 4B). For the PTU versus untreated comparison, meta-analysis of three available studies with adjusted risk estimates showed decreased risk for PTU (Figure 4C) whereas analysis of nine studies with crude estimates yielded no difference (Figure S1C). Increased crude risk relative to the untreated group was seen with CMZ/MMI + PTU exposure (Figure S1D). However, the untreated group analysis was associated with variable degrees of heterogeneity. Furthermore, thyroid status of the untreated group varied across studies ranging from exclusively hyperthyroid cohorts (one study),[14] to cohorts with stable euthyroidism (one study),[20] a mix of hyperthyroidism and euthyroidism (two studies),[32,33] and cohorts with unknown thyroid status (seven studies)[19,21,26–28,30,31] (Table S2).

3.4 | Risk of congenital anomalies in CMZ/MMI versus PTU groups

Crude risk estimates alone from 11 studies were available for the comparison of anomaly risk between the two thionamide compounds. An increased risk was seen for CMZ/MMI compared to PTU (Figure S2).

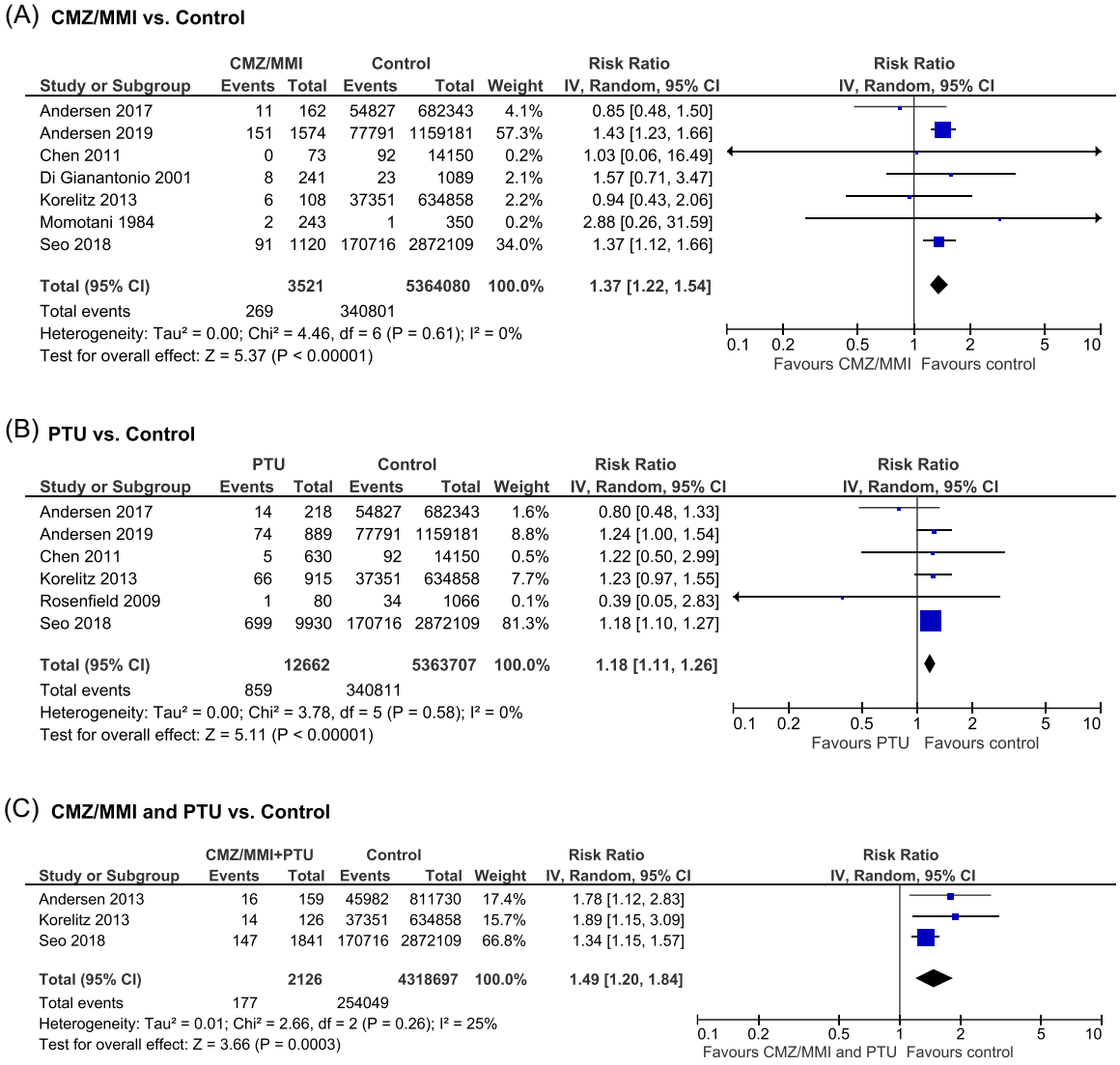

FIGURE 2 Meta-analysis of crude risk ratios for congenital anomalies after ATD exposure in pregnancy. CMZ/MMI, carbimazole/methimazole; controls, nondisease controls without ATD exposure; PTU, propylthiouracil

3.5 | Risk of congenital anomalies according to thyroid function

Four studies addressed anomaly risk according to thyroid status but were not comparable by meta-analysis. A 1984 Japanese hospital study by Momotani et al. reported a higher incidence of birth defects in the offspring of hyperthyroid mothers compared to offspring of euthyroid mothers (3% vs. 0.2%, $p < .01$).[14] In a second study from the same institution, Yoshihara et al. reported an increased risk of birth defects in children of hypothyroid compared to euthyroid mothers (9.3% vs 3.8%, $p = .03$) although this association disappeared after correction for maternal age and treatment.[33] A recent study by the same authors reported no difference in FT4 or TSH concentrations in PTU-treated mothers who delivered children with birth defects and those who delivered children without birth defects.[20] In a large Danish nationwide study, Andersen et al. reported an increased risk of congenital anomalies in a subsection of children of overtly hypothyroid women compared to children of euthyroid mothers although a proportion of these mothers had received ATD treatment (OR, 1.91; 95% CI, 1.12–3.25).[12]

3.6 | Risk of congenital anomalies according to ATD dose

Three studies evaluated anomaly risk in relation to ATD dose but were not comparable by meta-analysis. The two hospital studies by Momotani and Yoshihara showed no association between ATD dose and birth defects.[14,20] In contrast, a large Korean nationwide database study by Seo et al. reported that children of women who received a high cumulative dose of MMI had an increased anomaly risk compared to those who received lower doses (495 vs. <126 mg, OR, 1.87; 95% CI, 1.06–3.30). On the other hand, a dose response relationship was not seen with PTU exposure.[13]

