

In Utero Exposure to Antihypertensive Medication during the First Trimester: Is the Risk Worth Taking?

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Abstract

The aim of this study is to evaluate and present the evidence so far, regarding fetal outcomes after in utero exposure to anti-hypertensive medication. Hypertensive disorders during pregnancy constitute a significant risk factor for maternal and fetal outcomes, necessitating antihypertensive treatment. However, current data concerning the safety of in utero exposure to antihypertensive medication are controversial. While some studies recommend the administration of certain agents, others underline the possible adverse effects on fetal development. This review aims to summarize the outcomes of studies published during the last decade, referring to first trimester in utero exposure to antihypertensive agents. In general, α -methyl dopa, β -blockers and calcium channel blockers are the first or second treatment line for hypertension during pregnancy. However, ACEIs, ARBs and diuretics are mostly contraindicated, as the potential risk outweighs the benefits of their administration. Additionally, several drugs should be avoided, due to the lack of data regarding their safety. **Conclusion.** As current studies are restricted for ethical reasons, there is a significant lack of evidence concerning diverse antihypertensive agent use. In utero exposure to antihypertensive medication needs to be carefully evaluated and supported by further research.

Key Words: Drugs ■ Hypertension ■ Pregnancy ■ Safety ■ Side Effects.

Introduction

Hypertensive disorders are one of the leading causes of maternal and fetal pregnancy-related complications, affecting 5-10% of pregnancies (1). They include four main clinical entities: chronic hypertension, gestational hypertension, pre-eclampsia and pre-eclampsia superimposed on chronic hypertension (2). Of these categories, only chronic hypertension corresponds to the subject of this review, which focuses on pharmaceutical antihypertensive treatment during the first trimester.

Chronic hypertension is defined as blood pressure above 140/90 mmHg, recorded before pregnancy or before 20 weeks of gestation. Since chronic hypertension is diagnosed before or in the first half of pregnancy, therapy should be adminis-

trated in early pregnancy (3). During this period, organogenesis occurs and the fetus is more vulnerable to possible drug-induced effects. The existing literature provides controversial findings regarding the safety of antihypertensive drug administration. Some studies underline the potential risk for fetal development, whereas others dispute it, mentioning hypertension itself as a risk factor for fetopathy. Moreover, chronic hypertension is correlated with advanced maternal age and comorbidities such as diabetes mellitus and obesity, which makes the interpretation of the results more challenging (4). Thus, the aim of this review is to clarify the inconsistency of studies already published, by evaluating and presenting evidence of fetal outcomes after in utero exposure to antihypertensive medication.

Literature Search

The studies used in this review were identified by searching MEDLINE data base using PubMed Central NCBI. More specific, the Medical Subject Heading terms were: “congenital abnormalities OR congenital disorder OR congenital abnormality OR congenital anomaly OR congenital malformation OR birth defects pregnancy” AND “mothers OR pregnant OR gestational OR prenatal OR perinatal OR gestation”. The main Medical Subject Heading terms regarding antihypertensive medication, were applied in the literature search, based on the previous terms, followed by the name of each drug or drug class, as follows: “antihypertensive agent OR β -adrenergic receptor blocking agent OR β -blocker OR β -antagonist OR adrenergic β -3 receptor antagonists OR adrenergic β -2 receptor antagonists OR adrenergic β -1 receptor antagonists OR antiadrenergic OR atenolol OR bisoprolol OR carvedilol OR esmolol OR metoprolol OR propranolol”, “calcium channel blockers OR calcium channel antagonists OR nifedipine OR amlodipine OR CCBs”, “diuretics OR loop diuretics OR thiazides OR carbonic anhydrase inhibitors OR furosemide OR hydrochlorothiazide OR bumetanide OR amiloride OR eplerenone OR spironolactone OR acetazolamide”, “ α 2-adrenergic agonists OR clonidine OR methyl dopa”, “ACE inhibitors OR angiotensin-converting enzyme inhibitor OR captopril OR enalapril OR lisinopril OR ARBs OR angiotensin receptor blockers OR valsartan OR Olmesartan OR losartan OR RAS-inhibiting medication OR renin-angiotensin system blockers OR AT1 blockers”.

