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β -Blocker Use in Pregnancy and the Risk for Congenital Malformations An International Cohort Study

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Abstract

Background: β -Blockers are a class of antihypertensive medications that are commonly used in pregnancy.

Objective: To estimate the risks for major congenital malformations associated with first-trimester exposure to β -blockers.

Design: Cohort study.

Setting: Health registries in the 5 Nordic countries and the U.S. Medicaid database.

Patients: Pregnant women with a diagnosis of hypertension and their offspring.

Measurements: First-trimester exposure to β -blockers was assessed. Outcomes were any major congenital malformation, cardiac malformations, cleft lip or palate, and central nervous system (CNS) malformations. Propensity score stratification was used to control for potential confounders.

Results: Of 3577 women with hypertensive pregnancies in the Nordic cohort and 14 900 in the U.S. cohort, 682 (19.1%) and 1668 (11.2%), respectively, were exposed to β -blockers in the first trimester. The pooled adjusted relative risk (RR) and risk difference per 1000 persons exposed (RD_{1000}) associated with β -blockers were 1.07 (95% CI, 0.89 to 1.30) and 3.0 (CI, -6.6 to 12.6), respectively, for any major malformation; 1.12 (CI, 0.83 to 1.51) and 2.1 (CI, -4.3 to 8.4) for any cardiac malformation; and 1.97 (CI, 0.74 to 5.25) and 1.0 (CI, -0.9 to 3.0) for cleft lip or palate. For CNS malformations, the adjusted RR was 1.37 (CI, 0.58 to 3.25) and the RD_{1000} was 1.0 (CI, -2.0 to 4.0) (based on U.S. cohort data only).

Limitation: Analysis was restricted to live births, exposure was based on dispensed medication, and cleft lip or palate and CNS malformations had few outcomes.

Conclusion: The results suggest that maternal use of β -blockers in the first trimester is not associated with a large increase in the risk for overall malformations or cardiac malformations, independent of measured confounders.

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Chronic hypertension is increasingly prevalent in pregnancy (1), likely because of the higher prevalence of obesity in women of reproductive age and increasing maternal age at the time of pregnancy. Thus, antihypertensive medications have become a common exposure in early pregnancy (2–4). β -Blockers are one of the most frequently used classes of antihypertensive medication in pregnancy. An estimated 0.5% to 1% of pregnancies are exposed to β -blockers during the first trimester in the United States (2, 3), and the United Kingdom (4), and 0.1% in Sweden (5). β -Blockers (together with calcium-channel blockers and methyldopa) are recommended as a first-line therapy for the treatment of hypertension in pregnancy by professional organizations and societies (6, 7).

The association between β -blocker exposure in early pregnancy and risk for congenital malformations is controversial. β -Blockers cross the placenta (8), and at least some studies in animal models suggest a potential teratogenic effect (9). A recent systematic review and meta-analysis of studies involving pregnant women (10) did not find increased risk for congenital malformations overall but did report significantly increased risks for cardiac defects, cleft lip or palate, and neural tube defects. However, most included studies had significant limitations and were vulnerable to several sources of bias, including confounding by the mother's underlying hypertension. Confounding by indication is particularly problematic in evaluating this association because studies suggest that maternal chronic hypertension increases risk for malformations (11–13).

Because antihypertensive medications are used frequently in early pregnancy, understanding whether β -blockers increase the risk for congenital malformations is a research priority. Thus, we examined the association between first-trimester exposure to β -blockers in utero and congenital malformations overall and organ-specific malformations that have previously been associated with β -blockers, including cardiac defects, cleft lip or palate, and central nervous system (CNS) malformations. To reduce potential confounding by indication, we restricted the analysis to pregnancies with a diagnosis of hypertension. To maximize study power, we used data from national health registries in the 5 Nordic countries (Denmark,

Finland, Iceland, Norway, and Sweden) and the Medicaid database in the United States through the InPreSS (International Pregnancy Safety Study) consortium.

Methods

Study Overview

The InPreSS consortium is a collaborative among investigators from the 5 Nordic countries and the United States with access to high-quality data on medication exposure during pregnancy and infant outcomes (14). These data resources are analyzed with harmonized protocols to provide timely and accurate information on medication safety during pregnancy. The current study was based on 2 large population-based cohorts of births in the Nordic countries and the United States. The research was approved by applicable ethics review boards in Sweden, Iceland, Finland, and the United States (Appendix, available at [Annals.org](https://www.annals.org)). No ethics approval was required in Denmark or Norway.

Data Sources and Study Population

The Nordic cohort included women from Denmark, Finland, Iceland, Norway, and Sweden who gave birth to a live singleton infant between 1996 and 2010 ($N = 2\,310\,825$ pregnancies) according to nationwide health registries (15, 16). These registries contain prospectively collected health information on all inhabitants, including data on health conditions, medications, and outcomes (such as congenital malformations). A civil personal registration number is assigned to each resident at birth or immigration, permitting data linkage at the individual level among national registries. Reporting to the registries is mandatory and regulated by national laws (17). According to data availability, each Nordic country contributed data from different periods (Denmark, 1997 to 2010; Finland, 1996 to 2006; Iceland, 2003 to 2007; Norway, 2005 to 2010; and Sweden, 2006 to 2010). The Appendix gives details about the Nordic data sources used in the analysis.

The US MAX cohort ($N = 1\,358\,708$ pregnancies) was identified from the 2000-to-2010 Medicaid Analytic eXtract (MAX), a nationwide Medicaid database. The method used to create this cohort has previously been described in detail (18). The cohort has been used extensively to study medication safety during pregnancy (19–21).

Eligibility Criteria

The Nordic cohort included all hypertensive women with singleton pregnancies resulting in a live-born infant. The US MAX cohort included hypertensive pregnant women aged 12 to 55 years who were continuously enrolled in Medicaid from 3 months before the date of their last menstrual period (LMP) to 1 month after delivery; women were linked to their live-born infants using a deterministic algorithm (18). Infants were also required to have Medicaid insurance for 3 months after their date of birth, unless they died, in which case a shorter eligibility period was allowed. Both cohorts excluded pregnancies in which a woman filled a prescription for a known teratogenic medication (Appendix Table 1, available at [Annals.org](https://www.annals.org)) between 30 days before LMP and day 90 of pregnancy (first trimester) or in which a fetal chromosomal abnormality was detected in the infant in the first year of life in the Nordic cohort and before day 90 of life in the US MAX cohort (Figure 1).

