Prescription of antihypertensive medications during pregnancy in the UK

Lucia Cea Soriano[1,2,*], **Brian T Bateman**[3], **Luis A García Rodríguez**[1], and **Sonia Hernández-Díaz**[2]

[1]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain

[2]Department of Epidemiology, Harvard School of Public Health, Boston, United States

[3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital. Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, United States

Abstract

Purpose—To describe the management of antihypertensive medications in pregnancy by general practitioners in the United Kingdom (UK) and compare it with current guidelines.

Methods—We used electronic medical records from The Health Improvement Network (THIN) database from 1996-2010 to identify completed pregnancies. The study cohort included the first pregnancy identified during the study period in women aged 13-49. Information on both hypertension diagnoses and prescription of specific antihypertensive medications within the 90 days before the last menstrual period (LMP) and during pregnancy was ascertained from electronic medical records.

Results—Among 148,544 eligible pregnancies, we identified 1995 (1.3%) during which the women had pre-existing hypertension diagnosed by the LMP date. Overall, the prevalence of antihypertensive medications during the first trimester was 1.5%; beta-blockers were the most commonly prescribed antihypertensive. Among women with pre-existing hypertension, 36% were prescribed an antihypertensive medication during the 90 days before the LMP. Among those, 9.6 % and 22.2% had discontinued their medication by the first and second trimester, respectively. For contraindicated drugs such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) the corresponding discontinuation rates were around 25% and 70%. Women who switched therapy received preferably either methyldopa or an alpha-beta blocker.

Conclusions—In this population of UK pregnant women, prescription patterns of antihypertensive medications were dominated by recommended treatments, although some

[*]Correspondence to: Dr. Lucía Cea Soriano, Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain. Tel: +34-91-5313404; Fax: +34-91-5312871; luciaceife@gmail.com.

patients continued on contraindicated drugs throughout pregnancy or switched to preferred agents in a delayed fashion.

Keywords

Pregnancy; hypertension; treatment patterns; antihypertensive medications; THIN

Introduction

Antihypertensive drugs are routinely prescribed in pregnancy to reduce the progression to severe hypertension (systolic blood pressure of 160 mmHg).[1] Between 0.6% and 2% of women have chronic hypertension during pregnancy,[2-5] an additional 6-7% develop hypertension during gestation.[7] Severe hypertension during pregnancy can lead to substantial morbidity for the mother and the fetus.[8] However, there is controversy about the need for pharmacologic reduction of blood pressure levels at the beginning of pregnancy given the natural vasodilation that takes place within the first 20 weeks of gestation. Moreover, it is unclear whether antihypertensives diminish the risk of complications such as preeclampsia. [9,10]

Guidelines on the management of both chronic and gestational hypertension need to balance the potential benefits of these drugs during pregnancy for the mother against the potential harms to the developing fetus. Yet, data are limited on the safety of specific antihypertensive drugs during pregnancy. [11] Both labetalol and methyldopa are considered safe for use in pregnant women,[12,13] while angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are contraindicated during all trimesters of pregnancy based on their potential teratogenic and fetotoxic effects,[1] though this is controversial.[14]

Recommendations by the National Institute for Health and Clinical Excellence (NICE) guidelines on the management of hypertension and antihypertensive medications[2] issued in 2010 indicate labetalol as a first choice for hypertension in pregnancy, with methyldopa and nifedipine as other acceptable alternatives.[1] In earlier years, methyldopa was used as the first-line antihypertensive agent. [15] In order to determine the treatment patterns and management of antihypertensive medications during pregnancy in real clinical practice, we identified and evaluated a cohort of pregnancies within The Health Improvement Network (THIN), with special focus on women with pre-existing hypertension.