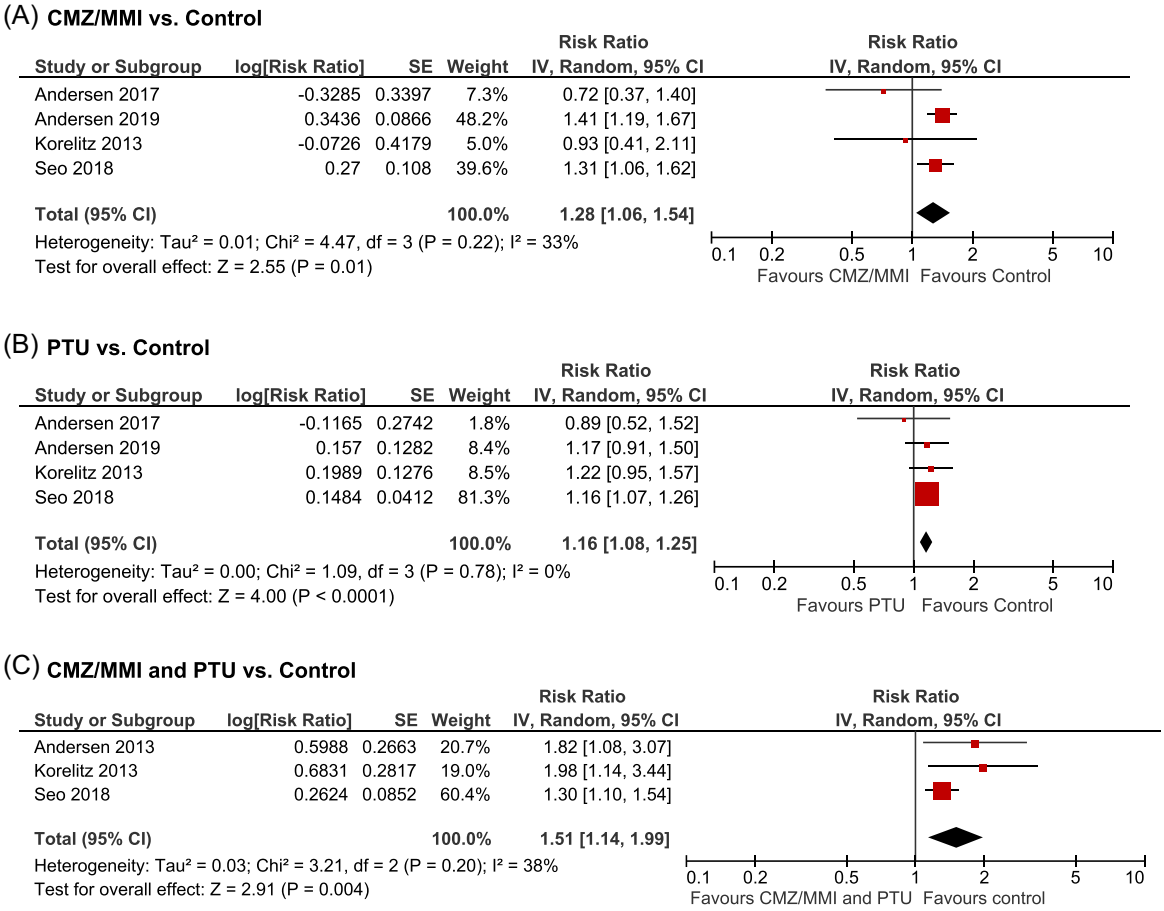

FIGURE 3 Meta-analysis of adjusted risk ratios for congenital anomalies after ATD exposure in pregnancy. CMZ/MMI, carbimazole/methimazole; controls, nondisease controls without ATD exposure; PTU, propylthiouracil

3.7 | Sensitivity analyses

Subgroup analyses was undertaken according to sample size (<500 exposures vs. >500 exposures), follow-up duration of the children (<1 vs. >1 year), and type of congenital anomalies (major anomalies only vs all anomalies) (Figure 5). Major anomalies were defined in four studies as anomalies with surgical, medical, or cosmetic significance.[19,29,32,34] No specific definition was provided in three studies[20,28,33] while one study defined it as readily detectable malformations on surface examination[14] (Table 1). Positive associations between ATD and birth defects were more likely to be seen in studies with >500 exposures, up to 1-year follow up, and studies that evaluated all anomalies as opposed to studies with fewer exposures, shorter follow-up duration, and evaluation of major anomalies only (Figure 5). These differences were not seen for the comparisons between the untreated and control groups.

3.8 | Test for publication bias

Funnel plots for publication reporting bias were created for the crude risk estimates for ATD exposures (Figure S3). The Harbod test for small study effects was not significant for the CMZ/MMI versus control ($p = .22$), PTU versus control ($p = .56$), or PTU versus untreated ($p = .51$) comparisons suggesting no bias for these analyses. Significant asymmetry towards smaller studies with negative associations was seen for the CMZ/MMI versus untreated comparison suggesting bias in this comparison (Figure S3c, $p = .02$) (Figure S3).

3.9 | AR difference

The baseline anomaly rate in the unexposed disease-free population was 61.5 per 1000 live births. This rate was computed from 9 out of the 10 studies in Table 1 with control group data. The study by Andersen, 2013, was not used for this computation due to overlap with Andersen, 2019. Based on the baseline rate, the excess number of anomalies per 1000 live births was 17.2 for patients exposed to CMZ/MMI, 9.8 for PTU exposure, and 31.4 for exposure to both CMZ/MMI and PTU. The corresponding number needed to treat for an additional harmful outcome (NNTH) was 58 for CMZ/MMI, 102 for PTU, and 32 for CMZ/MMI and PTU.