Ascertainment of β -Blocker Exposure

We determined medication exposure through the nationwide prescription drug registries in the Nordic cohort and by review of pharmacy dispensing records in the US MAX cohort. Medications are recorded according to the World Health Organization's Anatomical Therapeutic Chemical classification in the Nordic data and by generic drug name in the U.S. data.

In this study, a pregnancy was considered exposed if a woman filled a prescription for a β -blocker (Anatomical Therapeutic Chemical code C07) during the first trimester of pregnancy—that is, covering the period of embryogenesis. We excluded a pregnancy if an antihypertensive medication other than a β -blocker was dispensed between 90 days before LMP and the end of the first trimester (Figure 1) because some of these medications may also be associated with an increased risk for congenital malformations (22, 23). A pregnancy was considered unexposed if a woman did not fill a prescription for a β -blocker from the LMP to the end of the first trimester.

Congenital Malformations

We collected information on infants' congenital malformations overall and organ-specific malformations that previous studies suggested were associated with β -blocker exposure, including cardiac defects, cleft lip or palate, and CNS malformations. In the Nordic cohort, we retrieved this information from the medical birth, patient, and cause-of-death registries. During the study period, congenital malformations were recorded according to the International Classification of Diseases, 10th Revision (ICD-10), in Denmark, Norway, Sweden, and Iceland and with ICD, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Atlanta Clinical Modification for birth defects) in Finland (Appendix Table 2, available at [Annals.org](https://www.annals.org)). A malformation was defined if an ICD-10 or ICD-9-CM diagnosis was recorded for the infant in any of the available registers within 1 year after birth. In the US MAX cohort, we used algorithms based on inpatient and outpatient ICD-9-CM diagnoses and procedure codes in the maternal or infant record to identify congenital malformations diagnosed within 90 days after birth (Appendix Table 2). Codes from the maternal record were considered because infant Medicaid claims are sometimes recorded under the mother's name before the infant's eligibility for Medicaid is activated. This approach has been previously validated to identify certain major congenital malformations in the MAX data with high positive predictive value (24).

Covariates

We considered a broad range of covariates in our analyses. To take advantage of the data available in each data set, we allowed the assessed covariates to differ between the Nordic and US MAX cohorts. In both, we defined maternal age at delivery, calendar year of birth, parity, diabetes, and diabetes treatments in early pregnancy, including insulin and oral hypoglycemic agents. In the Nordic data, we assessed country of origin. In the US MAX data, we defined maternal race/ethnicity, renal disease, overweight or obesity, smoking, alcohol abuse, illicit drug use, multiple gestations, and exposure to potential teratogens. We also defined health care use variables (which may be markers of overall comorbidity burden)

in the US MAX data, including the number of physician visits for any reason and number of distinct non-antihypertensive prescription drugs during the 3 months before LMP.

Statistical Analysis

All analyses were run separately in the Nordic and US MAX cohorts, and the resulting effect estimates in each cohort were then combined using a meta-analytic approach. To compare pregnancies in which women were treated with β -blockers versus not treated with any antihypertensive medication during the first trimester, we calculated the crude prevalence of overall and organ-specific congenital malformations in the infant as well as unadjusted relative risks (RRs) (that is, prevalence ratio) with 95% CIs. We then further controlled for all available confounding variables using an approach based on propensity scores (PSs).

The PS was estimated using logistic regression and included all covariates shown in Table 1 and Appendix Table 3 (available at [Annals.org](https://annals.org)) without further selection. No interaction terms were considered. After generating the PS, we excluded observations from the nonoverlapping regions of the PS distributions and created 50 PS strata of equal size based on the distribution among treated women. In the Nordic cohort, 1 patient from the exposed group and 25 from the unexposed group were excluded because of trimming. In the US MAX cohort, 3 from the exposed group and 18 from the unexposed group were excluded. The untreated pregnancies were then weighted using the distribution of the treated women among PS strata (25). We assessed the balance of baseline characteristics in the weighted population using the standardized mean difference (the balance of a covariate was deemed acceptable if the absolute value of the standardized mean difference was $<10\%$). Adjusted RRs and risk differences were estimated using generalized linear models (PROC GENMOD in SAS [SAS Institute] with a weight statement). The model estimated the average treatment effect in exposed patients (that is, the increase in risk for malformations associated with β -blocker exposure compared with nonexposure in patients with the characteristics of those exposed to β -blockers).

Finally, the effect estimates in the Nordic and US MAX data were combined for each outcome by fixed-effects meta-analysis.

Sensitivity Analyses

We did several sensitivity analyses to test the robustness of our findings. First, to reduce the possibility of exposure misclassification, we required women to have filled a prescription for a β -blocker at least twice during the first trimester. Second, to capture women with plausible exposure to β -blockers in the first trimester, we widened the window to include those who filled at least 1 prescription between 30 days before LMP and the end of the first trimester in the Nordic data and in the 90 days before LMP with days' supply that overlapped the first trimester in the US MAX data. Third, to reduce potential dependency between multiple pregnancies, we restricted the analysis to pregnancies resulting in a woman's first birth observed in the study data. The resulting effect estimates from the Nordic and US MAX data were combined by fixed-effects meta-analysis, as in the main analysis. Fourth, we changed the reference group of the main analysis to compare the prevalence of congenital malformations in infants exposed to β -blockers versus calcium-channel blockers in the first

trimester of pregnancy and then calculated the unadjusted and PS-adjusted RRs with 95% CIs.

Finally, because the cohort was restricted to pregnancies that resulted in live birth, we sought to quantify the potential effect of missing pregnancies not resulting in live birth (that is, induced abortion, spontaneous abortion, or stillbirth) using methods previously described in detail (19, 20, 26) (Appendix).

Role of the Funding Source

The funders had no role in the design, conduct, or interpretation of the study.