Methods

THIN is an electronic medical records database that comprises computerized information entered by a group of primary care providers (PCPs) in the UK. Data from more than 4 million patients on demographics, visits to PCPs, diagnoses from specialist referrals and hospital admissions, results of laboratory tests, and prescriptions written, as well as free-text information, are recorded systematically and anonymized before being sent to THIN for use in research projects. Specific diagnoses and procedures (e.g., insertion of devices) are recorded using the Read classification[16,17] and prescription of drugs and devices are coded using a drug dictionary based on data from the Multilex classification

(www.firstdatabank.co.uk/8/multilex-drug-data- file). Both dictionaries are standard clinical terminology used in UK primary care. The validity of the database for pharmacoepidemiological research has been shown.[18] Ethics approval was received by the UK nationally accredited ethics committee, South East Multicentre Research Ethics Committee (SE-MREC) (SRC 12-013).

In the UK, PCPs are the gatekeepers to health care and centralize the prescription of drugs to their patients. The maternity care provided by the National Health System (NHS) includes PCPs, specialists and hospitals. PCPs typically continue the care of their patients during pregnancy, working together with nurses and midwives at their practices; all of them record the information in THIN. The first health professional most women see about their pregnancy care is their PCP (78%) and a high proportion of prenatal visits takes place at the PCP's practice (45%). [19]

Ascertainment of pregnancy cohort

We first identified women of childbearing age (13-49 years) from January 1st 1996 to December 31st 2010. Women were eligible only after they had been registered with their PCP for at least one year. Within this source population (N = 1,115,035), we identified pregnancies during the study period based on Read Codes indicative of i) conception (last menstrual period (LMP)), ii) end of pregnancy (deliveries, ectopic pregnancies, miscarriages, induced abortions, stillbirths and fetal deaths) and iii) other codes compatible with pregnancy (e.g. pregnancy tests, prenatal visit, alpha-fetoprotein tests, obstetric ultrasounds, amniocenteses, pregnancy complications, threatened abortions, and obstetric setting care). We then developed an algorithm including three sequential cycles that search for Read Code groups in hierarchical order to identify the timing of pregnancy.[20] We identified both *completed pregnancies* (N = 148,544) and *pregnancy losses* (including abortions, terminations, fetal death, stillbirth and neonatal death fatal) (N = 42,456). Completed pregnancies were linked to live-born infants by means of the family identification number and date of birth (89% successfully linked). Details on cohort identification have been described previously.[20]

Ascertainment of hypertension

Among completed pregnancies, we identified women with specific Read Codes suggestive of hypertension recorded anytime prior to LMP date. Appendix 1S shows the list of Read Codes.

Baseline characteristics, comorbidities and drug prescriptions

For baseline characteristics, we considered all the information available in the database any time prior to the LMP date, prioritizing the information closer to LMP. Variables abstracted included lifestyle factors such as smoking, demographic characteristics such as women's age and body mass index (calculated from recorded height and weight; weight in kg / (height in metres^2), most prevalent illnesses, prescriptions, and health care utilization indicators.

Ascertainment of antihypertensive drugs

Antihypertensive drugs are automatically recorded by the PCPs in the electronic medical records. The following drug classes were evaluated: diuretics, beta-blockers, alpha-beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), central alpha agonists agents, alpha agonist agents. The *pre-pregnancy period* was defined as the 90 days before the LMP date; *first trimester* was defined as the 90 days after LMP and *second trimester* as day 91 to day 180 of pregnancy.

Exposure to antihypertensive medication was defined as the presence of at least one prescription within each time frame. In a secondary analysis, we defined exposure considering the days supplied in the prescription and defining a time period as exposed when the days supply of any prescription covered at least one day of that time period (e.g. first trimester). Since results were essentially identical, we only present below the former definition.

Switching patterns in women with pre-existing hypertension

For each class of antihypertensive drugs used during the pre-pregnancy period, we determined the proportion of women who continued on this specific class of drugs (*continuers*), those who switched to a different agent/s (*switchers*) and those who did not receive any prescription for any antihypertensive agent (*discontinuers*) during the first or second trimester. *Continuers* were defined as women who received at least one prescription of the same antihypertensive agent received during the pre-pregnancy period by the end of first and second trimester, separately. *Switchers* were defined as women who received one or more prescriptions of antihypertensives different from the one prescribed in the pre-pregnancy period by the end of first and second trimester. *Discontinuers* were defined as women who did not receive any prescription of antihypertensive medications during the first or second trimester, respectively. In addition, for women not treated in the pre-pregnancy period, we identified those who received at least one prescription (initiators) during the first and second trimester.

