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Antihypertensive drug use during pregnancy: a population based study

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Abstract

Purpose. The study aimed at assessing if the European guideline on the use of antihypertensive drugs (AD) in pregnancy are followed in clinical practice. We also evaluated the association between the use of non-recommended drugs and individual characteristics.

Methods. This study analyzed a cohort of 86 171 singleton deliveries occurring between 2009-2010 in the Lombardy region, Italy. Women with first prescription of AD during pregnancy were considered as incident users. Methyldopa, labetalol and nifedipine were considered as "recommended drugs"; all other AD were considered as "non-recommended". Odds Ratio and 95% confidence intervals were estimated.

Results. Among the 1009 patients (1.2%) exposed to AD during pregnancy, 675 (66.9%) were incident users. Among the incident users, 31% received non-recommended drugs; this proportion decreased to 18% among women who started treatment in the third trimester. Women with at least four concomitant diseases had an elevated risk of receiving non-recommended drugs in pregnancy (OR 2.68; 95% CI 1.10-6.73).

Conclusions. Exposure to recommended antihypertensives increased during pregnancy. Nevertheless, a fraction of users that continued or began treatment with non-recommended medications was still present.

Key words
- antihypertensive drugs
- pregnancy
- clinical guidelines

INTRODUCTION

The hypertensive disorders in pregnancy can be classified as preexisting (*i.e.* chronic) or gestational hypertension on the basis of different diagnostic and therapeutic factors, and presence or absence of preeclampsia [1]. Chronic hypertension is characterized by a blood pressure of at least 140/95 mmHg before pregnancy or before the 20th week of gestation. Gestational hypertension is defined as a condition that develops beyond the 20th week of pregnancy and usually resolves within 42 days after delivery [2, 3].

Drug therapy for mild-to-moderate hypertension during pregnancy is generally not recommended for a blood pressure ≤ 149/95 mmHg [3]. Both hypertensive disorders and antihypertensive medication use in early pregnancy have been suggested to directly affect fetal development, and numerous studies have explored whether the prevalence of specific birth defects may be increased by hypertension or its treatment [4]. However, to date, the available scientific evidence suggest that drug treatment of hypertension is effective in preventing maternal complications, but it shows no efficacy in reducing the incidence of neonatal outcomes [5]. Severe hypertension should be treated with antihypertensive drugs: methyldopa and labetalol are considered the drugs of choice, whereas nifedipine is suggested as second-line therapy [3, 6]. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) is contraindicated during pregnancy [3, 6] because of the association with adverse fetal outcomes such as intrauterine growth retardation, neonatal hypotension, oligohydramnios, and patent ductus arteriosus [7, 8]. Also diuretics should no longer be considered for the treatment of hypertension because they can cause placental hypoperfusion [3]. Among β-blockers other than labetalol, atenolol is not recommended because it has been associated with intrauterine growth restriction, preterm delivery, neonatal hypoglycemia and bradycardia [2].

Many observational studies investigated the characteristics of drug use during pregnancy, but only a limited number specifically focused on the use of antihypertensives [9-11]. In particular, to our knowledge, none of these studies was aimed to evaluate the adherence to the guidelines in routine clinical practice.

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Our study aimed to assess if the European Society of Hypertension & European Society of Cardiology (ESH-ESC) guidelines on the use of antihypertensive drugs in pregnancy are followed in clinical practice. In particular, we estimated the proportion of pregnant women who are treated with non-recommended antihypertensives. We also assessed whether individual characteristics (such as age, study degree and health status) might be associated with the use of non-recommended medications during pregnancy.

MATERIALS AND METHODS

Definition of the study population

The study was conducted in the Lombardy region, Italy. All residents are covered by the National Health Service (NHS), which provides comprehensive hospital and outpatient care.

For the purpose of the study, a cohort of pregnant women who were previously included in an observational study designed to evaluate the effects of A/H1N1 pandemic vaccine in pregnancy was used [12]. The study population included all singleton pregnancies (live births and stillbirths) which occurred between 1 October 2009 and 30 September 2010. In case of multiple pregnancies during the study period only the first was included. The following exclusion criteria were applied: women not resident in the Lombardy region; women aged < 12 and > 55 years; multiple births; deliveries that took place before the 22nd and after the 45th week of gestation and deliveries with chromosome abnormalities or congenital viral infections reported in the birth registry. We did not include voluntary abortions and miscarriages (pregnancy loss before 180 days of amenorrhea) in the study, as the information on gestational age is not recorded.