Results

Our analysis involved 3577 women in the Nordic cohort and 14 900 in the US MAX cohort with hypertensive pregnancies resulting in live birth (Figure 1); 500 women in the Nordic data and 195 in the MAX data contributed more than 1 pregnancy. Among pregnancies in which women had a recorded hypertension diagnosis, 682 (19.1%) in the Nordic cohort and 1668 (11.2%) in the US MAX cohort were exposed to β -blockers. Appendix Table 4 (available at [Annals.org](https://www.annals.org)) shows the specific β -blockers dispensed.

Women treated with β -blockers in the first trimester were older than untreated women, were more likely to have given birth previously, and were more likely to use medication for diabetes (Table 1 and Appendix Table 3). In the US MAX cohort, treated women were more likely to smoke, be white, have additional indications for β -blockers (including migraines, anxiety, cardiac arrhythmia, congestive heart failure, and ischemic heart disease), and have filled prescriptions for propylthiouracil. Appendix Figure 1 (available at [Annals.org](https://www.annals.org)) shows the distribution of the PSs in the exposed and unexposed groups. After stratification on the PS, covariates were well balanced in exposed and unexposed women across the cohorts, with a standardized difference less than 10% for all variables (Table 1 and Appendix Table 3).

The fully adjusted results are as follows. The RRs in the Nordic and US MAX cohorts were 1.22 (95% CI, 0.88 to 1.71) and 1.01 (CI, 0.80 to 1.27), respectively, for malformations overall; 0.98 (CI, 0.52 to 1.84) and 1.16 (CI, 0.82 to 1.63) for cardiac defects; and 2.26 (CI, 0.47 to 10.8) and 1.81 (CI, 0.52 to 6.33) for cleft lip or palate (Table 2). The risk differences per 1000 persons exposed (RD_{1000}) in the Nordic and US MAX cohorts were 13.0 (CI, -8.0 to 34.1) and 0.4 (CI, -10.4 to 11.2), respectively, for malformations overall; -0.5 (CI, -12.8 to 11.8) and 3.0 (CI, -4.4 to 10.5) for cardiac defects; and 2.4 (CI, -2.8 to 7.6) and 0.8 (CI, -1.3 to 2.9) for cleft lip or palate. In the US MAX cohort, the RR for CNS malformations was 1.37 (CI, 0.58 to 3.25) and the RD_{1000} was 1.0 (CI, -2.0 to 4.0); in the Nordic cohort, the low number of CNS malformation events precluded a corresponding analysis. Pooling these estimates for the Nordic and US MAX cohorts resulted in RRs of 1.07 (CI, 0.89 to 1.30) for any major malformation, 1.12 (CI, 0.83 to 1.51) for any cardiac malformation, and 1.97 (CI, 0.74 to 5.25) for cleft lip or palate (Figure 2). The pooled RD_{1000} associated with β -blockers was 3.0 (CI, -6.6 to 12.6) for any major malformation, 2.1 (CI, -4.3 to 8.4) for any cardiac malformation, and 1.0 (CI, -0.9 to 3.0) for cleft lip or palate.

Relative risk estimates across the sensitivity analyses were consistent with those of the main analysis for malformations overall and cardiac malformations (Table 3). As in the main analysis, CIs were wide for cleft lip or palate in both cohorts. Changing the reference group from pregnancies unexposed to any antihypertensive agents to those exposed to calcium-channel blockers yielded imprecise estimates for specific malformations because of low numbers (Appendix Table 5, available at [Annals.org](https://annals.org)). The adjusted point estimates for overall malformations comparing patients exposed to β -blockers versus calcium-channel blockers suggested similar risk for the Nordic cohort (RR, 1.01 [CI, 0.48 to 2.14]) and US MAX cohort (RR, 1.22 [CI, 0.79 to 1.90]), but the CIs were wide.

Finally, we considered the potential effect of missing information on pregnancies that do not result in live births (Appendix Figure 2, available at [Annals.org](https://annals.org)). Under the most extreme scenarios modeled, the pooled adjusted estimate of RR would shift from 1.07 to 1.26 for overall malformations, 1.12 to 1.32 for cardiac malformations, 1.97 to 2.32 for cleft lip or palate, and 1.37 to 2.40 for CNS malformations.

Discussion

In the pooled estimates from this cohort study of 3.6 million pregnancies drawn from the registries of the 5 Nordic countries and the MAX data set in the United States, the upper bound of the 95% CI suggests an excess risk per 1000 persons exposed to β -blockers in the first trimester of no more than 12.6 for congenital malformations overall, 8.4 for cardiac malformations, 3.0 for cleft lip or palate, and 4.0 for CNS malformations after adjustment for confounding factors, including maternal hypertension. The risk estimates were generally consistent in the Nordic and U.S. data and across several sensitivity analyses in which we varied the exposure definition.

Several prior studies yielded conflicting results about the association between β -blocker exposure in utero and major congenital malformations. A recent meta-analysis summarized the results of 13 case-control or cohort studies that evaluated this association (10). The pooled results did not show an increase in risk for major congenital malformations overall but showed a 2-fold increase in risk for cardiac malformations and an approximately 3-fold increase in risks for cleft lip or palate and neural tube defects. However, the authors noted that the included studies were subject to several potential biases, including recall, confounding, and publication biases. The potential for confounding by indication was of particular concern because several recent studies have suggested that maternal hypertension itself may be a risk factor for malformations (11, 13). Subsequent to the meta-analysis, a case-control study from the National Birth Defects Prevention Study reported a nearly 2-fold increase in risk for congenital heart defects associated with early β -blocker exposure in pregnancy (22). However, this association was present for other classes of antihypertensive drug and for untreated hypertension, suggesting that it may be explained (at least in part) by the underlying hypertension. These findings (22) may also be vulnerable to recall bias because exposure data were collected up to 2 years after delivery. Another retrospective, population-based cohort study using data from Kaiser Permanente Southern California showed a 2.5-fold increase in risk for cardiac defects associated with first-trimester exposure that shifted to the null with adjustment for measured confounders (27). A case-malformed

control study from the EUROCAT (European Concerted Action on Congenital Anomalies and Twins) registries failed to find an association with congenital heart defects, oral clefts, or neural tube defects (28).