We defined the use of antihypertensives as *monotherapy* based on receiving prescriptions of only one type of antihypertensive class for each time frame of interest and *polytherapy* based on receiving prescriptions for more than one antihypertensive class in each time frame (i.e., would include both switchers and concomitant therapy).

In a secondary analysis, we evaluated the treatment patterns while restricting the cohort to women who had an antihypertensive treatment duration of at least one year before LMP date. Duration of treatment was computed by summing the number of days corresponding to consecutive prescriptions (allowing for an interval of 60 days or less between the end of one prescription and the start of the next one).

Analysis

The main characteristics and comorbidities of women with and without a history of hypertension were evaluated by descriptive analysis and their differences were compared

using the χ^2 test. Prescription of specific antihypertensive medications within the pre-pregnancy period and during pregnancy was estimated for all pregnant women. In addition, we evaluated the time trends of first trimester use over the study period. For women with pre-existing hypertension, we also examined the treatment patterns (continuers, discontinuers and switchers), both overall and by class, during first and second trimester of pregnancy; as well as use in monotherapy and polytherapy, separately. All statistical analyses were performed with the STATA package version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Baseline Characteristics

In our cohort of 148,544 completed pregnancies, 1,995 (1.3%) women had a recorded diagnosis of hypertension before their LMP date. Table 1 shows the principal baseline characteristics and comorbidities at LMP stratified by history of hypertension. Among women with pre-existing hypertension the mean age at LMP was 32.1 years, and it was 28.9 years for those without pre-existing hypertension. Compared with women without hypertension, women with pre-existing hypertension were more likely to be obese (33% vs. 10%, p<0.001), have diabetes (4.3% vs. 0.5%, p<0.001), hyperlipidemia (3.6% vs. 0.4%, p<0.001) and hypothyroidism (2.7% vs. 1.6%, p<0.001); while the distribution of other common comorbidities in this population was similar among groups.

Overall antihypertensive medication use

The prevalence of exposure to antihypertensive medications for the overall cohort of pregnancies was 1.5% during the pre-pregnancy period and 1.2% during the first trimester (Table 2). The most commonly prescribed class was beta-blockers, both during pre-pregnancy (0.8%) and during the first trimester (0.5%). Prescription of antihypertensive medications during the first trimester of pregnancy increased between 1996 and 2010, from 0.87% to 1.37% between 1996 and 2010. An increase was seen for all antihypertensive classes except for diuretics (0.23% to 0.18% from 1996 to 2010). A total of 54% of women treated in the pre-pregnancy period (N=387) had been on antihypertensive medications for at least one year.

Treatment patterns during pregnancy among women with pre-existing hypertension

Among women with hypertension, 36.1% received at least one prescription within the 3 months prior to the LMP date, with diuretics and beta-blockers being the most commonly prescribed classes (11% and 10.3%, respectively). The discontinuation rate during the first trimester was 9.6% and it rose up to 22.1% by the second trimester. The proportion of women who continued on the same antihypertensive agent was 88.1% by the end of the first trimester and decreased to 54.1% by the end of the second trimester. The proportion of switchers by the end of first trimester was 2.2% and increased to 22.2% by the end of second trimester. Most women with hypertension who did not receive any antihypertensive medication within the pre-pregnancy period (73.9%) remained untreated throughout their pregnancy, 96.1% and 93.5% during first and second trimester, respectively (Table 3).

Table 3 summarizes the treatment patterns (continuers, discontinuers and switchers) by antihypertensive class individually. Women using beta-blockers showed the greatest discontinuation rate by the end of first (13.2%) and second (26.3%) trimester. Women using alpha-beta blockers and central alpha agonists presented the lowest discontinuation rate by the end of the first and second trimesters: 4.4% and 7.9% and 5.6% and 6.7%, respectively.