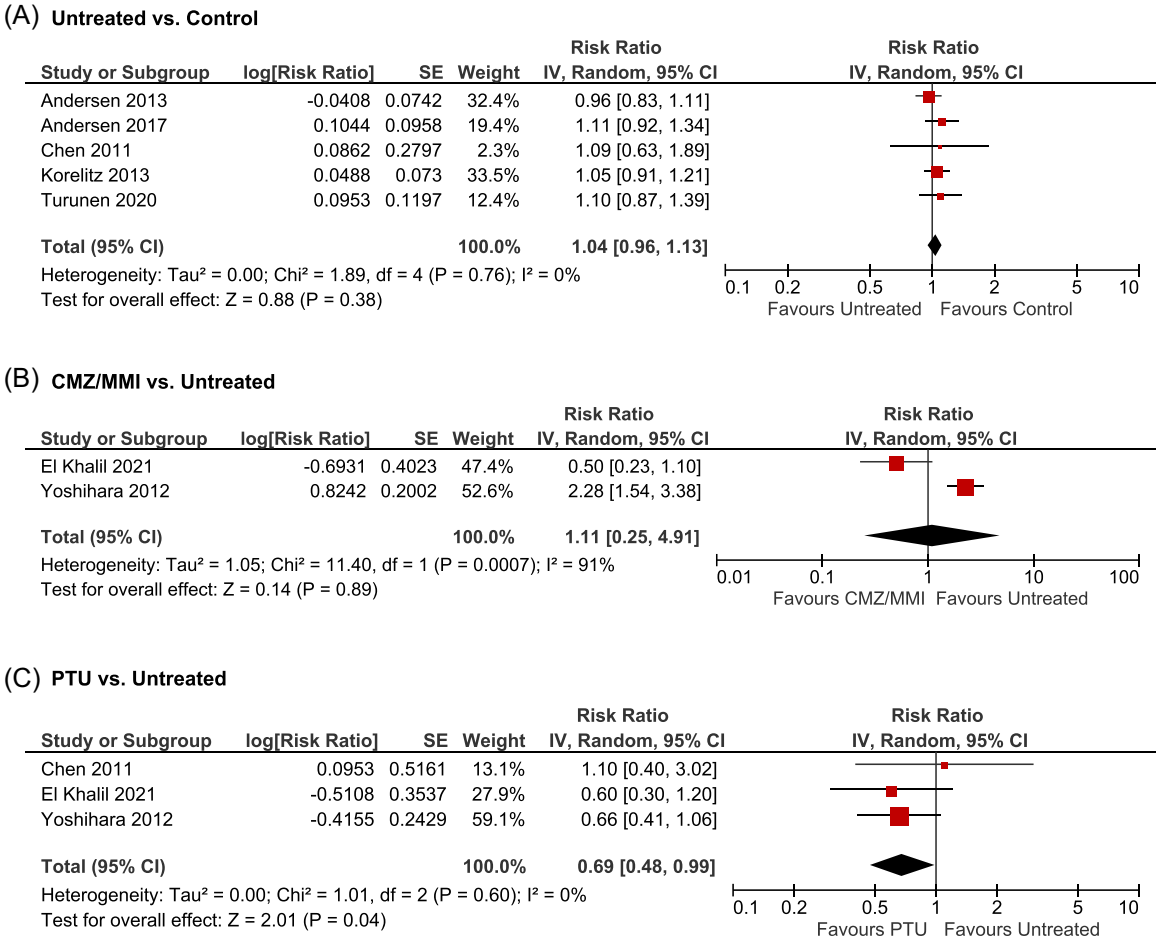

FIGURE 4 Meta-analysis of adjusted risk ratios for congenital anomalies in the untreated group. Estimates for Andersen 2013 in panel A were kindly provided by the authors. CMZ/MMI, carbimazole/methimazole; controls, nondisease controls without ATD exposure; PTU, propylthiouracil; Untreated, disease group without ATD exposure