Our study overcomes many of the limitations associated with prior studies in this area. Conducted by the InPreSS consortium, our study pooled data from large cohorts drawn from 6 countries, representing some of the largest cohorts assembled for the study of drug safety in pregnancy. Medication use was defined on the basis of exposure during the first trimester, an etiologically relevant window when assessing a medication's effect on organogenesis. Information on medication exposures was based on filled prescriptions and is thus free from recall bias. We restricted the analysis to women with hypertension, addressing the important issue of confounding by this common indication for β -blocker use. The data sources contained rich patient-level information, including maternal demographic characteristics, medical conditions, and medication exposures, and we used PS-based methods to adjust for such factors in the analysis.

Our observational study is also subject to certain limitations. β -Blocker exposure during the first trimester of pregnancy was based on filled prescriptions during this period, and we do not know whether the patient consumed the medication. To help overcome this limitation, we did a sensitivity analysis in which we redefined exposure as 2 or more dispensings of a β -blocker during the first trimester; the rationale was that if a woman refills a prescription, she likely consumed the medication. This sensitivity analysis yielded very similar point estimates to those of the main analysis for the assessment of overall and cardiac malformations. Another potential limitation of our study is that the covariates used for adjustment differed between the Nordic and US MAX data sets. However, we deliberately did the analysis in this manner to take advantage of all potentially relevant information available in each data set in an effort to generate the least biased effect estimates before pooling. Of note, effect estimates derived from each data set were similar. Our study considered exposure to β -blockers as a class; future studies should examine the risk associated with individual β -blockers and how it may vary with dose.

Our analysis was also restricted to pregnancies ending in live birth. We therefore explored the potential effect of missing information on pregnancies resulting in stillbirth or spontaneous or therapeutic abortion on our risk estimates in a series of sensitivity analyses. For the analyses of overall and cardiac malformations, changes to the risk estimates were relatively modest under the scenarios modeled. We also did a comparative safety analysis with calcium-channel blockers; however, risk estimates were generally imprecise because relatively few patients were exposed to calcium-channel blockers in the first trimester. Finally, despite large base cohorts, the risks for cleft lip or palate and neural tube defects are imprecisely estimated. Future, well-controlled studies done in similarly large cohorts will be needed to further refine these risk estimates.

β -Blockers are a first-line therapy for the treatment of hypertension in pregnancy (6) and are also commonly used in women of reproductive age who may inadvertently become pregnant (29). Our analysis was able to exclude a large increase in the relative and absolute risks for overall major malformations and for the most common class of birth defects, cardiac

malformations. In the setting of small numbers of outcomes, our study cannot exclude an increase in the RR for the less common malformation types, cleft lip or palate and CNS malformations. However, the point estimates from our analysis suggest a more modest increase in the RR for these malformations than earlier publications have reported (10). The potential risks to the fetus must be balanced against the risks to the mother associated with untreated hypertension during pregnancy.

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Appendix:: Additional Information

Ethics Review

Research using the Nordic data was approved by the Regional Ethical Research Board in Stockholm, Sweden; the National Bioethics Committee and Data Protection Authority in Iceland; and the steering committee of the Drugs and Pregnancy project, the National Institute for Health and Welfare, and the Social Insurance Institute in Finland. No ethics approval was required in Denmark and Norway. Research using the U.S. data was approved by the Institutional Review Board of Brigham and Women's Hospital, which granted a waiver of informed consent.

Details on the Nordic Databases Used in the Analyses

The Nordic cohort participants were identified through birth registries in Denmark, Iceland, Norway, and Sweden and through the Drugs and Pregnancy database in Finland. The Finnish database includes information from the Medical Birth Registry, the Malformation Registry, and the Registry on Induced Abortions combined with the Drug Reimbursement Registry. In the other Nordic countries, information on medications used during pregnancy was obtained directly from each country's prescription drug registry and data on congenital malformations were obtained by combining information from the birth registries, patient registries, and cause-of-death registries.

Effect of Restriction to Live Births

The cohorts included in the study contained information on live births only and not on pregnancies that ended in stillbirth or spontaneous or therapeutic abortion. If live birth frequency is the same in pregnancies exposed and unexposed to β -blockers within the levels of the covariates included as potential confounders, then the RR estimates obtained from our analyses will be unbiased. However, if nonlive births occur more frequently in pregnancies exposed to β -blockers, estimates from our main analysis may be biased toward the null (that is, the true risk underestimated by the reported RR and RD). We therefore sought to quantify the potential effect of missing nonlive births using methods previously described in detail and used in our prior evaluations of the teratogenic potential of medications (19, 26, 30). In this sensitivity analysis, we assumed that the frequency of nonlive birth (which included stillbirth and spontaneous or therapeutic abortion) in nonmalformed fetuses is 20%. Then, on the basis of literature-based estimates of the frequency of termination with recognized malformations, we modeled live birth probabilities in unexposed, malformed fetuses. Probabilities ranged from 75% to 55% for overall malformations, cardiac malformations, and cleft lip or palate and from 55% to 35% for CNS malformations given the higher frequency of termination expected for fetuses diagnosed with CNS malformations (31). We then assessed the potential effect of a 10% to 20% higher frequency of nonlive birth among those exposed to β -blockers (again, within levels of the covariates adjusted for through the use of PSs) on the RRs estimated in the main pooled estimate for the fully adjusted analysis.

The results of these analyses are shown in Appendix Figure 2. For overall malformations, cardiac malformations, and cleft lip or palate, the most extreme scenario modeled was a probability of live birth of 55% (assuming a 20% frequency of termination, spontaneous abortion, or stillbirth for reasons other than malformations and a 25% frequency of nonlive birth because of a malformation) and a 20% absolute decrease in the probability of live birth in patients exposed to β -blockers compared with those unexposed (for both malformed and nonmalformed fetuses). Based on these assumptions, the pooled adjusted estimate of RR would shift from 1.07 to 1.26 for overall malformations, 1.12 to 1.32 for cardiac malformations, and 1.97 to 2.32 for cleft lip or palate. When considering CNS malformations, we modeled a higher frequency of terminations. Here, the most extreme scenario considered was a 35% probability of live birth in the unexposed group with malformations (20% frequency of termination, spontaneous abortion, or still birth for reasons other than malformations and 45% frequency of nonlive birth because of a malformation) and a 20% absolute decrease in the probability of live birth in patients exposed to β -blockers. In this situation, the RR from the pooled adjusted estimate shifts from 1.37 to 2.40.