For drugs contraindicated in pregnancy, for ACEI the percentage of continuers decreased from 78.6% in the first trimester to 26.0% by the second trimester; for ARB agents, the proportion of continuers was 75.6% by the first trimester to 33.3% by the second. We calculated whether the total proportion of antihypertensive users or women with pre-existing hypertension changed by comparing estimates from the beginning and end of study period (1996/98 and 2008/2010). At the start of the study period, 15% of women with pre-existing hypertension were treated with an antihypertensive medication during the first trimester, compared with 46% by the end of study period. A similar pattern was observed in the second trimester (corresponding percentages: 16% vs. 40%).

Similar results of treatment patterns were found among women treated chronically for at least one year before LMP, with a slightly higher proportion of continuers (95.4% by first trimester and 63.8% by second trimester) (see supplementary table, Table S1).

Switching patterns during pregnancy among women with pre-existing hypertension

In Table 4 we present the switching patterns by the end of first and second trimester and by antihypertensive class. By the end of the first trimester, regardless of initial classes, most women had switched to a central alpha agonist or an alpha-beta blocker. For example, by the first trimester, 65% of calcium channel blockers users and 50% of beta-blockers users switched to central alpha agonists and 29.4% and 42.9% to alpha-beta blockers, respectively. This pattern remained constant within the second trimester for most classes and also among chronic users (see supplementary table, Table S2).

Monotherapy and polytherapy use among women with pre-existing hypertension

During the pre-pregnancy period, the antihypertensive classes diuretics, calcium channel blockers, alpha 1 agonists and ARB were generally taken as part of a multi-drug antihypertensive regimen (see supplementary table, Table S3). Among continuers, women tended to keep the same regimens (poly/monotherapy) received during the pre-pregnancy period. Those who switched treatment were more likely to be prescribed a single agent irrespective of their type of use (poly/monotherapy) during the pre-pregnancy period.

Discussion

Main Findings

In the current study of over 140,000 pregnant women living in the UK between 1996 and 2010, the overall prevalence of antihypertensive medications during the first trimester was 1.5%, with beta-blockers being the most commonly prescribed drugs. Of 1,995 pregnant women with pre-existing hypertension, close to 40% were prescribed an antihypertensive medication within the 3 months preceding the LMP date. Among these women, 7-26%

discontinued their antihypertensive therapy by the end of the second trimester, depending on the initial drug, and around 30% switched therapy, preferentially to central alpha agonists or alpha-beta blockers. The majority of women with pre-existing hypertension untreated before LMP remained without prescriptions during the first and second trimester.

Interpretation

The prevalence of antihypertensive medication use in this population is in line with previous estimates from the United States.[21,22] *Bateman et al.* reported a prevalence of 1.9% during the first trimester and *Andrade et* al. a prevalence of 1.2% using Medicaid and HMO Research Network sources, respectively. The slightly higher use in the US Medicaid population may be in part explained by differences in risk factors for hypertension (e.g., obesity) across study populations. In our population, close to 40% of women with pre-existing hypertension were on antihypertensives before their LMP[9,21] and the majority continued on their medications during the first trimester, which is consistent with prior studies. Interestingly, we found that women who switched drugs during pregnancy often switched to methyldopa, although the NICE guidelines issued in 2010 in the UK recommend labetalol as first line of choice. However, methyldopa was considered the first line[15] in earlier years and the observed patterns might reflect these previous recommendations. Similarly, consistent with the guidelines, PCPs in the UK tended to prescribe a single agent during pregnancy. [9] Yet, there were a proportion of women on polytherapy regimens, especially among women who continued pre-pregnancy treatment. It is possible that those women had more poorly controlled hypertension, necessitating the use of more than one anti-hypertensive agent.