Definition of the pregnancy period

The pregnancy onset was estimated by subtracting the gestational age (weeks of amenorrhea, as reported in the birth registry) from the date of birth. The pre-pregnancy period was defined as 180 days prior to the date of pregnancy onset. The first trimester was defined as the date of onset through day 90 of pregnancy, second trimester as day 91 to day 180, and third trimester as day 181 to delivery.

Sources of data

The following regional databases were used to retrieve the information: birth registry, hospital discharges, drug prescriptions and clinical investigations. These databases were updated by the regional health system for reimbursement purposes or for the evaluation of the clinical activity. The databases were linkable through an anonymised personal identification code.

The Lombardy birth registry was used to identify the cohort of pregnant women and to obtain information on the mother (*e.g.* education, occupational status, gestational age and parity).

The hospital discharge database included all hospital discharges of the mothers. The following information was used: age; date of admission and discharge; diagnosis and procedures according to the ICD-9.

The drug prescription database contains information on the prescriptions issued to outpatients by General Practitioners and covered by the NHS. For each prescription, the following information is available at regional level: patient code, date of prescription, drug authorization code and number of packages. No information is available on prescriptions issued during the hospitalization.

We used the clinical investigation database to obtain information on women presenting chronic diseases (such as diabetes, hypertension or epilepsy).

Therapeutic classes of antihypertensive drugs

The antihypertensive medications were classified as recommended and non-recommended during pregnancy according to the classification of the ESH-ESC guidelines [3]. Methyldopa (Anatomical Therapeutic Chemical classification system, ATC: C02AB01), labetalol (ATC: C07AG01) and the dihydropyridine calcium channel blocker nifedipine (ATC: C08CA05) belong to the recommended medicines group. All the other antihypertensives were not recommended; among these the following categories were examined: ACE inhibitors (ATC: C09A), ARBs (ATC: C09C), diuretics (ATC: C03A, C03B, C03C, C03D), other β-blockers (ATC: C07AA, C07AB) and combinations of antihypertensive substances (ATC: C07B, C07CA, C07CB, C09BA, C09BB, C09D, C03E, C02LA).

Definition of antihypertensive drugs users

A woman was considered to be a user of antihypertensive drugs if she had received at least one prescription of these medications in the 6 months prior to the date of onset or during pregnancy (by trimester of gestation).

Women who received at least one prescription of antihypertensive drugs both in the 6 months prior to pregnancy and during the gestation were considered as prevalent users; those who started therapy during pregnancy were new (incident) users. Within the cohort of women exposed to antihypertensive drugs during pregnancy, we classified women as exposed to either recommended or non-recommended drugs. The former group included subjects who received only recommended medications at any time during pregnancy, whereas women exposed to drugs that are not recommended in pregnancy received at least 1 prescription of non-recommended medications at any time during pregnancy. A further evaluation was conducted on incident users who were also classified according to the therapeutic category of first use (*i.e.* the therapeutic class the incident users began therapy with).

Statistical analysis

Prevalent users, new users and unexposed women were described on the basis of socio-demographic factors (age, marital status, socio-economic variables) and pregnancy history (previous deliveries and previous cesarean sections). Prevalent and incident users were compared through χ^2 test for categorical variables. The number of hospitalizations that occurred in the previous year, history of selected comorbidities, and me-

dication use in the six months preceding the beginning of pregnancy were considered as a proxy for general health status and healthcare utilization. Comorbidities were defined according to ICD-9 codes (of hospital discharges), ATC code (of drug prescriptions) and diseases allowance codes.

Five main categories of potential confounders were taken into account: demographic characteristics of the mothers; socio-economic status; history of previous pregnancy(ies); history of selected comorbidities and medications at pregnancy onset and health care utilization. Details on the specific confounders included in the study are provided in *Supplementary material 1,* available online at www.iss.it.

We analyzed the use of antihypertensives in prevalent and incident users by each trimesters of gestation. We also performed a pre-planned sensitivity analysis excluding prescriptions in the first six weeks of gestation, since they might have been filled before the diagnosis of pregnancy.

Age, nationality, socio-economic factors and health status of women in the study cohort were also investigated as possible determinants of the use of non-recommended drugs in pregnancy. We evaluated the association between these variables and exposure to drugs that are not recommended during pregnancy through a logistic regression model (all missing data were excluded from the analysis). Crude and adjusted odds ratios (OR), with 95% confidence intervals (CI) were estimated. STATA software (ver. 11.2) was used for the statistical analyses.