Inclusion and Exclusion Criteria

The authors performed the following search strategy for each specific drug class, using the previous Medical Subject Heading terms. After adjusting the investigation to the last 11-year period, the research was performed on studies published from January 2010 to June 2021. Further initial inclusion criteria included the use of the English language, the availability of the full text online and a study type referring to the human species. After this initial search the authors collected several papers for further evaluation. Among these, a certain number was excluded by reading the title or the abstract, according to the following exclusion criteria: 1) title not relevant, 2) not referring exclusively to pregnant patients, 3) an indication for the antihypertensive drug different from chronic hypertension, 4) papers not referring to the adverse fetal outcomes of the administered drug. The remaining papers were fully examined and only excluded if they presented perinatal effects or exclusively questioned second or third trimester exposure to antihypertensive agents. Finally, after removing several common papers among the results, the final number of papers included in this review was 48 (Table 1).

The papers included consist of 22 original (cases, cohorts and reposts) and 26 reviews (meta-analyses, systematic reviews, narrative reviews). The chart below presents the aforementioned studies and the number of participants for the original papers (Figure 1).

Table 1. Final number of papers that were included in the study according to the class of drugs

Papers	Drug class						Total
	B-blockers	RAS blockers [*]	CCBs [†]	Diuretics	A2 agonists [‡]	SADC [§]	
After database searching (N)	6,923	3,297	5,960	727	258	-	-
Excluded with titles and abstracts (N)	6,893	3,273	5945	701	238	-	-
Fully read (N)	30	24	18	26	20	-	-
Finally selected (N)	10	11	2	1	1	23	48

^{*}Renin angiotensin system blockers; [†]Calcium channel blockers; [‡]Alpha 2 adrenergic agonists; [§]Several Antihypertensive Drug Classes referring to the papers that included several antihypertensive drug classes and were identified from the research of more than one drug class study.

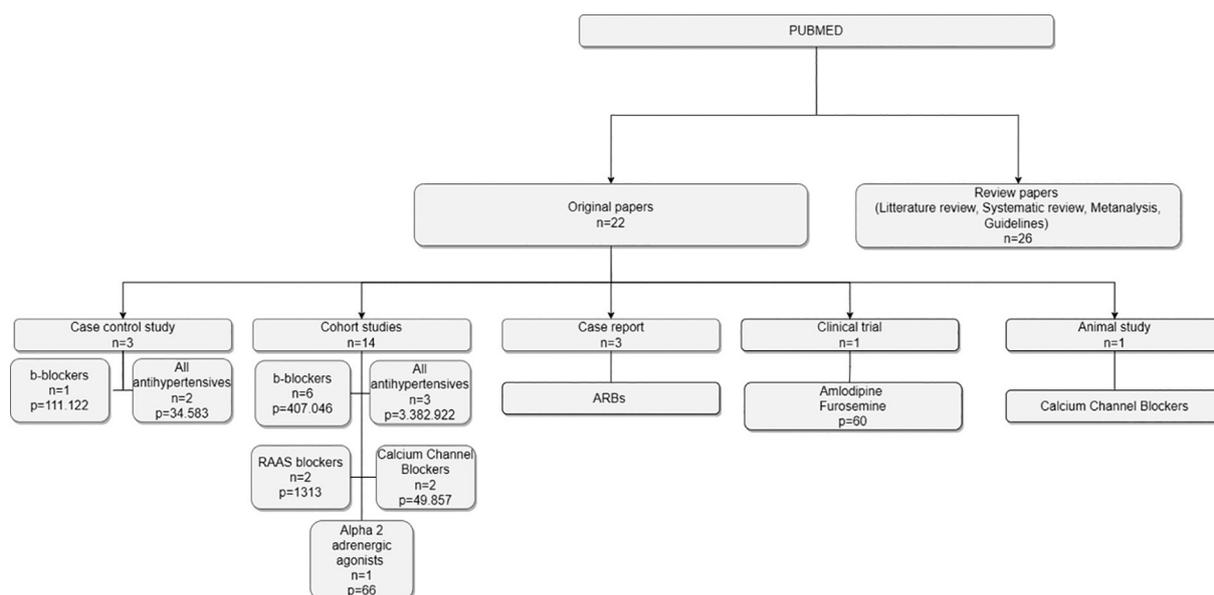


Figure 1. Details regarding the obtained studies.