4 | DISCUSSION

4.1 | Summary of findings

We have undertaken an updated meta-analysis on congenital anomaly risk in women exposed to ATD therapy in pregnancy. Our analysis incorporates data from several recent observational studies that have not been included in previous meta-analyses. As some of these newer studies contradict earlier findings, we sought to clarify the risk associated with both treated and untreated disease groups, using all available studies to date. To optimise the use of available data, we have pooled separate crude and adjusted risk estimates using random effects models and subgroup analyses to address heterogeneity. We show that compared to the general pregnant population, women exposed to CMZ/MMI, PTU, and to both CMZ/MMI and PTU had an increased risk of congenital anomalies. The magnitude of risk was higher for CMZ/MMI than for PTU exposure and was highest with exposure to both drugs. Risk estimates were generally driven by a small number of strongly weighted studies and differed only slightly between crude and adjusted models. Positive associations were more likely in studies with larger exposures, longer follow up of children, and in studies that evaluated all birth defects as opposed to major anomalies alone.

4.2 | Previous meta-analyses

Our study confirms increased anomaly risk after in utero ATD exposure but differ from previous studies with respect to the risk in the untreated disease group. Previous meta-analyses reported increased anomaly risks for ATDs relative to nondisease controls with greater risk estimates observed for CMZ/MMI than for PTU.[16–18,22] However, this risk becomes less certain when comparing the ATD associated risk with that of the untreated disease group. Earlier meta-analyses with fixed effect models showed increased crude risks for CMZ/MMI but not for PTU when compared to untreated disease groups.[17,18] In the random effects meta-analyses by Morales et al., adjusted risk estimates for the CMZ/MMI versus untreated groups were unavailable due to lack of studies[22] but the adjusted risk for PTU was similar to the untreated group albeit based on only two studies. In our study we found no increased risk for CMZ/MMI relative to the untreated group in both the crude and adjusted analyses.