RESULTS

The study cohort included 86 171 women, 1009 (1.2%) of whom were exposed to antihypertensive medications during pregnancy: 334 (33.1%) were prevalent users and 675 (66.9%) were new (incident) users *(Figure 1)*. The remaining part of the cohort (n = 85 162) included 352 women (0.4%) exposed to antihypertensive drugs in the pre-gestational period who had discontinued therapy at the onset of pregnancy. Prevalent users were older (mean age of 35.4 years) than the incident users and unexposed women (mean age of 32.8 years and 31.8 years, respectively) *(Table 1)*. Moreover, in comparison with incident users and unexposed women, prevalent users had a higher proportion of concomitant disease(s) and drug prescription(s) before the onset of pregnancy (59.9% *versus* 51.7% and 36.2%).

Pattern of antihypertensive drug use and comparison with clinical guidelines recommendations

In the cohort, the prevalence of use, decreased from 0.8% (n = 686) in the pre-gestational period to 0.3% (n = 280) during the first trimester and 0.2% during the second (n = 176) and the third trimester (n = 186) of pregnancy (*Supplementary material 2,* available online at www.iss.it). Around 50% (352/686) stopped treatment before pregnancy onset. This proportion was slightly lower (46/110; 42%) among women who were receiving recommended drugs in the pre-gestational period. The exposure to non-recommended drugs was higher in the first trimester (n = 172; 61.4%) and decreased to 25.6% (n = 45) and 26.3% (n = 49) in the second and third tri-

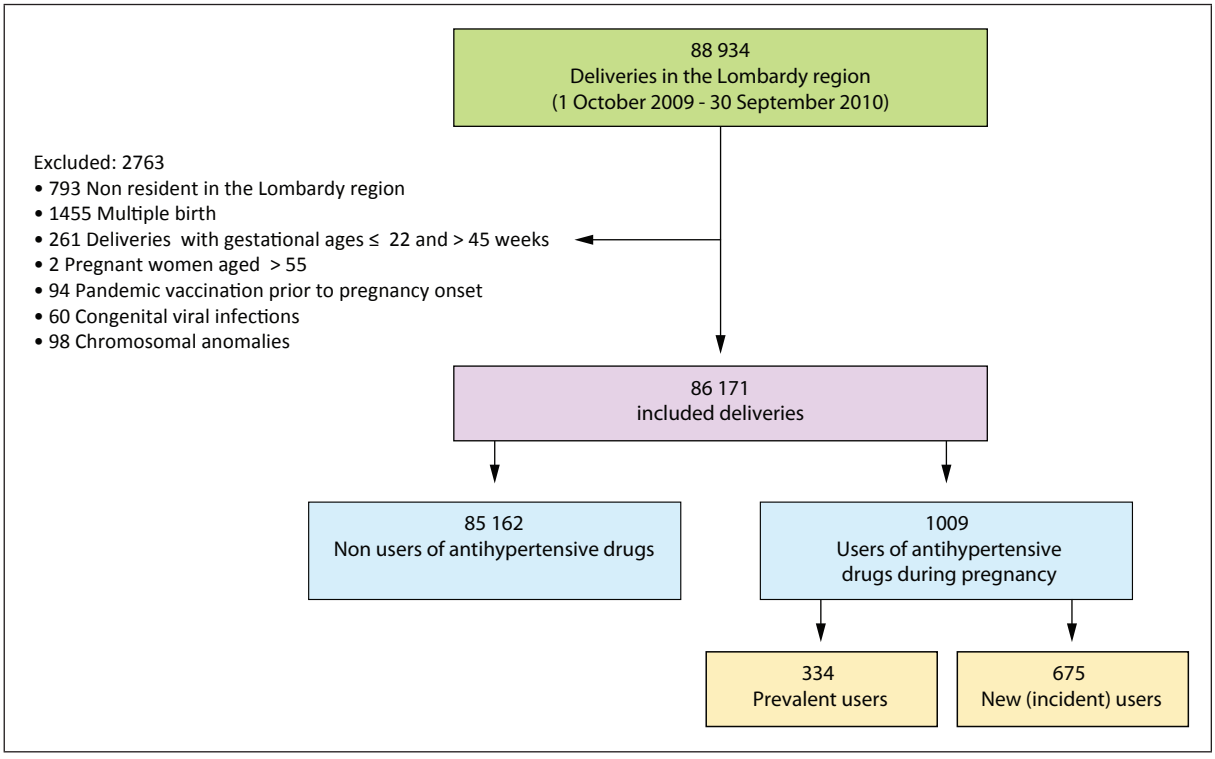

Figure 1
Flow-chart of women included in the study population. Users were classified as prevalent or incident users according to the beginning of the exposure to antihypertensive drugs (before or during pregnancy, respectively).