Definitions

The severity of hypertension is the main factor differentiating the use of each drug class. Mild hypertension is defined as Blood Pressure, BP 140-149/90-99 mmHg, moderate as BP 150-159/100-109 mmHg and severe as BP $\geq 160/\geq 110$ mmHg. In this review, terms such as mild-to-moderate hypertension and non-severe hypertension are considered as equivalent (1). Low birth weight is a term used to describe neonates who are born weighing less than 2.500gr. Preterm birth is defined as the live birth of a neonate prior to 37 weeks of gestation (3).

Following these criteria and definitions, recent existing literature regarding the safety of antihypertensive drug administration was reviewed.

Centrally Acting Alpha-2 Adrenergic Agonists

Alpha-2 adrenergic agonists inhibit vasoconstriction via a central mechanism by decreasing catecholamine release (5). The most frequently administered drugs for controlling chronic hypertension

during pregnancy are a-methyldopa and clonidine. A-methyldopa is the drug of choice recommended almost by all guidelines (1, 3, 5). Follow-up studies in the 1980s of children exposed to the drug in utero demonstrate that methyldopa has a record of safety in pregnancy. These findings are also verified by updated data. Specifically, recent studies suggest that treatment with methyldopa does not affect the maternal uterine artery Doppler pulsatility and Resistance Indices, and state that it does not impair placental circulation and subsequent fetal development (5). Clonidine is similar to methyldopa when it comes to safety and efficacy, but has a different mechanism of action as it stimulates α_2 -adrenergic receptors in the brainstem. It is recommended as a third-line agent for multidrug control of refractory hypertension during pregnancy (5). A retrospective cohort study that took place at the University of Washington Obstetric Hypertension Clinic indicated that clonidine has heterogeneous hemodynamic effects when used in pregnancy. According to this study, women whose response was characterized by a reduction in cardiac output delivered infants with a lower birth weight percentile (6).

B-Adrenergic Receptor Blocking Agents

B-adrenergic receptor blocking agents, commonly referred to as β -blockers or β -antagonists, are a diverse drug class that mainly works by blocking the β -adrenoreceptors in the peripheral circulation, heart, airways, liver, and pancreas. This blockage leads to a decrease in blood pressure following a series of mechanisms, including the reduction of myocardial contractility and of the secretion of angiotensin II (7). Within the drug class, there are different beta-1, beta-2, and alpha blocking activities, resulting in variations in efficacy and adverse effects after exposure to different drugs. Thus, fetal health outcomes after in utero exposure to β -blockers do not always constitute a class effect, as they may vary according to each specific medication used (7).

According to several international guidelines (1), labetalol is the most commonly prescribed

β -blocker for the treatment of hypertensive disorders in pregnancy, whereas atenolol is mostly contraindicated due to its potentially higher risk for adverse fetal outcomes (8). Since β -blockers and especially labetalol are considered to be first line agents for the treatment of both chronic and gestational hypertension, their safety for the developing fetus is of great scientific interest (1). The current literature focuses on two main categories of adverse fetal outcomes after first trimester in utero exposure to β -antagonists: major or organ-specific congenital anomalies and other distinct outcomes, such as birth weight and gestational age.

In general, β -blockers are considered to be safe for the developing fetus, as most studies exclude any major risk for overall major congenital anomalies (9-13). However, their association with minor or organ-specific congenital anomalies is less clear in the existing literature (Table 2).

Table 2. Safety of Antihypertensive Drugs during the First Trimester

Administered drugs	Number of studies*	Number of studies†
Centrally acting alpha-2 adrenergic agonists		
A-methyldopa	(1, 3, 5)	None reported
Clonidine	(5)	(6)
B-blockers	(2, 9, 10, 11, 12, 13)	(7, 8, 9, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22)
Labetalol	(1)	(7)
Atenolol	Mostly contraindicated (8)	(7, 8, 19)
Metoprolol	(7)	(19)
Propranolol	(7)	(19)
Calcium channel blockers	(13, 18, 24, 25)	(13‡, 15‡, 24‡)
Nifedipine	(1)	-
Amlodipine	Unclear (22)	Unclear (22)
Renin-angiotensin system blockers	(34§, 35§)	(28, 29, 30)
ACEIs	-	(27, 30, 31)
ARBs	-	(4, 26, 32, 33)
Renin inhibitors		
Aliskiren	Unclear (36)	Unclear (36)
Diuretics	(1)	(37, 38, 39)
Thiazide diuretics	(1, 36, 39, 40)	(5, 36, 41, 42)
Furosemide	(44, 45, 46)	(30, 37, 47)
Spironolactone	-	(5, 30, 45, 48)
Eplerenone	Unclear (30, 46)	Unclear (30)