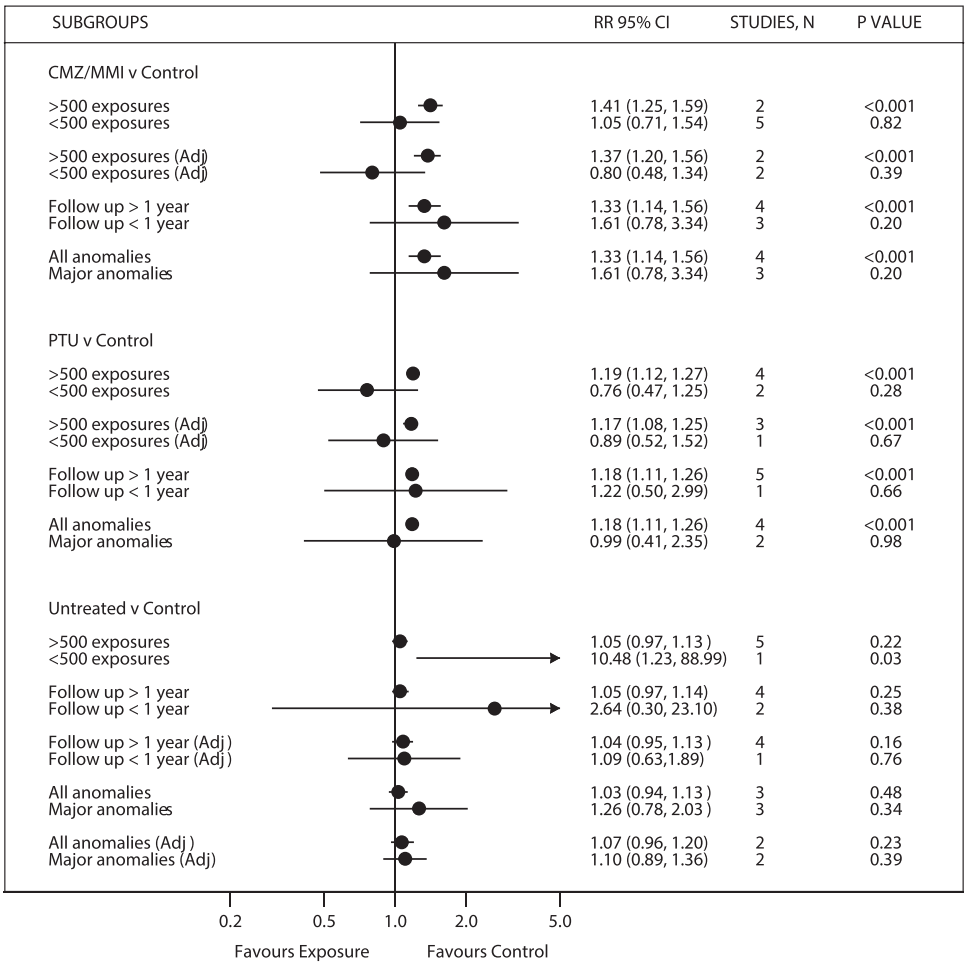

FIGURE 5 Subgroup analyses in ATD and untreated groups. ATD, CMZ/MMI, carbimazole/methimazole; controls, nondisease controls without ATD exposure; PTU, propylthiouracil; Untreated, disease group without ATD exposure

In the PTU versus untreated analysis, adjusted estimates from three studies showed reduced risk for PTU relative to the untreated group whereas crude estimates from nine studies showed no difference for the same comparison. The crude analysis is likely to be more credible for this comparison given that several large studies did not present adjusted data for the untreated disease comparisons.

Also worthy of note is that we observed no difference in crude or adjusted risks in the untreated versus non-disease controls, a seemingly paradoxical finding given that the untreated group had similar risks to the treated groups. This is in contrast to the study by Morales et al.[22] that reported increased risk for the untreated compared to nondisease controls. These inconsistencies are not unexpected given the heterogeneous nature of the untreated group in terms of disease activity and thyroid status. In some studies, this group consisted of patients with biochemical hyperthyroidism[14] while in others, patients were euthyroid[20] or comprised a mix of hyperthyroid and euthyroid patients.[32,33] Thus, it is plausible that risk estimates in the untreated group was influenced to some extent by thyroid status. For example, the 1984 study by Momotani et al.[14] reported increased anomaly risks in biochemically hyperthyroid patients compared to the euthyroid or CMZ/MMI treated patients. In contrast, Yoshihara et al. observed reduced risk relative to the CMZ/MMI group in a predominantly euthyroid untreated cohort. However, we were unable to explore these associations further since information on thyroid function was only available in four studies with study designs that were not amenable to meta-analysis.[12,14,20,33] Subsequent observational studies are increasingly less likely to contain pure biochemically hyperthyroid cohorts since contemporary practice is to correct hyperthyroidism except in the mildest cases.

4.3 | Clinical implications