Table 1
Baseline characteristics of the study population by use of antihypertensive drugs during pregnancy

	Use of antihypertensive drugs during pregnancy N = 1009 (1.2%)				P value	No use of antihypertensive drugs during pregnancy N = 85 162 (98.8%)	
	Prevalent users N = 334 (0.4%)		New users N = 675 (0.8%)				
Age group							
≤ 34	131	(39.2)	395	(58.5)		57 477	(67.5)
35-39	140	(41.9)	212	(31.4)	< 0.001	22 551	(26.5)
≥ 40	63	(18.9)	68	(10.1)		5134	(6.0)
Nationality							
Italian	247	(74.0)	505	(74.8)		60 792	(71.4)
Not Italian	87	(26.0)	170	(25.2)	0.76	24 358	(28.6)
Not reported	-	-	-	-		12	(0.01)
Study degree							
Elementary school/none	9	(2.7)	15	(2.2)		1905	(2.2)
Primary school	116	(34.7)	225	(33.4)	0.88	23 489	(27.6)
High school	141	(42.2)	302	(44.7)		37 178	(43.7)
University degree	62	(18.6)	127	(18.8)		21 622	(25.4)
Not reported	6	(1.8)	6	(0.9)		968	(1.1)
Occupational status							
Employed	250	(74.9)	477	(70.7)		58 830	(69.1)
Unemployed/seeking first occupation	12	(3.6)	25	(3.7)		3759	(4.4)
Student/other	1	(0.3)	7	(1.0)	0.45	813	(0.9)
Housewife	70	(21.0)	161	(23.9)		21 558	(25.3)
Not reported	1	(0.2)	5	(0.7)		202	(0.3)
Civil status							
Single	64	(19.2)	169	(25.0)		19 242	(22.6)
Married	246	(73.7)	452	(67.0)	0.09	61 525	(72.2)
Separated/divorced/widow	14	(4.2)	28	(4.1)		2633	(3.1)
Not declared/not reported	10	(2.9)	26	(3.9)		1762	(2.1)
Previous delivery(ies)							
Yes	183	(54.8)	296	(43.9)	0.001	38 600	(45.3)
No	151	(45.2)	379	(56.1)		46 562	(54.7)
Previous cesarean delivery(ies)							
Yes	58	(17.4)	89	(13.2)	0.07	9004	(10.6)
No	276	(82.6)	586	(86.8)		76 158	(89.4)
Number of comorbidities and medications used in the pregestational period							
0	134	(40.1)	326	(48.3)		54 355	(63.8)
1-3	192	(57.5)	337	(49.9)	0.04	30 162	(35.4)
> 3	8	(2.4)	12	(1.8)		645	(0.8)
Hospital admissions in the last year							
0	245	(73.4)	549	(81.3)		70 200	(82.4)
1-3	85	(25.4)	121	(17.9)	0.01	14 701	(17.3)
> 3	4	(1.2)	5	(0.7)		261	(0.3)

mester, respectively *(Figure 2a)*. This reduction mainly affected ACE inhibitors and ARBs (alone or combined with other antihypertensive): the proportion of users of these drugs was equal to 18.6% and 11.8% in the first trimester of pregnancy and decreased to 5.4% and 1.1% in the third trimester *(Supplementary material 2)*. The exposure to β-blockers (excluding labetalol) also decreased, from 24.3% in the first trimester to 13.1% and 13.4% in the second and third trimester, respectively. The proportion exposed to recommended drugs increased from 38.6% (n = 108) in the first trimester to 73.7% (n = 137) in the third trimester: dihydropyridine calcium antagonists accounted for 28.9% of the exposure in the first trimester and 47.3% in the third trimester *(Figure 2a)*. The increase in the exposure to methyldopa was even more evident (from 10.4% in the first trimester to 32.8% in the third trimester, *Supplementary material 2*). Even though the ESH-ESC guidelines considered labetalol as a recommended drug, only a negligible proportion of prevalent users (12/686; 1.7%) received the prescription at any time during pregnancy. The sensitivity analysis excluding the first six weeks of pregnancy, showed a limited reduction in the use of non-recommended drugs in the first trimester of pregnancy (from 61.4% to 53.0%, *Supplementary material 3,* available online at www.iss.it).

