# Major congenital malformations in offspring of women with chronic diseases—impact of the disease or the treatment?

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In a narrative review, we summarized previous findings on the risk of major congenital malformations in offspring of women with chronic hypertension, hypothyroidism, or depression compared with the background population, and evaluated whether exposure to medical treatment in the first trimester affected this risk. In a literature search in the PubMed database, cohort studies were included if they were published from 2010 to 2022 and contained data on major congenital malformations from ≥500 offspring of women with chronic hypertension, hypothyroidism, or depression during the first trimester of pregnancy, and data on both untreated and treated women. Data were compared with the background population of women without these diseases. In total, 7 cohort studies were identified. In comparison with the background population, 2 studies including 54,996 offspring of women with chronic hypertension showed an adjusted odds ratio of 1.20 to 1.30 for major congenital malformations in the offspring, regardless of antihypertensive treatment. One study including 16,364 offspring of women with hypothyroidism showed an adjusted odds ratio of 1.14 (1.06−1.22) for major congenital malformations in the offspring, regardless of thyroid substitution. Four studies including 48,913 offspring of women with depression showed adjusted odds ratios of 1.07 to 1.27 (0.91−1.78) for major congenital malformations in the offspring of untreated women. Three of these 4 studies showed similar prevalence of malformations in women treated for depression. The findings of this narrative review suggest that chronic hypertension and hypothyroidism, rather than exposure to their medical treatments in the first trimester, were associated with increased risk of major congenital malformations, whereas depression was generally not associated with major congenital malformations.

**Key words:** antidepressants, antihypertensive agents, depression, hypertension, hypothyroidism, major congenital malformation, preconception counseling, pregnancy, thyroid substitution

## Introduction

Infants born with major congenital malformations face a life with serious health and developmental consequences that often require medical or surgical treatment.[1] Although the pathophysiology of congenital malformations is widely unknown, it has been suggested that maternal chronic diseases are associated with congenital malformations in the offspring, either caused by the chronic disease itself or by its medical treatment.[2,3] The prevalence of chronic diseases in women of reproductive age is increasing.[4,5] Common chronic diseases in women of reproductive age are chronic hypertension, thyroid diseases, and depression, with a prevalence of up to 6%, 7%, and 15%, respectively.[4,6−8]

Previous studies have investigated whether exposure to medical treatment of chronic hypertension, hypothyroidism, and depression in the first trimester with antihypertensive agents, thyroid substitution, and antidepressants, respectively, increases the risk of congenital malformations. Some studies have found an increased risk of major congenital malformations in offspring exposed to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers,[9−11] certain antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) sertraline and citalopram,[12] and thyroid substitution[13] in the first trimester, whereas other studies found no teratogenic effects[14,15] or suggested that the underlying disease or exposure to antihypertensive medication in general could be the cause.[16−18] However, the size of these study populations, particularly for women with hypertension,[10,18] may not have been sufficient for robust results. Certain major congenital malformations such as those of the heart, ear, face, and neck, and neural tube defects may be more prevalent in women with chronic hypertension and/or depression,[19−22] but the effect of the underlying chronic disease when left untreated on major congenital malformations is still a field that warrants more attention. Knowledge about the impact of chronic diseases and of medical treatment in pregnancy on the risk of major congenital malformations can be useful for clinicians in counseling and screening for congenital malformations.

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We performed a narrative review of large populations to summarize previous findings on the risk of major congenital malformations in offspring of women with chronic hypertension, hypothyroidism, or depression compared with the background population, and evaluated whether exposure to the medical treatment affected the risk of major congenital malformations.

## Literature search

On March 15, 2022, we conducted a literature search for all cohort studies including data on offspring with major congenital malformations born to women with either chronic hypertension, hypothyroidism, or depression during pregnancy. We included cohort studies published between January 2010 and March 2022 in English with data on major congenital malformations including at least 500 offspring of women with either chronic hypertension, hypothyroidism, or depression during pregnancy and data on both untreated women and women who received medical treatment for these conditions in the first trimester. Literature reference lists of included cohort studies were checked for relevant literature and included, if indicated.

The PubMed database was searched in 3 separate searches focusing respectively on maternal chronic hypertension, hypothyroidism, and depression. All 3 searches included the following Medical Subject Headings (MeSH) terms and text words: congenital anomaly/congenital anomalies/congenital malformation/congenital malformations/congenital abnormality/congenital abnormalities/congenital deformity/congenital deformities/birth defect/birth defects AND pregnant/pregnancy/pregnancies/gestation AND cohort/cohort study/cohort studies.