Although there is still controversy regarding the safety of ACE inhibitors and angiotensin II receptor blockers during early pregnancy, given the potential effects on the developing fetus,[23] it is widely accepted that these drugs should be contraindicated in late pregnancy. [24,25,26] NICE guidelines recommend offering alternative medications before conception or to stop and change treatment as soon as pregnancy is diagnosed. While, in the current study, prescriptions for these drugs were often discontinued by the second trimester, it is still worrisome that a number of women received prescriptions throughout pregnancy. Given the safety concerns, women of reproductive age taking these medications and their PCPs may need further education regarding the safety of these medications in pregnancy.

Strengths and Limitations

This study was carried out using a large UK general practice population, with patients who are representative of the entire UK population with respect to age, sex and geography[27]. Despite the large size of the total study cohort, the number of women of childbearing age with pre-existing hypertension is relatively small, which limited our power and led to unstable estimates for some of the sub-analyses such as the study of temporal trends by individual antihypertensive class. Also of note, the patterns reflect only PCP management of hypertension since this database did not include pregnancies followed exclusively by specialists or at hospitals. However, in the UK most pregnancies are followed at least partially by the PCP, as approximately 80% of UK pregnant women choose their PCP as their first health professional. [19] . It is also important to note that the current study only

included women with completed pregnancies since our aim was to evaluate the prescriptions patterns beyond the first trimester. Women with fatal outcomes (such as miscarriages, abortions) may have had different patterns around conception. Finally, since exposure is based on prescriptions and we do not know if the medication was taken as prescribed, there may be some overestimation of actual use. However, medications prescribed mainly by specialists or in hospital settings would be under-recorded.

Our definition of hypertension was based on Read Codes suggestive of hypertension recorded in the PCP electronic medical record up to the LMP date. We did not validate hypertension diagnoses with the treating physician. However, when we followed a more conservative approach and defined hypertension as having a specific Read Code together with at least one antihypertensive prescription, the characteristics of this subgroup did not differ substantially.

Conclusion

In conclusion, women with pre-existing hypertension tend to continue on antihypertensive agents during pregnancy. Prescription patterns were dominated by the recommended treatments, although we observed a delay in switching patients to preferred treatments and some patients were prescribed contraindicated drugs throughout pregnancy. Further studies are warranted to investigate the safety and effectiveness of these medications on this population for the improvement the quality of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Redman CW. Hypertension in pregnancy: the NICE guidelines. Heart. 2011; 97:1967–1969. [PubMed: 21990386]

2. [Accessed in September 2012] Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. http://www.nice.org.uk/nicemedia/live/13098/50475/50475.pdf

3. Ahmad AS, Samuelsen SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. BJOG. 2012; 119:1521–1528. [PubMed: 22925135]

4. Roberts CL, et al. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. Hypertens Pregnancy. 2008; 27:285–297. [PubMed: 18696357]

5. Povoa AM, Costa F, Rodrigues T, Patricio B, Cardoso F. Prevalence of hypertension during pregnancy in Portugal. Hypertens Pregnancy. 2008; 27:279–284. [PubMed: 18696356]

6. Bateman BT, et al. Hypertension in women of reproductive age in the United States: NHANES 1999-2008. PLoS One. 2012; 7:e36171. [PubMed: 22558371]

7. Thadhani R, Solomon CG. Preeclampsia--a glimpse into the future? N Engl J Med. 2008; 359:858–860. [PubMed: 18716304]

8. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002; 100:369–377. [PubMed: 12151166]

9. Nakhai-Pour HR, Rey E, Berard A. Discontinuation of antihypertensive drug use during the first trimester of pregnancy and the risk of preeclampsia and eclampsia among women with chronic hypertension. Am J Obstet Gynecol. 2009; 201:180.e1–180.e8. [PubMed: 19646568]

10. Krzesinski JM. Hypertension at pregnancy. Rev Med Liege. 1999; 54:415–423. [PubMed: 10394240]

11. ACOG Practice Bulletin No. 125: Chronic hypertension in pregnancy. Obstet Gynecol. 2012; 119:396–407. [PubMed: 22270315]