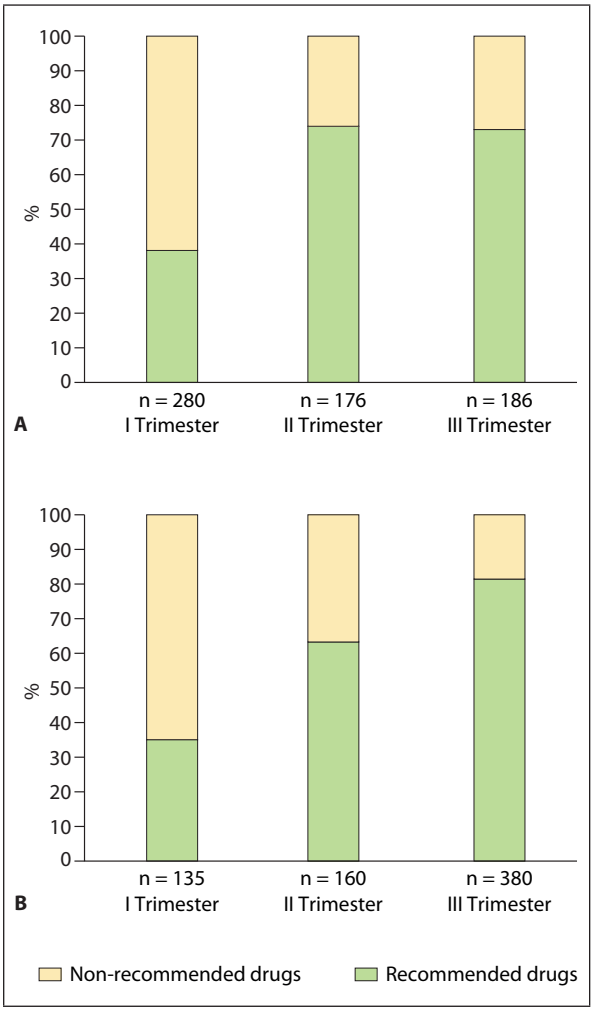

Figure 2
a) Proportion of prevalent users exposed to recommended and non-recommended drugs by trimester of pregnancy.
b) Proportion of incident users exposed to recommended and non-recommended drugs (incident prescription) by trimester of pregnancy.

Among women who received no antihypertensive drugs in the 6 months prior to the onset of pregnancy, the proportion of incident users increased from 0.1% in the first trimester (n = 135), to 0.2% in the second (n = 160) and 0.5% in the third trimester (n = 380) (*Supplementary material 4*, available online at www.iss.it). In the first trimester, the exposure to recommended medications (35.6%) was lower than non-recommended categories (64.4%); the majority of women was exposed to dihydropyridine calcium channel blockers or methyldopa in the second (63.7%) and in the third trimester (82.6%, *Figure 2b*). The sensitivity analysis excluding the first six weeks of pregnancy did not show any differences (data not shown). Patients who started their treatment with non-recommended drugs mainly received prescriptions of β-blockers, ACE inhibitors (alone or in combinations) and ARBs (alone or in combinations) while diuretics were less represented. The exposure to these drugs decreased during late pregnancy. The use of β-blockers and ACE inhibitors was halved by the second and third trimester. The reduction was even more evident for ARBs; the proportion of users of these agents decreased from 5.6% in the second trimester to 0.5% in the third trimester *(Supplementary material 4)*.

Association between socio-demographic factors and medical history with non-recommended drugs in pregnancy

The number of concomitant diseases and drug prescriptions before the onset of pregnancy were associated with higher probability of receiving a non-recommended therapy *(Table 2)*. This risk increased with the number of comorbidities, reaching its maximum for women with at least four concomitant diseases (OR = 2.68; 95% CI 1.10 to 6.73). Age, nationality, study degree, occupational status and medical history (*e.g.* previous deliveries, previous caesarean sections and number of hospitalizations in the year before pregnancy onset) were not associated with the risk of receiving non-recommended drug therapy in pregnancy.

DISCUSSION

This population-based drug utilization study investigated how the recommendations of the ESH-ESC guidelines on the use of antihypertensive drugs in pregnancy are followed in clinical practice. As expected, the exposure to non-recommended drugs was higher in the first trimester of pregnancy among both prevalent and incident users. The pattern of use in the first trimester did not show relevant differences when the first six weeks of pregnancy were removed from the analysis. Although the proportion of women receiving recommended antihypertensive drugs increased during pregnancy, a small proportion of new users began treatment with non-recommended medications and contraindicated ones (*e.g.* for ACE inhibitors a contraindication is reported in the

Table 2
Association between socio-demographic and health factors and the treatment with non-recommended drugs during pregnancy