In addition to the search words above, the first literature search included the following MeSH terms and text words: hypertension/chronic hypertension/maternal hypertension/pregestational hypertension, which resulted in 323 titles. The second literature search included these MeSH terms and text words: hypothyroidism/maternal hypothyroidism/hypothyroid/underactive thyroid, which resulted in 29 titles. The third literature search included the MeSH terms and text words: depression/maternal depression/depressive disorder/untreated depression, which resulted in 98 titles. The titles and abstracts of the identified cohort studies were screened for relevance. Seven cohort studies were included: 2 dealing with chronic hypertension[19,20] (Table 1), 1 with hypothyroidism[23] (Table 2), and 4 with depression[21,22,24,25] (Table 3). All cohort studies included data on women with one of these chronic diseases with and without medical treatment for the condition, and a background population of women without these chronic diseases, except for the study by Bérard et al,[24] which included women with depression only. In addition, all cohort studies included women treated for these chronic diseases in the first trimester, except for Turunen et al,[23] which included women with hypothyroidism treated at some point during pregnancy. Finally, all included cohort studies controlled for potential confounders, such as maternal age, body mass index, parity, smoking, and socioeconomic status, by use of logistic regression analysis.

## Definition of congenital malformations

Congenital malformations were defined according to International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnosis codes in 3 studies,[19,20,25] and according to the EUROCAT register system,[26] a European-based register system for epidemiologic surveillance of congenital malformations with a coding and classification system, in 4 studies.[21–24] In addition, 3 of these studies also used ICD-9 and/or ICD-10 codes.[21,23,24]

## Studies on chronic hypertension

Two cohort studies including data on 54,996 offspring of women with chronic

**TABLE 1**
**Prevalence of major congenital malformations in offspring of women with chronic hypertension in the first trimester**

| | Chronic hypertension | |
|---|---|---|
| | Bateman et al,[19] 2015 United States | Li et al,[20] 2011 United States |
| Study period | 2000–2007 | 1995–2008 |
| Offspring, n | 878,126 | 465,754 |
| Method for diagnosis of malformations | ICD-9 codes | ICD-9 codes |
| Women without chronic hypertension, n | 858,337 | 414,567 |
| Prevalence of malformations (%) | 3.5 | 5.4 |
| Women with chronic hypertension, n (%) | 19,789 (2) | 35,207 (8)[a] |
| Prevalence of malformations (%) | 5.4 | 7.1 |
| Treated women with chronic hypertension, n | 8307 | 4622 |
| Prevalence of malformations (%) | 5.9 | 7.2 |
| Untreated women with chronic hypertension, n | 11,482 | 30,585 |
| Prevalence of malformations (%) | 5.1 | 7.1 |
| Adjusted odds ratio | | |
| Treated/background | 1.30 (1.20–1.50) | — |
| Treated with ACE inhibitors/background | — | 1.05 (0.70–1.57) |
| Treated with other antihypertensives/background | — | 1.31 (1.16–1.47) |
| Untreated/background | 1.20 (1.10–1.30) | 1.25 (1.19–1.31) |

*ACE*, angiotensin-converting enzyme; *ICD-9*, International Classification of Diseases, Ninth Revision.

[a] Total number of pregnant women was 48,088 of whom 35,207 were in the first trimester.

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**TABLE 2**
**Prevalence of major congenital malformations in offspring of women with hypothyroidism during pregnancy**

| | Hypothyroidism Turunen et al,[23] 2019 Finland |
|---|---|
| Study period | 2004−2013 |
| Offspring, n | 571,785 |
| Method for diagnosis of malformations | ICD-9 codes EUROCAT |
| Women without hypothyroidism, n | 550,860 |
| Prevalence of malformations (%) | 4.2 |
| Women with hypothyroidism, n (%) | 16,364 (3) |
| Prevalence of malformations (%) | 5.0 |
| Treated women with hypothyroidism, n | 6132 |
| Prevalence of malformations (%) | 4.7 |
| Untreated women with hypothyroidism, n | 10,232 |
| Prevalence of malformations (%) | 5.2 |
| Adjusted odds ratio | |
| Women with treated or untreated hypothyroidism/background | 1.14 (1.06−1.22) |
| Women with treated hypothyroidism/background | 1.10 (1.00−1.20) |

*ICD-9*, International Classification of Diseases, Ninth Revision.

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hypertension in the first trimester were identified[19,20] (Table 1).