US MAX cohort

Nordic cohort

Appendix Figure 1.

Histograms Showing the Distribution of the Propensity Score (PS) in the β -Blocker Exposed and Unexposed in the First Trimester of Pregnancy

Panel 1. Overall malformations

Panel 2. Cardiac malformations

Panel 3. Cleft lip/palate

Panel 4. Central nervous system malformations

Appendix Figure 2.
Impact of restriction to livebirths.

Appendix Table 1.

Teratogenic Medications

Database	Drugs
Medicaid Analytic eXtract (MAX)	Warfarin, antineoplastic agents (actinomycin, busulfan, chlorambucil, colchicine, cyclophosphamide, doxorubicin, mercaptopurine, methotrexate, vinblastine, vincristine), lithium, isotretinoin, misoprostol, thalidomide
Nordic cohort	Retinoids, antineoplastic agents and immunosuppressants (ATC codes D05BB, L01, L04)

ATC = Anatomical Therapeutic Chemical classification system.

Appendix Table 2.

Ascertainment of Congenital Malformations

Malformation Group	US MAX Data (ICD-9)*	Nordic Data (ICD-9 and ICD-10)
Overall	1 major malformation	ICD-9-CM codes: 740.xx-759.xx ICD-10 codes: Q00.0-Q89.9 (except Q17.0, Q38.1, Q53, Q65.0-Q65.6, Q82.5, Q86)
1. Central nervous system defects	740.xx-742.xx	ICD-9 codes: 740.xx-742.xx ICD-10 codes: Q00-Q07
2. Eye anomalies	743.xx (excluded if only 743.6x and 743.8x)	
3. Ear anomalies	744.xx (excluded if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)	
4. Cardiac malformations	745.xx-746.xx, 747.0x-747.4x, 747.83 (excluded if only 745.5 AND preterm, 746.02 AND preterm, 746.4x, 746.6x, 746.99, 747.0x AND preterm, 747.3 AND preterm)	ICD-9 codes: 745-747 ICD-10 codes: Q20.0-Q26.4, Q26.8, Q26.9
5. Vascular (non-cardiac) malformations	747.6x-747.9x (excluded if only 747.83)	
6. Respiratory malformations	748.xx (did not count if only 748.1x)	
7. Oral cleft	749.xx	ICD-9 codes: 749.xx ICD-10 codes: Q35-Q37
8. Gastrointestinal malformations	750.xx-751.xx (did not count if only 750.0x, 750.1x, 750.50, 751.0x)	
9. Genital (male and female) malformations	752.xx (did not count if only 752.42, 752.52) (in addition, did not count 752.5x if preterm)	
10. Urinary malformations	753.xx (did not include if only 753.7x)	
11. Musculoskeletal malformations	754.xx and 756.xx (did not count if only 754.3x, 754.81, 754.82, 756.2x)	
12. Limb defects	755.xx (excluded if only 755.65)	
13. Other malformations	757.xx; 759.xx (excluded if only 757.2-757.6, 759.81-759.83)	

ICD-9 = International Classification of Diseases, Ninth Revision; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10 = International Classification of Diseases, 10th Revision; US MAX = U.S. Medicaid Analytic eXtract; x = any possible digit.

* In the US MAX cohort, a malformation was defined if any 1 of the following 3 criteria were met: an ICD-9-CM diagnosis was recorded for a specific malformation on >1 date, a diagnosis for a specific malformation was recorded on 1 dates and a relevant corrective surgery or procedure code was recorded, or a diagnosis for a specific malformation was recorded on 1 dates and the infant died within 30 d of birth. If the malformation was defined on the basis of codes from the maternal record alone (and not the infant record) and these codes were also present during the first 105 d of pregnancy (the time

point after which anomalies may begin to be identified in-utero), the outcome was excluded because the diagnosis likely reflects a maternal congenital malformation.

Appendix Table 3.

Additional Characteristics of Births With Hypertension, by β -Blocker Exposure in the First Trimester of Pregnancy

Characteristic	Nordic Cohort					US MAX Cohort		
	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%) [*]		Standardized Difference, %	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%) [*]
	Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers	Unexposed to Antihypertensive Medications		Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers
Nordic country of birth								
Denmark	455 (66.7)	2030 (70.1)	455 (66.8)	1910 (66.5)	0.6	*	*	*
Finland	<25	50 (1.7)	< 25 (3.4)	111 (3.9)	−2.7	*	*	*
Iceland	<3	13 (0.4)	<3 (0.1)	1 (0.0)	3.3	*	*	*
Norway	45 (6.6)	300 (10.4)	45 (6.6)	183 (6.4)	1.0	*	*	*
Sweden	157 (23.0)	502 (17.3)	157 (23.1)	665 (23.2)	−0.3	*	*	*
Maternal race/ethnicity								
Caucasian	*	*	*	*	—	744 (44.6)	4657 (35.2)	743 (44.6)
African American	*	*	*	*	—	626 (37.5)	5737 (43.4)	624 (37.5)
Hispanic	*	*	*	*	—	144 (8.6)	1518 (11.5)	144 (8.7)
Asian	*	*	*	*	—	48 (2.9)	318 (2.4)	48 (2.9)
Native American	*	*	*	*	—	21 (1.3)	215 (1.6)	21 (1.3)
Other	*	*	*	*	—	54 (3.2)	508 (3.8)	54 (3.2)
Unknown	*	*	*	*	—	31 (1.9)	279 (2.1)	31 (1.9)
Parity								
1	242 (35.5)	1074 (37.1)	242 (35.5)	1049 (36.6)	−1.0	*	*	*
2	277 (40.6)	1188 (41.0)	276 (40.5)	1087 (37.9)	2.7	*	*	*
3	99 (14.5)	429 (14.8)	99 (14.5)	447 (16.6)	−2.1	*	*	*
4	64 (9.4)	204 (7.0)	64 (9.4)	257 (9.0)	0.4	*	*	*
Maternal medical/obstetric conditions								
Renal disease	*	*	*	*	—	35 (2.1)	264 (2)	35 (2.1)