The management of hyperthyroidism in pregnancy requires a fine balance between the competing priorities of controlling hyperthyroidism and minimising ATD exposure.[10] PTU is considered the safer thionamide option in pregnancy, but as our study shows, the risk of birth defects associated with PTU exposure is not negligible with a 16% higher risk than in the unexposed general population. The recommended approach of switching from CMZ/MMI to PTU on conception also did not reduce anomaly risk and in fact exposure to both drugs appeared to be associated with higher risk ratios than

single drug exposure. However, these findings should be interpreted in the context of the methodological challenges inherent in registry-based studies. Expert commentators have highlighted that the use of prescription databases to extrapolate the timing of ATD switch in dual exposure studies may result in imprecise and inconsistent exposure windows across studies.[15,36] For example, the study by Andersen et al.[27] was restricted to women who switched ATDs after conception, while studies by Korelitz[30] and by Seo[13] included women who switched ATDs preconception. Thus, further studies using more accurate exposure timings will be required to clarify the risk associated with switching ATDs.

Also, it is plausible that women who switched drugs were those with more severe disease and hence those who required higher treatment doses. Nonetheless, these findings call for caution with current treatment recommendations. Pending further data, the only strategy guaranteed to reduce thionamide associated anomaly risk in biochemically hyperthyroid women is pregnancy prevention through preconception counselling.[37] Where conception is probable then preconception switch to PTU carries a lower anomaly risk than switching during pregnancy. Hyperthyroid women who become pregnant should be treated in the first trimester with the lowest effective dose of PTU to maintain thyroid hormones in the reference range. This approach is indirectly supported by the dose response analysis in the large Korean study by Seo et al.,[13] although this relationship was proven for CMZ/MMI and not for PTU. Furthermore, consideration should be given to discontinuing treatment altogether in women with mild disease although the optimal thyroid function threshold at which ATDs can be safely stopped remains to be proven.