*Studies which report that administration is mostly safe with minor risk; †Studies which report fetal adverse outcomes; ‡Based only on a small number of cases; §When accounting for confounders.

Certain studies (9, 11, 14-16) suggest that an increase in cardiovascular malformations, cleft lip or palate and central nervous system malformations is present or cannot be excluded. J. E. H. Bergman et al. (14), in a recent case-malformed-control study, found that there were significantly increased odds of multi-cystic renal dysplasia occurring after maternal exposure to combined alpha- and beta-blockers. Fisher et al. (17) in the 2017 analysis of National Birth Defects Prevention Study data associated β -blockers' use with an increased risk of Coarctation of the Aorta, Pulmonary Valve Stenosis, Perimembranous Ventricular Septal Defects and Secundum Atrial Defects. Some previous studies are based on a small number of cases, do not include an untreated comparison group, and are characterized by heterogeneity. These outcomes should, therefore, be interpreted with caution, as they could potentially be attributed to the severity of the underlying maternal hypertension. Wu et al. (10) in a recent updated meta-analysis of observational studies found no association between β -blocker exposure and an increased risk of heart malformations, cleft lip or palate. Other authors (2, 12, 13) also supported the absence of an association between drug exposure and congenital cardiac anomalies.

Moreover, β -antagonists have been accused of other adverse fetal health outcomes. Fitton et al. (8), in a recent data linkage cohort study, associated in-utero exposure to β -blockers with an increased risk of preterm birth, low birth weight and being Born Small for Gestational Age, SGA. Other studies (7, 15, 18-22) suggest similar findings. Furthermore, some of them introduce the increased risk of fetal growth restriction (FGR), (7, 19, 22, 23) and perinatal mortality (15). Duan et al. (7) analyzed the effect of diverse β -blocker subtypes on birth weight, suggesting that labetalol and atenolol were associated with the highest rate of low birth weight and an increased risk of being born SGA. On the other hand, after metoprolol and propranolol exposure, the risk of being born SGA was not significantly increased (7). Tanaka K et al. (19) found that the incidence of FGR (Fetal

Growth Restriction) was higher in fetuses exposed to propranolol and atenolol, followed by metoprolol exposure, whereas bisoprolol and carvedilol were not strongly associated with FGR.

Calcium Channel Blockers

The Calcium Channel Blocker drug class, also known as CCBs, is classified in two categories: dihydropyridines and non-dihydropyridines. The drugs most commonly administered in pregnancy belong in the first category and, among them, nifedipine is recommended by various guidelines as an alternative for first line and second line therapy in non-severe and severe hypertension during pregnancy (1). The antihypertensive therapeutic effect of nifedipine and other dihydropyridines is mainly due to peripheral arterial vasodilation secondary to inhibition of calcium in vascular smooth muscle cells (24). According to several animal studies (13, 18, 24) high doses of CCBs administered to pregnant rats and rabbits were associated with an increased risk of cardiovascular and skeletal malformations, such as digital and limb defects. This association was not found in human fetuses, thus CCBs are not considered to be teratogenic in humans (13, 18, 24, 25). Only a few studies (13, 15, 24) indicated that CCB use during the first trimester was associated with an increased risk for malformations and congenital anomalies of the upper gastrointestinal tract, but they were based on a small number of cases. Ritchie et al. (24) reported an increase in the miscarriage rate following first trimester in utero exposure to CCBs. Fitton et al. (15), in a recently published systematic review, suggested conflicting results after exposure to CCBs with some evidence of increased perinatal mortality and preterm birth. Moreover, according to a recent review, fetal outcomes after amlodipine exposure varied widely, including normal birth, developmental delay, arm weakness and even loss of cardiac activity at 12 weeks' gestation (22) (Table 2). All in all, CCBs are effective for antihypertension treatment during pregnancy, and they are considered to be safe for the developing fetus (13).