Characteristic	Nordic Cohort					US MAX C		
	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%) [*]		Standardized Difference, %	Crude, <i>n</i> (%)		PS-A
	Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers	Unexposed to Antihypertensive Medications		Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers
Overweight/obese	*	*	*	*	—	143 (8.6)	1074 (8.1)	143 (8.6)
Alcohol use	*	*	*	*	—	15 (0.9)	116 (0.9)	15 (0.9)
Illicit drug use	*	*	*	*	—	30 (1.8)	294 (2.2)	28 (1.7)
Multiple gestation	*	*	*	*	—	110 (6.6)	689 (5.2)	110 (6.6)
Smoking	*	*	*	*	—	108 (6.5)	721 (5.5)	105 (6.3)
Potential indications for β-blockers								
Migraines	*	*	*	*	—	147 (8.8)	622 (4.7)	146 (8.8)
Anxiety	*	*	*	*	—	152 (9.1)	785 (5.9)	151 (9.1)
Congestive heart failure	*	*	*	*	—	18 (1.1)	103 (0.8)	18 (1.1)
Cardiac arrhythmia	*	*	*	*	—	104 (6.2)	235 (1.8)	103 (6.2)
Ischemic heart disease	*	*	*	*	—	27 (1.6)	121 (0.9)	27 (1.6)
Potential teratogens								
Danazol	*	*	*	*	—	0 (0)	0 (0)	0 (0)
Progestins	*	*	*	*	—	60 (3.6)	356 (2.7)	60 (3.6)
Methimazole	*	*	*	*	—	24 (1.4)	14 (0.1)	21 (1.3)
Propylthiouracil	*	*	*	*	—	51 (3.1)	35 (0.3)	48 (2.9)
Corticosteroids	*	*	*	*	—	239 (14.3)	1360 (10.3)	238 (14.3)
Fluconazole	*	*	*	*	—	55 (3.3)	373 (2.8)	55 (3.3)
Anticonvulsants	*	*	*	*	—	15 (0.9)	103 (0.8)	15 (0.9)
Health care use variables								
Number of physician visits for any reason (by quartile)								
0 to 2	*	*	*	*	—	78 (4.7)	946 (7.2)	78 (4.7)
3 to 4	*	*	*	*	—	182 (10.9)	1832 (13.9)	181 (10.9)
5 to 7	*	*	*	*	—	398 (23.9)	3274 (24.7)	398 (23.9)

Characteristic	Nordic Cohort					US MAX Cohort		
	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%) [*]		Standardized Difference, %	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%) [*]
	Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers	Unexposed to Antihypertensive Medications		Exposed to β -Blockers	Unexposed to Antihypertensive Medications	Exposed to β -Blockers
8	*	*	*	*	—	1010 (60.6)	7180 (54.3)	1008 (60.5)
Number of distinct nonantihypertensive prescription drugs (by quartile)								
0	*	*	*	*	—	72 (4.3)	1521 (11.5)	72 (4.3)
1 to 2	*	*	*	*	—	297 (17.8)	2698 (20.4)	297 (17.8)
3 to 4	*	*	*	*	—	353 (21.2)	2812 (21.3)	353 (21.2)
5	*	*	*	*	—	946 (56.7)	6201 (46.9)	943 (56.6)

PS = propensity score; US MAX = U.S. Medicaid Analytic eXtract.

* Not available.

Appendix Table 4.

Specific β -Blockers to Which Women Were Exposed During the First Trimester in the Nordic and US MAX Cohorts

β -Blocker	US MAX Cohort, <i>n</i>	Nordic Cohort, <i>n</i>
Atenolol	395	31
Bisoprolol	51	5
Labetalol	677	487
Metoprolol	338	92
Pindolol	11	46
Propranolol	167	13

US MAX = U.S. Medicaid Analytic eXtract.

Appendix Table 5.

Risk for Congenital Malformations After Exposure to β -Blockers Versus CCBs in the First Trimester of Pregnancy

Congenital Malformation	Prevalence, (%)		RR (95% CI)	
	β -Blocker-Exposed (<i>n</i> = 682)	CCB-Exposed (<i>n</i> = 107)	Unadjusted	PS-Adjusted
Nordic				
Overall	48 (7.0)	9 (8.4)	0.84 (0.43–1.63)	1.01 (0.48–2.14)
Cardiac	15 (2.2)	4 (3.7)	0.59 (0.20–1.73)	0.58 (0.17–1.85)
CNS	*	*	*	*
Cleft lip/palate	*	*	*	*

Congenital Malformation	Prevalence, (%)		RR (95% CI)	
	β -Blocker-Exposed (n = 682)	CCB-Exposed (n = 107)	Unadjusted	PS-Adjusted
	β -Blocker-Exposed (n = 1,668)	CCB-Exposed (n = 700)		
US MAX				
Overall	78 (4.7)	33 (4.7)	0.99 (0.67–1.48)	1.22 (0.79–1.90)
Cardiac	37 (2.2)	16 (2.3)	0.97 (0.54–1.73)	1.02 (0.56–1.84)
CNS	<11	<11	2.52 (0.3–20.88)	6.06 (0.20–185.7)
Cleft lip/palate	<11	<11	0.42 (0.08–2.07)	0.40 (0.06–2.77)

CCB = calcium-channel blocker; CNS = central nervous system; PS = propensity score; RR = relative risk; US MAX = U.S. Medicaid Analytic eXtract.

* Cannot be estimated because of restrictions on reporting observations with small cell sizes. Cell sizes <11 cannot be presented because of restrictions on reporting small numbers in the US MAX data.