In Bateman et al,[19] the prevalence of major congenital malformations in 8307 women with treated chronic hypertension was 5.9%, as opposed to 3.5% in the background population of women without chronic hypertension, corresponding to an adjusted odds ratio (AOR) of 1.30 (1.20−1.50). The prevalence of major congenital malformations in 11,482 women with untreated chronic hypertension was 5.1%, corresponding to an AOR of 1.20 (1.10−1.30) compared with the background population (Table 1).

In Li et al,[20] the prevalence of major congenital malformations in 4622 women with treated chronic hypertension was 7.2%, as opposed to 5.4% in the background population of women without chronic hypertension. For the 424 women treated with ACE inhibitors, the AOR was 1.05 (0.70−1.57), and for the 4198 women treated with other antihypertensives, the AOR was 1.31 (1.16−1.47) compared with the background population. The prevalence of major congenital malformations in 30,585 women with untreated chronic hypertension was 7.1%, corresponding to an AOR of 1.25 (1.19−1.31) compared with the background population (Table 1).

## Studies on hypothyroidism

One cohort study including data on 16,364 offspring of women with hypothyroidism during pregnancy was identified.[23] The prevalence of major congenital malformations in these women with hypothyroidism was 5.0%, as opposed to 4.2% in the background population of women without hypothyroidism, corresponding to an AOR of 1.14 (1.06−1.22). In 6132 women with hypothyroidism treated with thyroid substitution at some point during pregnancy, the prevalence of major congenital malformations was 4.7%, corresponding to an AOR of 1.10 (1.00−1.20) compared with the background population. The prevalence of major congenital malformations in 10,232 women with untreated hypothyroidism was 5.2% (Table 2).

## Studies on depression

Four cohort studies[21,22,24,25] including data on 48,913 offspring of women with depression in the first trimester were identified (Table 3).

In Ban et al,[21] there were 10,401 women with depression treated with either SSRIs, tricyclic antidepressants (TCA), or SSRIs and TCAs combined, respectively. The prevalence of major congenital malformations in 10,401 women with treated depression was 2.8%, as opposed to 2.7% in the background population of women without depression, corresponding to an AOR of 1.01 (0.88−1.17) for women treated with SSRI, 1.09 (0.87−1.38) for women treated with TCA, and 1.02 (0.50−2.06) for women treated with SSRIs and TCAs combined. The prevalence of major congenital malformations in 13,432 women with untreated depression was 2.8%, corresponding to an AOR of 1.07 (0.96−1.18) compared with the background population (Table 3).

The study by Bérard et al[24] included a cohort only consisting of women with depression. No background population of women without depression was included. The prevalence of major congenital malformations in 3640 women with depression treated with either SSRIs, TCAs, serotonin and norepinephrine reuptake inhibitors (SNRIs), or other antidepressants was 12.1%, as opposed to 11.1% in 14,847 women with untreated depression. The AOR was 1.07 (0.93−1.22) for women treated with SSRI, 1.16 (0.86−1.56) for women treated with TCA, 1.10 (0.87−1.38) for women treated with SNRI, and 0.93 (0.59−1.47) for women treated with other antidepressants compared with women with untreated depression (Table 3).

In Jimenez-Solem et al,[22] the prevalence of major congenital malformations in 4183 women treated with SSRIs was 5.0%, as opposed to 3.5% in the background population of women without depression, corresponding to an AOR of 1.33 (1.16−1.53). The prevalence of major congenital malformations in 806

**TABLE 3**
**Prevalence of major congenital malformations in offspring of women with depression in the first trimester**