	Women exposed to antihypertensive drugs during pregnancy (n = 1009)		OR crude	95% CI	OR adjusted[a]	95% CI
	Exposed to non-recommended drugs (n = 412)	Exposed to recommended drugs (n = 597)				
Age group at delivery						
≤ 34	208	318	Ref.		Ref.	
35-39	148	204	1.11	0.84-1.46	1.08	0.82-1.43
≥ 40	56	75	1.14	0.77-1.68	1.13	0.76-1.66
Nationality						
Italian	306	446	Ref.		Ref.	
Not Italian	106	151	1.02	0.77-1.36	1.02	0.77-1.36
Study degree						
Other study degree	336	472	Ref.		Ref.	
University degree	70	119	0.83	0.60-1.15	0.83	0.60-1.16
Not reported[b]	6	6	-	-	-	-
Occupational status						
Employed	303	424	Ref.		Ref.	
Unemployed	108	168	0.90	0.68-1.19	0.91	0.69-1.21
Not reported[b]	1	5				
Previous delivery(ies)						
No	213	317	Ref.		Ref.	
Yes	199	280	1.06	0.82-1.36	1.06	0.83-1.37
Previous cesarean delivery(ies)						
No	353	509	Ref.		Ref.	
Yes	59	88	0.97	0.68-1.38	0.97	0.68-1.39
Number of comorbidities and medications in the pregestational period						
0	165	295	Ref.			
1	133	187	1.27	0.95-1.71		
2	75	78	1.72	1.18-2.50		
3	27	29	1.66	0.95-2.91		
≥ 4	12	8	2.68	1.10-6.73		
Hospital admissions in the last year						
0	325	469	Ref.			
≥ 1	87	128	0.98	0.72-1.33	0.90	0.66-1.23

[a]OR adjusted for number of comorbidities and medications in the pregestational period.
[b]Not reported data were not considered in the analysis.

summary of product characteristics) even in late pregnancy. The assessment of the association between the use of non-recommended drugs in pregnancy and health factors showed a significantly elevated risk among women who had at least four concomitant diseases.

Our extensive search of the literature identified only a few articles reporting on the use of antihypertensive drugs in pregnancy. Our study estimated that only a limited proportion of women (1.2%) were exposed to antihypertensives. This prevalence is lower than those estimated in two studies in the United States (4.4% and 3.1%) [9, 10]. This difference might be partly attributable to the exclusion, in our study population, of multiple births pregnancies, which are more likely to develop preeclampsia and other hypertensive disorders [13], as well as to differences in medical care and attitudes towards pharmacotherapy [14]. We also found a substantial heterogeneity in the range of antihypertensive agents used across all trimesters of pregnancy and in the approach to the management of patients entering pregnancy on antihypertensives. Although professional guidelines generally suggest methyldopa and labetalol as first-line treatments, dihydropyridine calcium antagonists were the most commonly dispensed antihypertensives in any trimester of pregnancy and reached the highest level of exposure among the new users in the third trimester.

According to the ESH-ESC guidelines, ACE inhibitors and ARBs should never be used in pregnancy. However, only limited reliable data are available about the safety of these drugs, especially in the first trimester of pregnancy [15, 16] since a confounding by indication is likely to operate. There are difficulties in discriminating between the effects of the drug and the severity of the hypertension in observational studies [17]. Exposure in the second half of pregnancy has been associated with oligohydramnios (probably resulting from impaired fetal renal function), neonatal anuria, growth abnormalities, skull hypoplasia, and fetal death [18]. For these reasons, it is recommended that women taking ACE inhibitors and, by extrapolation, ARBs be switched to another antihypertensive class of drugs before conception whenever possible [19]. In our cohort, about 12% of women were exposed to ACE-inhibitors or ARBs during the first trimester, 5.4% in the second and 3.4% in the third trimester. These proportions are similar to those observed by Bateman *et al*. [10] who found that use of ACE inhibitors occurred in 4.9% of antihypertensive users in the second trimester and 1.1% in the third trimester.

With regard to atenolol, it is considered prudent to avoid its use during pregnancy [19] on the basis of data suggesting that its use during pregnancy was associated with fetal growth restriction [20]. However, β-blockers other than labetalol were widely represented in our cohort; in particular, atenolol, bisoprolol and nebivolol were more frequently used. Even though not recommended, these drugs were the second most prescribed medications during the first trimester. Diuretics should no longer be considered for treatment of hypertension because they may decrease placenta blood flow [3]; the exposure to this category in our cohort was negligible.

We assume that patterns of antihypertensive drug use observed in our study are reproducible. The content of the ESH-ESC guidelines is widely shared by other guidelines [2,6], and an Italian translation was available [21]. Moreover, similar recommendations were included in a handbook on the use of drugs in pregnancy, which was promoted by the Italian Medicines Agency and distributed in 2004 to all Italian physicians [22]. About half of the patients taking antihypertensive drugs during the pre-gestational period interrupted the treatment at pregnancy onset and an additional proportion stopped during the first trimester. Two factors might explain these findings: the recommendations to treat women with severe hypertension together with an overestimation of the teratogenic risk associated with the use of drugs during pregnancy [23].