Renin-Angiotensin System Blockers

The renin-angiotensin system, RAS plays a vital role in regulating blood pressure and homeostasis. Angiotensin-converting enzyme inhibitors, ACEIs, and angiotensin receptor blockers, ARBs, interfere with this system and therefore are amongst the first-line medications for the management of hypertension in non-pregnant women (26). They modulate RAS by either inhibiting an enzyme responsible for the conversion of angiotensin I to angiotensin II or by antagonizing the effects of angiotensin II at its receptors (27). Since strong evidence is associated with congenital malformations after second and third trimester exposure, these drugs are contraindicated during late pregnancy (28). However, it remains unclear whether their use is teratogenic if exposure is limited only to the first trimester (29).

Pieper (30) found out that exposure to these drugs during all three trimesters can cause birth defects, while the incidence of congenital malformations after only first trimester exposure is lower. The most common abnormalities amongst them are those of the cardiovascular, central nervous and urogenital systems. Taking into consideration that the fetal RAS develops mainly within the first ninety days of gestational age, exposure to RAS blockers in early pregnancy can lead to renal hypoperfusion and ischemia. As a result, exposure to these drugs has been linked with the need to perform a caesarean section, or with complications such as early miscarriage, stillbirth, elective termination of pregnancy, small for gestational age, preterm birth, low birth weight, low Apgar score and neonatal anuric renal failure (28). However, according to Buawangpong et al, ACEIs prenatal exposure was related to overall congenital malformations, preterm delivery, low birth weight, miscarriage, and elective termination of pregnancy (27). Furthermore, these drugs are known to cause fetal RAS blockage syndrome, which may occur not only following exposure during the second and third trimester, but also after use of these drugs at the beginning of pregnancy (27). This syndrome consists of fetal hypotension and anuria with oligohydramnios, leading to Potter sequence,

which includes lung hypoplasia, skull ossification, facial deformations and contractures of limbs (30, 31) (Table 2).

Concerning the ARBs, recent studies have confirmed that there is a higher rate of birth defects in cases with ARBs exposure lasting longer than 6 gestational weeks, and this may reveal a teratogenic vulnerability in the second half of the first trimester (26, 32). Moreover, ARBs are more dangerous than ACEIs with increasing risk for renal impairment, due to their higher blocking effect and longer half-life (4, 33).

On the other hand, some studies conclude that there is no increased risk for congenital malformations after first trimester exposure to RAS blockers, when accounting for the underlying hypertension and confounders, such as advanced maternal age, the presence of diabetes mellitus and obesity (34, 35) (Table 2).

Renin Inhibitors

The renin inhibitors, whose main representative is aliskiren, are another drug class whose use has an effect on the RAS system. Concerning aliskiren, due to lack of data it is unknown whether the placenta is permeable by this drug. Consequently, it is not clear if this drug can cause congenital malformation to the fetus (36) (Table 2).

Diuretics

The use of diuretic treatment during pregnancy remains debatable, mainly due to theoretical concerns about reduced plasma volume (5). While the European Society of Hypertension 2013 guidelines (37) and others (38, 39) contraindicate the use of diuretics in pregnancy, the National Heart, Lung, Blood Institute suggest diuretics as an alternative second line treatment (1).

Thiazide Diuretics

Thiazide diuretics act by inhibiting the sodium/chloride cotransporter located in the distal convoluted tubule of a nephron. According to Hyperten-

sion Canada guidelines (40) and ACOG (41), thiazide diuretics can be used as a second-line treatment for non-severe hypertension. Nevertheless, the European Society of Cardiology and the Society of Obstetric Medicine of Australia and New Zealand do not recommend their use in pregnancy (36, 42). Recent studies (5) have indicated that thiazides may cause volume contraction and electrolyte abnormalities, but this appears to be rare with small doses. Moreover, NICE guidelines (43) have proposed that diuretics, particularly chlorthalidone, should not be used since they might be associated with a high risk of congenital malformations and neonatal complications, such as thrombocytopenia, hypoglycemia and electrolyte disorders. Despite the previous suggestions, there is not sufficient evidence that low-dose thiazide diuretics are harmful for pregnancy (1), so women with pre-existing hypertension may continue their current antihypertensive medication (36).