12. Khedun SM, Moodley J, Naicker T, Maharaj B. Drug management of hypertensive disorders of pregnancy. Pharmacol Ther. 1997; 74:221–258. [PubMed: 9336024]

13. Seely EW, Ecker J. Clinical practice. Chronic hypertension in pregnancy. N Engl J Med. 2011; 365:439–446. [PubMed: 21812673]

14. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011; 343:d5931. [PubMed: 22010128]

15. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. Heart. 2004; 90:1499–1504. [PubMed: 15547046]

16. O'Neil M, Payne C, Read J. Read Codes Version 3: a user led terminology. Methods Inf Med. 1995; 34:187–192. [PubMed: 9082130]

17. Stuart-Buttle CD, Read JD, Sanderson HF, Sutton YM. A language of health in action: Read Codes, classifications and groupings. Proc AMIA Annu Fall Symp. 1996:75–79. [PubMed: 8947631]

18. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007; 16:393–401. [PubMed: 17066486]

19. [Accessed in September 2012] Delivered with care: a national survey of women's experience of maternity care. https://www.npeu.ox.ac.uk/files/downloads/reports/Maternity-Survey-Report-2010.pdf

20. Cea-Soriano L, Garcia Rodriguez LA, Fernandez Cantero O, Hernandez-Diaz S. Challenges of using primary care electronic medical records in the UK to study medications in pregnancy. Pharmacoepidemiol Drug Saf. 2013

21. Bateman BT, et al. Patterns of outpatient antihypertensive medication use during pregnancy in a Medicaid population. Hypertension. 2012; 60:913–920. [PubMed: 22966012]

22. Andrade SE, et al. Outpatient use of cardiovascular drugs during pregnancy. Pharmacoepidemiol Drug Saf. 2008; 17:240–247. [PubMed: 18200619]

23. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012; 60:444–450. [PubMed: 22753220]

24. From the Centers for Disease Control and Prevention. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy--United States, Canada, and Israel, 1987-1995. JAMA. 1997; 277:1193–1194. [PubMed: 9103332]

25. Boix E, Zapater P, Pico A, Moreno O. Teratogenicity with angiotensin II receptor antagonists in pregnancy. J Endocrinol Invest. 2005; 28:1029–1031. [PubMed: 16483184]

26. Ratnapalan S, Koren G. Taking ACE inhibitors during pregnancy. Is it safe? Can Fam Physician. 2002; 48:1047–1049. [PubMed: 12113190]

27. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011; 19:251–255. [PubMed: 22828580]

Key points

- In this population, antihypertensive medications were prescribed to 1.5% of women during the first trimester, with beta-blockers being the most commonly prescribed drugs.

- Most women with pre-existing hypertension not treated with antihypertensive medications before the LMP remained without prescriptions through the end of the second trimester.

- Most women treated with central-alpha agonists or alpha-beta-blockers continued their medication after the first trimester.

- Although these prescription patterns are consistent with current guidelines, a proportion of women continued on contraindicated drugs such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers throughout pregnancy.

Table 1

Baseline characteristics at LMP

Baseline Characteristics		Overall (%)		Pre-existing Hypertension 1995 (%)		Non Hypertension 146549 (%)	
Age							
	13-19 years	12158	8.2	24	1.2	12134	8.3
	20-29 years	63768	42.9	565	28.3	63203	43.1
	30-39 years	68352	46.0	1285	64.4	67067	45.8
	40-49 years	4266	2.9	121	6.1	4145	2.8
Smoking							
	Non smoker	77827	52.4	1195	59.9	76632	52.3
	Current	37018	24.9	379	19.0	36639	25.0
	Former	20520	13.8	343	17.2	20177	13.8
	Unknown	13179	8.9	78	3.9	13101	8.9
BMI							
	<20	15306	10.3	72	3.6	15234	10.4
	20-24	57435	38.7	514	25.8	56921	38.8
	25-29	27782	18.7	520	26.1	27262	18.6
	30 and more	16568	11.2	673	33.7	15895	10.8
	Unknown	31453	21.2	216	10.8	31237	21.3
Comorbidities							
	Anxiety	16252	10.9	295	14.8	15957	10.9
	Asthma	22746	15.3	341	17.1	22405	15.3
	Diabetes	862	0.6	85	4.3	777	0.5
	Hyperlipidemia	673	0.5	71	3.6	602	0.4
	Hypothyroidism	2385	1.6	54	2.7	2331	1.6
	IHD	201	0.1	19	1.0	182	0.1
	Osteoarthritis	2460	1.7	70	3.5	2390	1.6
	Rheumatoid Arthritis	692	0.5	18	0.9	674	0.5
	Respiratory Diseases	24829	16.7	368	18.4	24461	16.7