A major strength of our study is the capability to take into account the role of many potential confounders (including socio-economic status) which were identified through the use of multiple databases. The study design was based on registry-collected information and consequently the classification of exposure was independent from the selection of confounding factors and outcomes. We lack comparative data from other Italian Region; however, the Lombardy region represents around the 18% of the pregnancies occurring in Italy, and the level of medication use observed in Lombardy is similar to that observed in the rest of Italy [24].

As for other studies that analyze the information on medication dispensing provided by prescription databases we do not know whether the medication was actually taken, especially around the beginning of pregnancy. To take into account the potential misclassification, we conducted a sensitivity analysis excluding the prescriptions occurring in the first six weeks of the first trimester. The sensitivity analysis did not show relevant differences in the prescriptions of antihypertensive drugs, indicating that the possible misclassification did not affect our results. Unlike other studies, we were not able to control our estimates for some confounding factors such as smoking history, alcohol consumption, and BMI, which represented risk factors for hypertension.

CONCLUSIONS

Even though several studies have been published on the use of drugs in pregnancy, to our knowledge no other studies assessed the adherence to the recommendations included in the European guidelines. Our findings suggest that the proportion of patients receiving non-recommended antihypertensives decreased during pregnancy; nevertheless, the proportion of users that continued or began treatment with non-recommended medications, even in the late pregnancy, is a matter of concern. Further studies are needed to provide further comparisons on the implementation of guidelines at regional level, as well as additional evidence about the safety of different antihypertensive drugs to define the optimal approach to therapy during pregnancy.

Authors contributions

GT, FT, RDC conceived the study; CD, FT, RDC, GT designed the study; CD, FT, RDC analyzed the data; CD, GT wrote the manuscript; CD, GT, FT, RDC, CZ, AC contributed to the discussion and reviewed the manuscript. GT will act as guarantor for the paper. All authors saw, commented upon, and approved the final version of the paper.

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Details of ethics approval

This project was designed as an ancillary analysis of the study "A retrospective cohort study to evaluate the safety of H1/N1 pandemic vaccination during pregnancy" which was approved by the ethics committee of the National Institute of Health (26 May 2010; CE-ISS 10/289). Only data already acquired to conduct the main study [9] were analyzed in the present one. For this type of study formal consent is not required.

Conflict of interests

The authors declare that they have no conflict of interest.

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Supplementary Materials for

Antihypertensive drug use during pregnancy: a population based study

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Supplementary material 1
Definition of comorbidities and medications in the pre-gestational period

Comorbidities and medications	ICD 9[a] codes	ATC codes[b]	Disease allowance codes
Pulmonary/Respiratory	490-496	R03	007; 024
Neurological and psychiatric diseases	290-319; 330-359	N04, N05, N06DA, N06DX	005; 011; 014; 017; 029; 038; 044; 046
Hematological diseases (not including malignancies)	280-289		
Diabetes	250	A10	012; 013
Digestive/intestinal antinflammatory	555-558	A07E	
Immunosuppressive drugs		L04A	
Antidepressants		N06A	
Antiepileptics		N03A	
Drugs for peptic ulcer and gastro-oesophageal reflux disease		A02B	
Oral contraceptives		G03A	
Drugs for human fertilization		G03G; G03D; H01AA; H01CC; L02AE	
NSAIDs		M01A;N02B	
Folic acid (before the pregnancy onset)		B03BB	
Folic acid (during first trimester of pregnancy)		B03BB	
Iron supplementation		B03AA; B03AB; B03AC; B03AE	
Antibacterial for systemic use		J01	
Thyroid diseases		H03AA	027; 035
Autoimmune diseases			003; 006; 009; 028; 030; 034; 036; 037; 047; 054; 056
Immunodeficiencies			020; 048; 050; 052
Rare diseases			RAx; RBx; RCx; RDx; RFx; RGx; RIx; RJx; RLx; RMx; RNx

[a]ICD 9 codes: International Classification of Diseases, IX[th] revision.
[b]ATC codes: Anatomical Therapeutic Chemical (ATC) classification system.