| | Depression | | | |
|---|---|---|---|---|
| | Ban et al,[21] 2014 United Kingdom | Bérard et al,[24] 2017 Canada | Jimenez-Solem et al,[22] 2012 Denmark | Nordeng et al,[25] 2012 Norway |
| Study period | 1990–2009 | 1998–2009 | 1997–2009 | 2000–2006 |
| Offspring, n | 349,127 | 18,487 | 848,786 | 63,395 |
| Method for diagnosis of malformations | ICD-10 codes EUROCAT | ICD-9 codes ICD-10 codes EUROCAT | EUROCAT | ICD-10 codes |
| Women without depression, n | 325,294 | — | 843,797 | 61,648 |
| Prevalence of malformations (%) | 2.7 | — | 3.5 | 2.5 |
| Women with depression, n (%) | 23,833 (7) | 18,487 | 4989 (0.6) | 1604 (3) |
| Prevalence of malformations (%) | 2.8 | 11.3 | 4.9 | 2.7 |
| Treated women with depression, n | 10,401 | 3640 | 4183 | 556 |
| Prevalence of malformations (%) | 2.8 | 12.1 | 5.0 | 2.3 |
| Untreated women with depression, n | 13,432 | 14,847 | 806 | 1048 |
| Prevalence of malformations (%) | 2.8 | 11.1 | 4.7 | 2.9 |
| Adjusted odds ratio | | | | |
| SSRI treated/background | 1.01 (0.88–1.17) | — | 1.33 (1.16–1.53) | 1.07 (0.60–1.91) |
| TCA treated/background | 1.09 (0.87–1.38) | — | — | — |
| SSRI+TCA treated/background | 1.02 (0.50–2.06) | — | — | — |
| SSRI treated/untreated | — | 1.07 (0.93–1.22) | — | — |
| TCA treated/untreated | — | 1.16 (0.86–1.56) | — | — |
| SNRI treated/untreated | — | 1.10 (0.87–1.38) | — | — |
| Treated with other antidepressants/untreated | — | 0.93 (0.59–1.47) | — | — |
| Untreated/background | 1.07 (0.96–1.18) | — | 1.27 (0.91–1.78) | 1.12 (0.78–1.62) |

*ICD-9*, International Classification of Diseases, Ninth Revision; *ICD-10*, International Classification of Diseases, Tenth Revision; *SNRI*, serotonin and norepinephrine reuptake inhibitor; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant.

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women with untreated depression was 4.7%, corresponding to an AOR of 1.27 (0.91–1.78) compared with the background population (Table 3).

In Nordeng et al,[25] the prevalence of major congenital malformations in 556 women treated with SSRIs was 2.3%, as opposed to 2.5% in the background population of women without depression, corresponding to an AOR of 1.07 (0.60–1.91). The prevalence of major congenital malformations in 1048 women with untreated depression was 2.9%, corresponding to an AOR of 1.12 (0.78–1.62) compared with the background population (Table 3).

## Other chronic diseases

The risk of major congenital malformations is well-described in diabetes mellitus,[27,28] but less so in other chronic diseases in women of reproductive age. We therefore focused on selected chronic diseases that are common in women of reproductive age and the medical treatment of these conditions.[4,6–8] Asthma is another prevalent chronic disease in women of reproductive age.[4,6–8] However, in the literature on asthma and major congenital malformations, all studies defined asthma as a condition treated with asthma medication[29–31] and did not include women with untreated asthma.[29–34]

## Chronic hypertension and congenital malformations

The biological mechanisms causing congenital malformations are not fully understood. In women with chronic hypertension, uteroplacental insufficiency leading to compromised fetal blood flow in early pregnancy may play a role in the development of congenital malformations in the offspring.[19] Underlying changes in energy metabolism may play a role in congenital malformations in women with hypothyroidism.[35]

The 2 cohort studies on chronic hypertension[19,20] demonstrated similarly elevated AORs of 1.20 to 1.30 for major

congenital malformations in offspring of women with chronic hypertension, irrespective of antihypertensive treatment, compared with the background population. These findings are reassuring for women becoming pregnant while using antihypertensive treatment because they imply that the underlying chronic hypertension rather than the use of antihypertensive medication had an independent impact on the development of major congenital malformations.[19,20] Two meta-analyses from 2011 and 2021 of 5 and 14 observational studies, respectively, showed that women treated with ACE inhibitors or angiotensin receptor blockers during early pregnancy have a higher risk of major congenital malformations in the offspring compared with healthy controls. However, most included studies were small and probably subject to bias; some studies did not include a normotensive background population to investigate the potential role of the underlying condition, and no randomized controlled trials were found.[10,18] In early pregnancy, treatment with ACE inhibitors or angiotensin receptor blockers has not been associated with higher risk of major congenital malformations relative to other antihypertensive agents.[15,18] Our findings suggest that women with chronic hypertension could probably continue their usual antihypertensive agents including ACE inhibitors or angiotensin receptor blockers before pregnancy and in the first trimester to remain medically well-treated and to avoid deterioration of the underlying hypertensive condition without increasing the risk of major congenital malformations in the offspring. However, change to other antihypertensive agents approved for use in pregnancy should take place before the second trimester because exposure to ACE inhibitors and angiotensin receptor blockers beyond the first trimester is associated with oligohydramnios, abnormal fetal renal development, and neonatal renal failure.[11,36]

## Hypothyroidism and congenital malformations

The cohort study on hypothyroidism[23] demonstrated an elevated AOR of 1.14 (1.06−1.22) for major congenital malformations in the total group of women with hypothyroidism and also in the subgroup treated with thyroid substitution at some point during pregnancy compared with the background population. This increased risk of congenital malformations seemed to be driven by inconsistent levothyroxine use; consistent levothyroxine use might reduce the risk of major congenital malformations. In the first trimester, the fetus' requirement for thyroid hormones is supplied by the mother because its own thyroid hormone production begins after 12 weeks of gestation.[37] Thus, it is likely that the hypothyroidism per se increased the risk of major congenital malformations because of the inadequate level of thyroid hormones.