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β -Blockers are among the most commonly used antihypertensive medications during pregnancy, but concerns have been raised about their potential teratogenic effects. These authors analyzed data from data from nationwide health registries in 5 Nordic countries and the U.S. Medicaid population to examine the risk for congenital malformations in offspring of women with hypertension who were exposed to β -blockers during the first trimester of pregnancy.

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Figure 1. Nordic and US MAX cohort selection.

ATC = Anatomical Therapeutic Chemical; LMP = last menstrual period; US MAX = U.S. Medicaid Analytic eXtract. * From 30 d before LMP through first trimester. These included warfarin, antineoplastic agents (actinomycin, busulfan, chlorambucil, colchicine, cyclophosphamide, doxorubicin, mercaptopurine, methotrexate, vinblastine, and vincristine), lithium, isotretinoin, misoprostol, and thalidomide for the US MAX cohort and retinoids, antineoplastic agents, and immunosuppressants (ATC codes D05BB, L01, and L04) for the Nordic cohort. † From 90 d before LMP through first trimester (ATC codes C02, C03, C04, C05, C08, and C09), or (for US MAX) a Beta-blocker in the 90 d before LMP but not in the first trimester. ‡ Excluded because of missing data on parity, i.e., the checkbox for parity on the maternity record had not been filled in.

Figure 2. Meta-analytic pooled estimates for the Nordic and US MAX cohorts.

Risk for congenital malformations after exposure to β -blockers in the first trimester of pregnancy, adjusted RR (95% CI), and adjusted RD₁₀₀₀ (95% CI). Cell sizes <11 cannot be presented for the US MAX data because of restrictions on reporting small numbers. RD₁₀₀₀ = risk difference per 1000 persons exposed; RR = relative risk; US MAX = U.S. Medicaid Analytic eXtract.

Table 1. Characteristics of Births With Hypertension, by β -Blocker Exposure in the First Trimester of Pregnancy*

Characteristic	Nordic Cohort				US MAX Cohort					
	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%)		Standardized Difference, %	Crude, <i>n</i> (%)		PS-Adjusted, <i>n</i> (%)		Standardized Difference, %
	Exposed to β -Blockers (<i>n</i> = 682)	Unexposed to Antihypertensive Medications (<i>n</i> = 2895)	Exposed to β -Blockers (<i>n</i> = 681)	Unexposed to Antihypertensive Medications (<i>n</i> = 2870)		Exposed to β -Blockers (<i>n</i> = 1668)	Unexposed to Antihypertensive Medications (<i>n</i> = 13 232)	Exposed to β -Blockers (<i>n</i> = 1665)	Unexposed to Antihypertensive Medications (<i>n</i> = 13 214)	
Maternal age										
19 y	3 (0.4)	16 (0.6)	3 (0.4)	11 (0.4)	0.8	71 (4.3)	1538 (11.6)	71 (4.3)	524 (4.0)	1.5
20–24 y	30 (4.4)	205 (7.1)	29 (4.3)	123 (4.3)	–0.2	303 (18.2)	4240 (32.0)	303 (18.2)	2254 (17.1)	3.0
25–29 y	129 (18.9)	787 (27.2)	129 (18.9)	563 (19.6)	–1.7	529 (31.7)	3764 (28.4)	528 (31.7)	4193 (31.7)	–0.1
30–34 y	256 (37.5)	1109 (38.3)	256 (37.6)	1053 (36.7)	1.9	418 (25.1)	2189 (16.5)	417 (25.0)	3408 (25.8)	–1.7
35–39 y	203 (29.8)	624 (21.6)	203 (29.8)	858 (29.9)	–0.2	257 (15.4)	1151 (8.7)	257 (15.4)	2120 (16.0)	–1.7
40 y	61 (8.9)	154 (5.3)	61 (9.0)	261 (9.1)	–0.5	90 (5.4)	350 (2.6)	89 (5.3)	714 (5.4)	–0.3
Year of birth										
1997	20 (2.9)	49 (1.7)	20 (2.9)	87 (3.0)	–0.6	NA	NA	NA	NA	NA
1998	<20 (<2.9)	62 (2.1)	17 (2.5)	63 (2.2)	2.0	NA	NA	NA	NA	NA
1999	20 (2.9)	95 (3.3)	20 (2.9)	76 (2.6)	1.7	NA	NA	NA	NA	NA
2000	37 (5.4)	104 (3.6)	37 (5.4)	148 (5.2)	1.2	<11 (<0.7)	15 (0.1)	<11 (<0.7)	18 (0.1)	–0.5
2001	30 (4.4)	134 (4.6)	30 (4.4)	124 (4.3)	0.4	55 (3.3)	566 (4.3)	55 (3.3)	434 (3.3)	0.1
2002	30 (4.4)	133 (4.6)	30 (4.4)	138 (4.8)	–1.9	78 (4.7)	696 (5.3)	78 (4.7)	597 (4.5)	0.8
2003	22 (3.2)	126 (4.4)	22 (3.2)	104 (3.6)	–2.2	107 (6.4)	1034 (7.8)	107 (6.4)	843 (6.4)	0.2
2004	36 (5.3)	175 (6.0)	36 (5.3)	150 (5.2)	0.3	134 (8.0)	1345 (10.2)	134 (8.0)	1030 (7.8)	0.9
2005	45 (6.6)	182 (6.3)	45 (6.6)	191 (6.7)	–0.1	147 (8.8)	1509 (11.4)	147 (8.8)	1182 (8.9)	–0.4
2006	76 (11.1)	290 (10.0)	76 (11.2)	331 (11.5)	–1.1	193 (11.6)	1563 (11.8)	193 (11.6)	1572 (11.9)	–1.0

* Percentages may not sum to 100 due to rounding.