Loop Diuretics

Loop diuretics act by inhibiting the sodium-potassium-chloride co-transporter in the thick ascending loop of Henle. Paulino Vigil-De et al. (44) and others (45) confirmed that furosemide is not associated with adverse pregnancy outcomes when used in women with mild/moderate chronic hypertension. However, according to the European Society of Cardiology (37) and others (30, 46), bumetanide and furosemide can cause oligohydramnios, as well as fetal electrolyte abnormalities.

Potassium-Sparing Diuretics/ Mineralocorticoid Receptor Antagonists

Spironolactone is contraindicated during the pre-conception period and throughout pregnancy because of its antiandrogenic effect that can lead to fetal feminization (5, 30, 45, 47). However, an early study on male rats did not indicate any evidence of an antiandrogenic effect (47). The available literature includes only one case report describing ambiguous genitalia in a human newborn of a mother treated with spironolactone until the fifth week of

gestation (48). However, eplerenone does not act as an androgen receptor blocker (47). The European Society of Cardiology underlined the deficiency of data regarding the use of eplerenone during pregnancy (36). Consequently, eplerenone should only be used in pregnant women when treatment with other diuretics is ineffective (30) (Table 2).

Discussion

To the best of our knowledge, the current evidence about each antihypertensive drug class, based on already published literature, varies widely. While the use of several drug classes is strongly encouraged due to the existence of sufficient data, the field remains unclear concerning some others. According to the 2018 European Society of Cardiology Guidelines, α -methyl dopa, β -blockers, mainly represented by labetalol and calcium channel blockers, primarily represented by nifedipine, are the first-line treatment for hypertension in pregnancy (36). Indeed, we did not find any concrete evidence against those drugs. However, some other drug classes, such as ACEIs, ARBs or spironolactone, should not be routinely prescribed to women of reproductive age, in order to avoid possible adverse fetal outcomes, on the basis of several studies.

Nevertheless, considerable attention must be paid when regulating antihypertensive therapy in a pregnant woman, taking into consideration the need for applying a personalized treatment plan. It is of utmost importance that the benefits of the therapy administered outweigh the potential risks for the developing fetus. Both earlier and recent studies demonstrate that untreated hypertension is associated with possible adverse maternal and fetal outcomes. Specifically, it is associated with a high risk of pre-eclampsia, growth restriction and congenital heart disease (3). Consequently, it is not surprising that the findings of this review should be interpreted with caution. The teratogenicity observed could be attributed to maternal factors and comorbidities coexisting with hypertension during pregnancy, such as obesity, advanced maternal age and diabetes mellitus (26). Furthermore,

it is feasible that several limitations might have impacted the results. Certain studies were designed for a small sample size, while some included heterogeneous study groups. Another potential source of error could be the possibility of recall bias and the lack of adjustment for other confounding factors such as maternal age and Body Mass Index. Inevitably, there is limited evidence concerning the safety of the use of several drug classes due to the impossibility of conducting further research because of ethical restrictions.

Conclusion

Hypertensive disorders are one of the most common complications of pregnancy. The effectiveness and relative safety of certain antihypertensive medications makes them suitable for administration during the first trimester. However, specific drugs should be avoided during this gestational period, such as ACEIs, ARBs or spironolactone, since they are supported by deficient data. The necessity of designing further studies, as well as re-evaluating the data already assessed appears to be imperative.

What Is Already Known on This Topic:

Antihypertensive treatment is a necessity in cases of hypertensive disorders during pregnancy, as the risk for maternal and fetal outcomes is quite significant. However, the safety of in utero exposure to antihypertensive medication is ambiguous. Some studies recommend the administration of certain agents, while others underline the possible adverse effects on fetal development.

What This Study Adds:

This study summarizes the possible adverse outcomes of antihypertensive agents during the first trimester of gestation. In utero exposure to some of these drugs raises caution regarding their effectiveness and safety. The present review quotes the most recent data, offering a most recent and clear depiction of current antihypertensive drugs effects during the first gestational trimester.

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