## Depression and congenital malformations

The 4 cohort studies on depression[21,22,24,25] found no increased risk of major congenital malformations in offspring of untreated women with depression compared with the background population. Three of the 4 cohort studies demonstrated similar prevalence of major congenital malformations in women with treated depression, whereas 1 study found an increased risk of major congenital malformations in offspring of women treated with SSRIs. The number of women with depression was small, and the association between major congenital malformations and SSRIs might be confounded by indication.[22] Overall, the present evidence indicates that women with depression could probably continue the use of antidepressants before pregnancy and during the first trimester without increasing the risk of major congenital malformations in the offspring.

## Strengths and limitations

The systematic approach to the literature search in the PubMed database including both MeSH terms and text words was a strength of this study. Cohort studies were included only if they consisted of at least 500 offspring to limit bias and insecurities in the data, and numbers of women with and without medical treatment for their chronic disease were given to evaluate the potential effect of the underlying disease and its medical treatment. All cohort studies contained AORs to adjust for covariates such as maternal age, diabetes mellitus, hypertensive disorders, and other risk factors that could increase the risk of major congenital malformations.

It was a limitation that only 2 cohort studies on chronic hypertension, 1 on hypothyroidism, and 4 on depression could be identified, and 1 of the studies[24] did not include a background population for comparison. Likewise, most of the included studies used data obtained at delivery to identify major congenital malformations. This introduces ascertainment bias because some of the fetuses may be identified with major congenital malformations during pregnancy, leading to discontinuation of pregnancy. However, this may only represent a minority of the cases with major congenital malformations, as observed in women with diabetes mellitus.[38] These factors limit the possibility for solid conclusions. It was a pragmatic choice to only search for cohort studies in the PubMed database published in the last 12 years. It is possible that searches for case−control studies, searches in other databases, and extension of the search period would have identified more studies. However, a longer search period would possibly include studies on medical agents that are not part of modern treatment. It was also a limitation that the included studies used different methods for diagnosing major congenital malformations (either ICD diagnosis codes or the EUROCAT register system). Data on exercise, smoking, alcohol consumption, folic acid supplementation, and other lifestyle choices that may affect early fetal development were not investigated. Women with mental illness are less likely to plan pregnancy, but otherwise women with chronic disease may be more likely to take folic acid supplementation and to abstain from tobacco and alcohol consumption before pregnancy.[39] It was a potential source of bias that women identified as carrying a

fetus with a malformation may subsequently be examined carefully for medical conditions. Furthermore, infants with major congenital malformations are more likely to be delivered preterm, and infants born preterm are probably examined more carefully for presence of malformations.[19] However, in the study by Bateman,[19] there was an association between malformations and both treated and untreated hypertension, including after adjustment for preterm delivery. None of the other included studies evaluated the potential association between major congenital malformations and preterm delivery.

## Conclusion

The prevalence of major congenital malformations in offspring of women with chronic hypertension or hypothyroidism was higher than that of the background population, irrespective of medical treatment. In offspring of women with untreated depression, the prevalence of major congenital malformations was not increased, and in 3 of the 4 studies, no increased prevalence of major congenital malformations was found in women treated for depression. Women of reproductive age with chronic diseases often have regular encounters with the healthcare system, and therefore ideally have better access to preconception care, counseling, and support regarding adherence to medical advice.[39] This potentially offers an opportunity for the individual woman and her healthcare provider to discuss potential benefits and disadvantages of continuing or discontinuing usual medical treatment in the first trimester of pregnancy.

This narrative review supports that underlying chronic hypertension and hypothyroidism, rather than their medical treatment, increase the risk of major congenital malformations. Antihypertensive agents, thyroid substitution, and probably also antidepressants may be continued in the first trimester of pregnancy without increasing the risk of major congenital malformations in the offspring. Further studies of appropriate size investigating the impact of chronic diseases such as maternal chronic hypertension, hypothyroidism, and depression, and their medical treatments on risk of major congenital malformations are warranted. ■

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