Table 2.
Risk for Congenital Malformations After Exposure to β -Blockers in the First Trimester of Pregnancy

Congenital Malformation	Prevalence, N (%)		RR (95% CI)		RD1000 (95% CI)	
	Exposed (<i>n</i> = 682)	Unexposed (<i>n</i> = 2895)	Unadjusted	PS-Adjusted	Unadjusted	PS-Adjusted
Nordic cohort						
Overall	48 (7.0)	152 (5.3)	1.34 (0.98 to 1.83)	1.22 (0.88 to 1.71)	17.9 (−3.0 to 38.7)	13.0 (−8.0 to 34.1)
Cardiac	15 (2.2)	55 (1.9)	1.16 (0.66 to 2.04)	0.98 (0.52 to 1.84)	3.0 (−9.1 to 15.1)	−0.5 (−12.8 to 11.8)
CNS	*	*	*	*	*	*
Cleft lip/palate	3 (0.4)	4 (0.1)	3.18 (0.71 to 14.19)	2.26 (0.47 to 10.8)	3.0 (−2.1 to 8.2)	2.4 (−2.8 to 7.6)
US MAX cohort [‡]						
	Exposed (<i>n</i> = 1668)	Unexposed (<i>n</i> = 13 232)				
Overall	78 (4.7)	534 (4.0)	1.16 (0.92 to 1.46)	1.01 (0.80 to 1.27)	6.4 (−4.3 to 17.1)	0.4 (−10.4 to 11.2)
Cardiac	37 (2.2)	224 (1.7)	1.31 (0.93 to 1.85)	1.16 (0.82 to 1.63)	5.3 (−2.1 to 12.7)	3.0 (−4.4 to 10.5)
CNS	<11 (<0.7)	36 (0.3)	1.32 (0.56 to 3.13)	1.37 (0.58 to 3.25)	0.9 (−2.1 to 3.9)	1.0 (−2.0 to 4.0)
Cleft lip/palate	<11 (<0.7)	13 (0.1)	1.83 (0.52 to 6.42)	1.81 (0.52 to 6.33)	0.8 (−1.3 to 2.9)	0.8 (−1.3 to 2.9)

CNS = central nervous system; PS = propensity score; RD1000 = risk difference per 1000 persons exposed; RR = relative risk; US MAX = U.S. Medicaid Analytic eXtract.

* Cannot be estimated because of restrictions on reporting observations with small cell sizes.

[‡] Cell sizes <11 cannot be presented because of restrictions on reporting small numbers in US MAX data.

Sensitivity Analyses Examining the Risk for Congenital Malformations After Exposure to β -Blockers in the First Trimester of Pregnancy

Table 3.

Congenital Malformation	Hypertension-Restricted Cohort												Meta-analysis of PS-Adjusted RR (95% CI)
	Nordic Cohort						US MAX Cohort						
	Total, <i>n</i>		Outcome Events, <i>n</i>		RR (95% CI)		Total, <i>n</i>		Outcome Events, <i>n</i>		RR (95% CI)		
	Exposed	Unexposed	Exposed	Unexposed	Unadjusted	PS-Adjusted	Exposed	Unexposed	Exposed	Unexposed	Unadjusted	PS-Adjusted	
Exposure based on 2 dispensings in the first trimester													
Overall	283	2895	22	152	1.48 (0.96–2.28)	1.35 (0.70–2.61)	717	13 232	36	534	1.24 (0.90–1.73)	1.10 (0.79–1.52)	
Cardiac	283	2895	6	55	1.12 (0.49–2.57)	0.97 (0.26–3.58)	717	13 232	17	224	1.40 (0.86–2.28)	1.23 (0.76–2.00)	
CNS	*	*	*	*	*	*	717	13 232	<11	36	1.54 (0.47–4.98)	1.82 (0.56–5.93)	
Cleft lip/palate	283	2895	<3	*	5.11 (0.94–27.81)	2.40 (0.15–38.07)	717	13 232	<11	13	2.84 (0.64–12.56)	2.46 (0.56–10.76)	
Exposure based on 1 dispensing 30 d before the LMP through the end of the first trimester (Nordic cohort) or the days' supply overlapping the first trimester (US MAX cohort)													
Overall	750	2827	51	149	1.29 (0.95–1.75)	1.16 (0.82–1.66)	1886	13 232	85	534	1.12 (0.89–1.40)	0.97 (0.78–1.21)	
Cardiac	750	2827	15	55	1.03 (0.58–1.81)	0.98 (0.51–1.86)	1886	13 232	38	224	1.19 (0.85–1.67)	1.03 (0.74–1.45)	
CNS	*	*	*	*	*	*	1886	13 232	<11	36	1.36 (0.61–3.06)	1.41 (0.63–3.18)	
Cleft lip/palate	750	2827	3	4	2.83 (0.63–12.61)	1.29 (0.21–7.82)	1886	13 232	<11	13	1.62 (0.46–5.68)	1.62 (0.46–5.67)	

Congenital Malformation	Hypertension-Restricted Cohort												Meta-analysis of PS-Adjusted RR (95% CI)	
	Nordic Cohort						US MAX Cohort							
	Total, <i>n</i>		Outcome Events, <i>n</i>		RR (95% CI)		Total, <i>n</i>		Outcome Events, <i>n</i>		RR (95% CI)			
	Exposed	Unexposed	Exposed	Unexposed	Unadjusted	PS-Adjusted	Exposed	Unexposed	Unadjusted	PS-Adjusted	Exposed	Unexposed	Unadjusted	PS-Adjusted
Cohorts restricted to the mother's first observed birth														
Overall	608	2409	43	127	1.34 (0.96–1.87)	1.49 (1.02–2.17)	1618	13 072	78	523	1.20 (0.96–1.52)	1.04 (0.83–1.31)	1.15 (0.94–1.40)	
Cardiac	608	2409	13	46	1.12 (0.61–2.06)	1.19 (0.61–2.33)	1618	13 072	37	221	1.35 (0.96–1.91)	1.19 (0.85–1.68)	1.19 (0.88–1.62)	
CNS	*	*	*	*	*	*	1618	13 072	<11	36	1.35 (0.57–3.19)	1.40 (0.59–3.33)	*	
Cleft lip/palate	608	2409	3	3	3.96 (0.80–19.58)	4.53 (0.59–34.85)	1618	13 072	<11	12	2.02 (0.57–7.15)	2.15 (0.60–7.66)	2.65 (0.90–7.79)	

CNS = central nervous system; LMP = last menstrual period; PS = propensity score; RR = relative risk; US MAX = U.S. Medicaid Analytic eXtract.

* Cannot be estimated because of restrictions on reporting observations with small cell sizes.