Supplementary material 2
Utilization pattern of antihypertensive drugs among prevalent users

	I Trimester		II Trimester		III Trimester	
	N	(%)	N	(%)	N	(%)
Total non-recommended drugs[a]	**172**	**(61.4)**	**45**	**(25.6)**	**49**	**(26.3)**
β-blockers[b]	68	(24.3)	23	(13.1)	25	(13.4)
ACE inhibitors	37	(13.2)	9	(5.1)	7	(3.8)
ACE inhibitors, associations	15	(5.4)	1	(0.6)	3	(1.6)
Angiotensin II receptor blockers	26	(9.3)	-	-	-	-
Angiotensin II receptor blockers, combinations	7	(2.5)	1	(0.6)	2	(1.1)
Diuretics	10	(3.6)	4	(2.3)	3	(1.6)
Diuretics, combinations	12	(4.3)	1	(0.6)	2	(1.1)
Combined α and β blockers	4	(1.4)	2	(1.1)	2	(1.1)
Calcium channel antagonists non dihydropyridines	4	(1.4)	5	(2.8)	4	(2.2)
Imidazoline receptor agonists	6	(2.1)	3	(1.7)	5	(2.7)
β-blockers and diuretics	2	(0.7)	-	-	-	-
α-blockers	2	(0.7)	2	(1.1)	-	-
Total recommended drugs[a]	**108**	**(38.6)**	**131**	**(74.4)**	**137**	**(73.7)**
Calcium channel antagonists dihydropyridines	81	(28.9)	92	(52.3)	88	(47.3)
Methyldopa	29	(10.4)	48	(27.3)	61	(32.8)

[a]Users may contribute to more than one category.
[b]The β-blockers category mainly included atenolol, bisoprolol and nebivolol.

Supplementary material 3
Utilization pattern of antihypertensive drugs among prevalent users: sensitivity analysis (prescriptions of antihypertensive drugs in the first six weeks of gestation were excluded)

	I Trimester	
	N = 155	(%)
Total non-recommended drugs[a]	**82**	**(52.9)**
β-blockers[b]	39	(25.2)
ACE inhibitors	12	(7.7)
ACE inhibitors, associations	7	(4.5)
Angiotensin II receptor blockers	10	(6.5)
Angiotensin II receptor blockers, combinations	3	(1.9)
Diuretics	4	(2.6)
Diuretics, combinations	4	(2.6)
Combined α and β blockers	4	(2.6)
Calcium channel antagonists non dihydropyridines	3	(1.9)
Imidazoline receptor agonists	5	(3.2)
β-blockers and diuretics	1	(0.6)
α-blockers	2	(1.3)
Total recommended drugs[a]	**73**	**(47.1)**
Calcium channel antagonists dihydropyridines	50	(32.3)
Methyldopa	29	(18.7)

[a]Users may contribute to more than one category.
[b]The β-blockers category mainly included atenolol, bisoprolol and nebivolol.

Supplementary material 4
Utilization pattern of antihypertensive drugs among new (incident) users

	I Trimester[a]		II Trimester[b]		III Trimester[c]	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Total non-recommended drugs	**87**	**(64.4)**	**58**	**(36.3)**	**66**	**(17.4)**
β-blockers[d]	24	(17.8)	13	(8.1)	17	(4.5)
ACE inhibitors	11	(8.1)	10	(6.3)	14	(3.7)
ACE inhibitors, associations	11	(8.1)	6	(3.8)	7	(1.8)
Angiotensin II receptor blockers	10	(7.4)	9	(5.6)	2	(0.5)
Angiotensin II receptor blockers, combinations	6	(4.4)	5	(3.1)	8	(2.1)
Diuretics	8	(5.9)	3	(1.9)	8	(2.1)
Diuretics, combinations	7	(5.2)	2	(1.3)	5	(1.3)
Combined α and β blockers	4	(2.9)	4	(2.5)	3	(0.8)
Calcium channel antagonists non dihydropyridines	3	(2.2)	-	-	1	(0.3)
Imidazoline receptor agonists	1	(0.7)	2	(1.3)	2	(0.5)
β-blockers and diuretics	1	(0.7)	2	(1.3)	2	(0.5)
α-blockers	1	(0.7)	1	(0.6)	1	(0.3)
Other substances	1	(0.7)	-	-	-	-
Total recommended drugs	**48**	**(35.6)**	**102**	**(63.7)**	**314**	**(82.6)**
Calcium channel antagonists dihydropyridines	46	(34.1)	89	(55.6)	285	(75.0)
Methyldopa	4	(2.9)	18	(11.2)	33	(8.7)

Data shown in the table were referred to patients starting treatment in each of the trimesters of pregnancy.
[a] 3 women started treatment with two different antihypertensive drugs in the first trimester.
[b] 4 women started treatment with two different antihypertensive drugs in the second trimester.
[c] 6 women started treatment with two different antihypertensive drugs in the third trimester.
[d] The β-blockers category mainly included atenolol, bisoprolol and nebivolol.