4.4 | Methodological considerations

Our study faced several methodological challenges. Only few studies presented adjusted risk estimates. While adjusted models provide more precise estimates, restricting analyses to studies with adjusted risks alone ignores potentially useful data in an area where data is challenging to source. To maximise published data, we presented separate crude and adjusted estimates which reassuringly showed comparable results for the majority of studies overall. In addition, most studies were underpowered for the outcome of birth defects given that such defects are relatively rare events.[38] As shown in the subgroup analysis studies with less than 500 exposures were less likely to report an association compared to those with over 500 exposures. In some studies, assessments for birth defects were carried out at birth or in the early months of life and would have missed those anomalies that presented in later infancy. In our analysis, studies with up to a year's follow up were more likely to yield positive results compared to studies that followed up children for less than a year. Also, positive associations were more likely in studies that evaluated all congenital anomalies compared to those that evaluated major anomalies alone.

In addition, we were unable to analyse the severity and subtypes of birth defects due to the low frequency and inconsistent reporting of subtypes across studies. This is relevant given that the patterns of defects have been shown to differ according to the class of ATD exposure.[39] CMZ/MMI has been associated with severe defects including components of the CMZ/MMI embryopathy[12,13,27,33] while PTU is linked with less severe anomalies of the head and neck,[39] urinary tract,[13,39] and musculoskeletal systems.[13] A pooled analysis of subtype specific risk was however beyond the scope of the present study and will require sufficient numbers of studies with comparable data. Lastly, the characteristics of the unexposed disease control group differed across studies making it unlikely that the untreated group represented a homogenous disease group. The funnel plot analysis in the CMZ versus untreated group comparison showed significant bias towards small studies with nonsignificant risk estimates. While this bias may be due to missing or unreported studies it is more likely that it reflects the heterogeneity in the untreated group and effectively limits any conclusions in this group.

4.5 | Recommendations for future observational studies

Based on the above considerations we highlight several key suggestions for future observational studies that will facilitate data synthesis. (1) Control groups should reflect the unexposed background population as well as the untreated disease population, and the two groups should be handled as separate comparison groups in the analysis. (2) Due to the rarity of birth defects in the general population, large sample sizes are needed to show effects and power calculations should be incorporated in study designs. For example, based on prevalence data reported in Andersen et al.,[27] a sample size of approximately 500 exposures and 2000 controls (exposure to control ratio, 1:4) will be required for a two-sided α of 0.05 and power (β) of 0.8. (3) Study follow-up should include at least a year's follow-up of children to capture delayed presentations. (4) Information on anomaly rates should be systemically collected and should include data on all anomalies, major anomalies, and where possible a breakdown of anomalies by organ systems to further analyse the anomaly patterns. (5) Risk estimates should be adjusted for relevant confounders and presented alongside crude risks to allow data synthesis for both crude and adjusted risks. (6) Information on ATD dose is desirable and should be included wherever possible to enable meaningful dose response analyses. (7) Data on thyroid function in the exposure and disease control groups is particularly needed and outcome data in untreated women with mild hyperthyroidism will be invaluable in understanding the merits of current guideline strategies.

5 | CONCLUSIONS

Our meta-analysis has shown that ATD therapy in pregnancy carries a small risk of congenital anomalies. The magnitude of risk is slightly higher for CMZ/MMI than for PTU and switching ATDs postconception does not appear to reduce this risk although studies with more accurate exposure timings are required to clarify the impact of switching ATDs in pregnancy. The risk associated with mild thyroid dysfunction and the

optimal thyroid function threshold at which ATDs can safely be withdrawn in pregnancy will require further studies.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Concept and design: Onyebuchi E. Okosieme and Medha Agrawal. *Data acquisition*: Onyebuchi E. Okosieme, Medha Agrawal, and Steffan Lewis. *Data analysis*: Onyebuchi E. Okosieme and Medha Agrawal. *Writing and editing*: Onyebuchi E. Okosieme, Medha Agrawal, Steffan Lewis, Lakdasa Premawardhana, Colin M. Dayan, and Peter N. Taylor.

DATA AVAILABILITY STATEMENT

Not applicable as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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