IHD: Ischemic heart diseases

*
p-values were computed comparing the distribution of each variable between those with pre-existing HTN and non-HTN, all p values were <0.05

Table 2

Antihypertensive medication exposure during pregnancy

Antihypertensive medication class	3 months prior N (%)		1st trimester N (%)		1st month N (%)		2nd month N (%)		3rd month N (%)	
Antihypertensive overall	2160	1.5%	1740	1.2%	1498	1.0%	1345	0.9%	1110	0.7%
Diuretics	458	0.3%	346	0.2%	310	0.2%	265	0.2%	191	0.1%
% among users of antihypertensives		21.2%		19.9%		20.7%		19.7%		17.2%
Beta blockers	1251	0.8%	875	0.6%	776	0.5%	630	0.4%	423	0.3%
% among users of antihypertensives		57.9%		50.0%		51.8%		46.8%		31.4%
Alpha-Beta blockers	134	0.1%	239	0.2%	117	0.1%	186	0.1%	222	0.1%
% among users of antihypertensives		6.2%		13.%		7.8%		13.8%		16.5%
ACEI	234	0.2%	196	0.1%	190	0.1%	167	0.1%	110	0.1%
% among users of antihypertensives		10.8%		11.%		12.7%		12.4%		8.2%
Calcium Channel Blockers	242	0.2%	206	0.1%	185	0.1%	169	0.1%	126	0.1%
% among users of antihypertensives		11.2%		11.%		12.3%		12.6%		9.4%
Central-alpha agonists	110	0.1%	276	0.2%	113	0.1%	195	0.1%	261	0.2%
% among users of antihypertensives		5.1%		15.%		7.5%		14.5%		19.4%
Alpha agonists	29	0.0%	26	0.0%	24	0.0%	20	0.0%	19	0.0%
% among users of antihypertensives		1.3%		1.5%		1.6%		1.5%		1.4%
ARB	60	0.0%	47	0.0%	42	0.0%	40	0.0%	29	0.0%
% among users of antihypertensives		2.8%		2.7%		2.8%		3.0%		2.2%

ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers

Table 3

Treatment patterns along the first and second trimester according with pre-existing hypertension status

Pre-existing hypertension	3 months prior N (%)		Stopping treatment N (%)		Initiators Continuers N (%)		Switchers N (%)	
	N	%	N	%	N	%	N	%
FIRST TRIMESTER								
No treatment	1274	63.9	1224	96.1	50	3.9	NA	
Treated	721	36.1	69	(9.6)	636	88.1	16	2.2
Individual class agents (not mutually exclusive N=721)								
	N	%	N	%	N	%	N	%
Diuretics	220	11.0	20	9.1	177	80.5	23	10.5
Beta-blockers	205	10.3	27	13.2	150	73.2	28	13.7
Alpha-Beta-blockers	114	5.7	5	4.4	104	91.2	5	4.4
ACEI	192	9.6	13	6.8	151	78.6	28	14.6
Calcium Channel	148	7.4	8	5.4	123	83.1	17	11.5
Central-alpha agonists	89	4.5	5	5.6	79	88.8	5	5.6
Alpha 1 agonists	27	1.4	2	7.4	22	81.5	3	11.1
ARB	45	2.3	3	6.7	34	75.6	8	17.8
2ND TRIMESTER								
No treatment	1274	63.9	1191	93.5	83	6.5	NA	
Treated	721	(36.1)	163	22.1	392	54.4	166	23.0
Individual class agents (not mutually exclusive, N=721)								
	N	%	N	%	N	%	N	%
Diuretics	220	11.0	57	25.9	74	33.6	89	40.5
Beta-blockers	205	10.3	54	26.3	87	42.4	64	31.2
Alpha-Beta-blockers	114	5.7	9	7.9	91	79.8	14	12.3
ACEI	192	9.6	44	22.9	50	26.0	98	51.0

Pre-existing hypertension	3 months prior		Stopping treatment		Initiators Continuers		Switchers	
	N (%)		N (%)		N (%)		N (%)	
Calcium Channel	148	7.4	18	12.2	74	50.0	56	37.8
Central-alpha agonists	89	4.5	6	6.7	76	85.4	7	7.9
Alpha agonists	27	1.4	3	11.1	12	44.4	12	44.4
ARB	45	2.3	10	22.2	15	33.3	20	44.4

ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers

Table 4

Treatment patterns during the first trimester of pregnancy across women with pre-existing hypertension by class

SWITCHERS

1ST TRIMESTER

	Diuretics N (%)	Beta blockers N (%)	Alpha beta blocker N (%)	ACEI N (%)	Calcium channel N (%)	Central alpha agonists N (%)	Alpha agonists N (%)	ARB N (%)
Diuretics (N=23)	NA	5 (21.7)	6 (26.1)	4 (17.4)	2 (8.7)	12 (52.2)	1 (04.3)	-
Beta-blockers (N=28)	6 (21.4)	NA	12 (42.9)	2 (7.1)	5 (17.9)	14 (50.0)	1 (3.6)	2 (7.1)
Alpha-Beta-blockers (N=5)	1 (20.0)	1 (20.0)	NA	1 (20.0)	1 (20.0)	4 (80.0)	-	-
ACEI (N=28)	2 (7.1)	2 (7.1)	13 (46.4)	NA	4 (14.3)	13 (46.4)	-	2 (7.1)
Calcium Channel (N=17)	1 (5.9)	1 (5.9)	5 (29.4)	1 (5.9)	NA	11 (64.7)	-	1 (5.9)
Central alpha agonists (N=5)	3 (60.0)	-	2 (40.0)	-	2 (40.0)	NA	1 (20.0)	1 (20.0)
Alpha agonists (N=3)	-	2 (66.7)	1 (33.3)	-	-	1 (33.3)	NA	-
ARB (N=8)	1 (12.5)	-	2 (25.0)	-	-	6 (75.0)	-	NA

SWTICHERS

2ND TRIMESTER

	Diuretics N (%)	Beta blockers N (%)	Alpha beta blocker N (%)	ACEI N (%)	Calcium channel N (%)	Central alpha agonists N (%)	Alpha agonists N (%)	ARB N (%)
Diuretics (N=89)	NA	7 (7.9)	36 (40.4)	6 (6.7)	10 (11.2)	48 (53.9)	2 (2.5)	-
Beta-Blockers (N=64)	2 (3.1)	NA	29 (45.3)	-	5 (7.8)	36 (56.2)	-	2 (3.1)
Alpha-Beta-blockers (N=14)	-	-	NA	-	1 (7.1)	13 (92.9)	-	-
ACEI (N=98)	12 (12.2)	3 (3.1)	32 (32.7)	NA	8 (8.2)	57 (58.2)	-	1 (1.0)
Calcium Channel (N=56)	-	3 (5.4)	21 (37.5)	1 (1.8)	NA	36 (64.3)	-	-
Central alpha- agonists (N=7)	-	3 (42.9)	-	-	4 (57.1)	NA	1 (14.3)	-
Alpha agonists (N=12)	1 (8.3)	-	2 (16.7)	-	2 (16.7)	10 (83.3)	NA	-
ARB (N=20)	-	1 (5.0)	7 (35.0)	-	1 (5.0)	13 (65.0)	-	NA

ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers