Antihypertensive prescribing patterns and hypertension control in females of childbearing age

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Purpose. The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to treat hypertension (HTN) during pregnancy presents well-established risks to a developing fetus. A cross-sectional study was conducted to evaluate the current state of antihypertensive prescribing and contraceptive use in females of childbearing age within a large safety-net health system.

Methods. The retrospective cross-sectional study focused on females aged 18-49 years with a documented diagnosis of HTN. The proportion of patients prescribed an ACE inhibitor or ARB and using a documented form of contraception was calculated. Documented forms of contraception included oral contraceptives, intrauterine devices, injections, implants, and surgical intervention.

Results. A total of 4,187 patients were identified from the HTN registry; after application of exclusion criteria 3,045 patients were included in the study population. The mean age was 39 years (range, 18-49 years). The most frequently prescribed classes of antihypertensive medications were ACE inhibitors and ARBs (one or the other was used by 1,146 patients [37.6%]), followed by thiazide diuretics (n = 710, 23.3%) and calcium channel blockers (n = 599, 19.7%). Of the 1,146 patients prescribed an ACE inhibitor or ARB, 553 (48%) were using a documented form of contraception.

Conclusion. Rates of ACE inhibitor or ARB prescribing to females of childbearing age were high despite the teratogenic risks, and fewer than half of patients had documented protection from pregnancy. Provider and patient education and potential creation of best practice alerts in the electronic medical record regarding the risks of using ACE inhibitors and ARBs in females of childbearing age are warranted.

Keywords: angiotensin converting enzyme inhibitor, angiotensin receptor blocker, contraception, hypertension, reproductive-aged women

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Hypertension (HTN) affects one-third of all females in the United States, and the prevalence of HTN in females of childbearing age continues to rise.[1] The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) during pregnancy presents well-established risks to a developing fetus.[2] Therefore, the American College of Obstetricians and Gynecologists (ACOG) recommends against the use of ACE inhibitors, ARBs, and renin inhibitors in females of childbearing age unless there is a compelling indication such as proteinuric renal disease.[3] If use of these medications is unavoidable or strongly indicated, then females should be counseled regarding teratogenic and other risks, and effective contraception is recommended.[3] The ACOG recommendation differs from the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline for management of high blood pressure (BP) in adults, which recommends ACE inhibitors and ARBs as first-line options for most patients with HTN

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regardless of age or gender.[4] The ACC/AHA guideline further states that for females with HTN who become pregnant or are planning to become pregnant, antihypertensive therapy should be changed to methyldopa, nifedipine, and/or labetalol, given the safety profile of these medications during pregnancy.[4]

Despite the prevalence of HTN in females of childbearing age and the common use of ACE inhibitors and ARBs to manage HTN, there is a limited body of published data describing use of these agents in this population. Another area of interest is the frequency of contraceptive use in females with HTN who are treated with an ACE inhibitor or ARB. The authors identified 3 previous studies in this area, with the most recent published more than 10 years ago.[5-7] Two retrospective studies evaluated the incidence of contraceptive use in females of childbearing age who were taking an ACE inhibitor or ARB; the study populations comprised 101 and 6,467 females, respectively.[5,6] One of those studies found that of the patients taking an ACE inhibitor or ARB, 66% were using a form of contraception.[5] In the other retrospective study, contraceptive use was remarkably lower, at only 11.7%.[6] The third study we identified aimed to quantify ACE inhibitor, ARB, and statin prescribing to female patients of childbearing age and rates of documented discussions of teratogenic risk before and after educational intervention.[7] Risk documentation occurred for 20% of patients, indicating that physicians' baseline awareness of teratogenic risks and risk documentation was lacking.[7] After the intervention (n = 131), the frequency of risk documentation was 2.4 times greater than before intervention.

These studies showed that ACE inhibitors and ARBs are commonly prescribed antihypertensive medications for females of childbearing age and that many patients do not have a documented form of contraception despite the teratogenic risks. The purpose of the study described here was to evaluate the current state of antihypertensive prescribing and contraceptive use for females of childbearing age within a large safety-net health system, a practice setting not included in previous studies. The findings will be used to identify potential safety issues that warrant further educational approaches to prescribers, particularly those who provide care to an underserved patient population.

KEY POINTS

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are frequently prescribed to females of childbearing age despite teratogenic risks.
- In a large sample of younger female patients within a safety-net health system, less than 50% of patients prescribed an ACE inhibitor or ARB had documented protection from pregnancy.
- Provider and patient education and creation of best practice alerts in the electronic medical record regarding the risks of ACE inhibitor and ARB use in females of childbearing age are proposed solutions to help mitigate risk.

Methods

Study design. The retrospective cross-sectional study was approved by the Denver Health Sponsored Programs and Research Office and the Colorado Multiple Institutional Review Board. The study was conducted at Denver Health, which is a large, urban safety-net health system located in Denver, CO. Denver Health is Colorado's primary safety-net institution and has provided $2.8 billion in uncompensated care over the last 15 years while serving as a model for other safety-net institutions across the nation. Denver Health provides care for one-third of Denver's population on an annual basis. Twenty-one percent of Denver Health's patients are uninsured, compared to 10% of those at other Colorado hospitals. Further, the institution cares for the needs of special populations such as the poor, the uninsured, pregnant teens, persons addicted to alcohol and/or other substances, victims of violence, and the homeless. The electronic medical record (EMR) was used to obtain a list of female patients 18 to 49 years of age with a diagnosis of HTN as defined by the health system's HTN registry. According to the US Centers for Disease Control and Prevention, childbearing age can be defined as 16 to 49 years of age. Patients 16 or 17 years of age (pediatric patients) are considered to be a vulnerable population and were excluded from the study. To be included in the HTN registry, patients must have had HTN on their current problem list or documentation of an International Classification of Diseases code (ICD-9 or ICD-10) for HTN documented in the EMR at least twice within the last 5 years. Patients must also have been seen by their primary care provider within the last 18 months. From this list, the proportion of patients prescribed an ACE inhibitor or ARB and using a documented form of contraception was calculated. Oral contraceptives, vaginal contraceptive rings, and contraceptive patches were identified from a patient's medication list. Injections were identified from the medication list and Current Procedural Terminology (CPT) codes. Insertion and removal of intrauterine devices (IUDs), contraceptive implants, and fallopian tube inserts were identified using the medication list and documented ICD-10 and CPT codes. Surgical interventions, including tubal ligation and hysterectomy, were identified using ICD-10 codes. Exclusion criteria were as follows: age of <18 years, pregnancy in the last 3 months, history of

eclampsia or preeclampsia, and current incarceration.

Primary and secondary outcomes. The primary outcome was the percentage of patients prescribed an ACE inhibitor or ARB and using a documented form of contraception. Secondary outcomes were controlled BP (BP of <130/80 mm Hg) and the percentage of patients prescribed an ACE inhibitor or ARB with proteinuria (a urine albumin-to-creatinine ratio [ACR] of ≥30 mg/g) and/or heart failure.

Statistical analysis. Descriptive statistics were used to summarize baseline characteristics. Chi-square testing was used to evaluate categorical variables. Continuous data were characterized using the *t* test. The a priori level of statistical significance was $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics. A total of 4,187 patients were identified from the HTN registry. From that list, 1,142 were excluded due to pregnancy in the last 3 months or a history of eclampsia or preeclampsia. As a result, 3,045 patients were included in the study (Figure 1). Baseline characteristics are listed in Table 1. The mean age was 39 years (range, 18-49 years). The most frequently patient-reported race/ethnicity was Hispanic (45.5%), followed by Black (25.3%) and white (22.1%). Twenty percent of patients were current smokers, and 22% had known diabetes mellitus. The most frequently prescribed classes of antihypertensive medications were ACE inhibitors and ARBs (one or the other was used by 1,146 patients [37.6%]), followed by thiazide diuretics (n = 710, 23.3%) and calcium channel blockers (n = 599, 19.7%).

Primary outcome. Of the 1,146 patients prescribed an ACE inhibitor or ARB, 553 (48%) were using a documented form of contraception and 593 (52%) were not. Among patients with documented contraception, surgical intervention (n = 308, 55.7%), IUD (n = 99, 17.9%), and implant (n = 70, 12.7%) were the most common forms (Table 2).

Secondary outcomes. Of the 1,146 patients prescribed an ACE inhibitor or ARB, 138 (12%) had documented proteinuria and 48 (4%) had a diagnosis of heart failure. Regardless of antihypertensive agent, 944 of 3,039 patients (31%) had controlled BP. Rates of BP control were not different between patients prescribed ACE inhibitor or ARB therapy and those in other antihypertensive medication categories (data not shown). BP data were missing for 6 patients.

Exploratory analysis. Among the 3,039 patients for whom BP data were available, there were significant differences in BP control relative to age group. The BP control rates for patients 18 to 40 years of age, 41 to 44 years of age, and 45 to 49 years of age were 32.0%, 25.5%, and 32.2%, respectively (P = 0.035). The prescribing of ACE inhibitors or ARBs increased with the age of patients in these 3 age categories. ACE inhibitor or ARB prescribing rates for patients 18 to 40 years of age, 41 to 44 years of age, and 45 to 49 years of age were 24.5%, 46.2%, and 52.9%, respectively (P < 0.001). Analyzing contraception use between age categories, we found that patients 18 to 40 years of age, 41 to 44 years of age, and 45 to 49 years of age had rates of documented contraception use of 44.7%, 51.7%, and 45.7%, respectively (P = 0.016).

Figure 1. Application of patient inclusion and exclusion criteria.

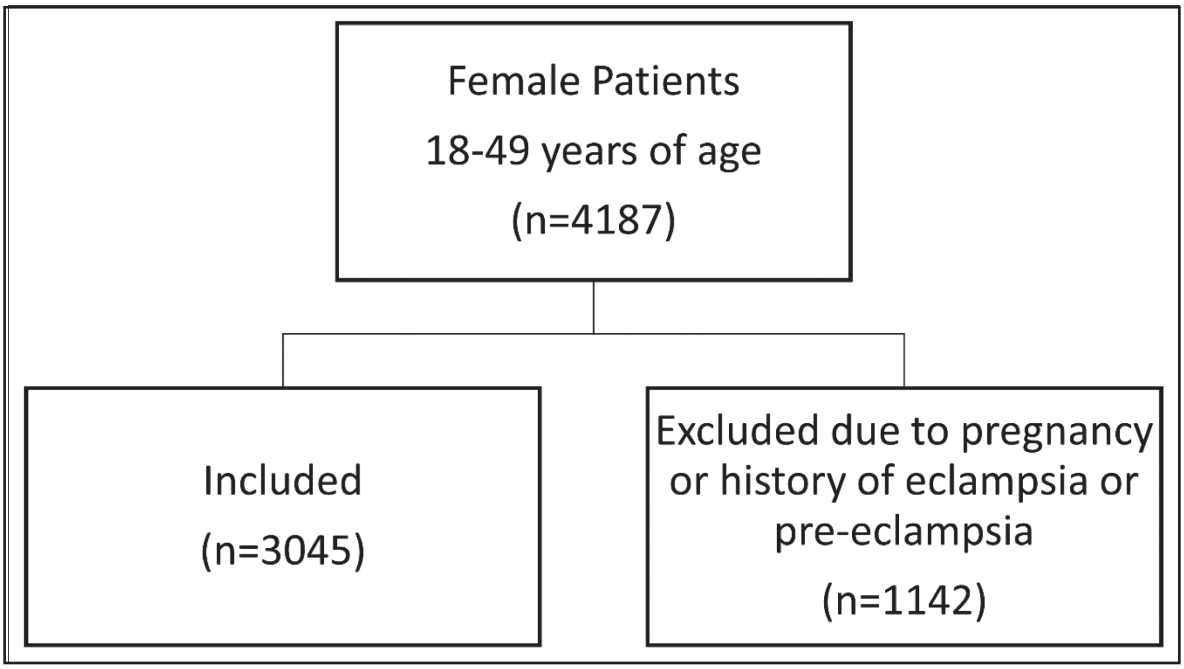

Table 1. Baseline Characteristics of Patients in Study Population (n = 3,045)

Characteristic	No. (%)[a]
Age range, y	
18 to 40	1,502 (49.3)
41 to 44	571 (18.8)
45 to 49	972 (31.9)
Race/ethnicity	
Hispanic	1,386 (45.5)
Black	769 (25.3)
White	674 (22.1)
Other	216 (7.1)
Primary language	
English	2,231 (73.3)
Spanish	648 (21.3)
Other	166 (5.4)
Medical history	
Current smoking	600 (19.7)
Diabetes mellitus	675 (22.2)
Chronic kidney disease	97 (3.2)
Heart failure	79 (2.6)
Selected clinical/laboratory data	
Systolic BP, mean (SD), mm Hg	131.7 (16.4)
Diastolic BP, mean (SD), mm Hg	84.2 (10.7)
Pulse, mean (SD), beats/min	83.8 (13.2)
BMI (kg/m^2), mean (SD)	33.8 (9.0)
Serum potassium, mean (SD), mEq/L	3.8 (0.4)
Serum creatinine, mean (SD), mg/dL	0.8 (0.6)
Antihypertensive use[b]	
ACE inhibitor or ARB	1,146 (37.6)
Thiazide diuretic	710 (23.3)
Calcium channel blocker	599 (19.7)
Beta-blocker	267 (8.8)
Alpha/beta-blocker	119 (3.9)
Loop diuretic	118 (3.9)
Potassium-sparing diuretic	93 (3.1)
Other[c]	80 (2.6)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; SD, standard deviation.
[a]All data are number (percentage) of patients unless specified otherwise.
[b]Some patients were using more than 1 agent.
[c]Included clonidine, guanfacine, hydralazine, methyldopa, minoxidil, and reserpine.

Discussion

The results of the study highlight the fact that ACE inhibitors and ARBs are frequently prescribed to females of childbearing age despite teratogenic risks. Less than half of patients prescribed an ACE inhibitor or ARB had documented protection from pregnancy. This rate of contraception use is lower than that reflected in the most recent data (for 2015-2017) from the National Survey of Family Growth, which indicated that 64.9% of females 15 to 49 years of age were currently using contraception.[8] Documented forms of contraception included oral contraceptives, vaginal rings, patches, IUDs, injections, implants, and surgical intervention. The ACOG guidelines recommend against the use of ACE inhibitors, ARBs, and renin inhibitors in women of childbearing age unless there is a compelling indication such as proteinuric renal disease.[3] Heart failure is another compelling reason to use an ACE inhibitor or ARB. However, very few patients in our study had either of these compelling indications.

The study included a patient population larger than those in previous studies evaluating similar outcomes. Overall, our findings were similar to findings in previous studies. Compared to the study of Martin et al,[5] our study found a lower rate of ACE inhibitor or ARB prescribing amongst females of childbearing age (37.6% vs 47%); however, documented contraceptive use was lower in our study (48% vs 66%). Further, when comparing contraception use in patients 40 years of age or younger, the rate of documented contraception was 44.7% in our study versus 30.8% in the study by Martin et al. One key finding in our exploratory analysis was a doubling of the rate of ACE inhibitor or ARB prescribing to those 41 to 49 years of age versus 18 to 40 years of age, meaning there were potentially more discussions with patients about the safe use of ACE inhibitors or ARBs in the younger female population with HTN.

Table 2. Forms of Contraception Used by Study Population (n = 553)

Type of Contraception	No. (%)
Surgical intervention	308 (55.7)
IUD	99 (17.9)
Implant	70 (12.7)
Combination pill	36 (6.5)
Progestin-only pill	25 (4.5)
Injection	15 (2.7)
Patch	0 (0)
Ring	0 (0)

Abbreviation: IUD, intrauterine device.

Because the study was conducted in a large, urban safety-net health system, it highlights an opportunity for pharmacists to address health disparities in an underserved population as they relate to the safe prescribing and monitoring of ACE inhibitors or ARBs in females of childbearing age with HTN. Pharmacists could play a role in developing best practice alerts within the EMR and provide patient and provider education on the risks of ACE inhibitor and ARB use during pregnancy. An opportunity for pharmacists to manage the HTN population through collaborative practice agreements could allow for improvement in the safe management and monitoring of patients with HTN. Additionally, this vulnerable population could benefit from telephonic outreach by a pharmacist to improve the safe prescribing and monitoring of medications and evaluate BP control in patients able to self-monitor BP at home.

There were several limitations to our study, including the inability to identify patients for whom contraceptive use was not necessary (eg, patients with same-sex partners or male partners with a vasectomy, patients practicing abstinence). Additionally, it was not possible to identify condom (or other barrier method) use or proper contraception counseling with the data extraction methodology. Provision of adequate contraception counseling should be considered to indicate appropriate care; without this information, the analysis may have underestimated the proportion of patients who received appropriate care. Moreover, the patients' originally prescribed HTN regimens were not known. It may be that ACE inhibitors and ARBs were being used as second- or third-line agents for BP control after other agents were not tolerated, in which case their use would be reasonable. Finally, the study evaluated prescribing patterns only and not patient adherence to medications.

Of the 6.1 million pregnancies in the United States in 2011, nearly half (45%, or 2.8 million) were unintended.[9] Although ACOG and 2017 ACC/AHA guidelines have conflicting recommendations for HTN management in females of childbearing age, ACE inhibitors and ARBs should be avoided whenever possible due to teratogenic risks, regardless of whether patients are actively trying to become pregnant. The findings of our study highlight the need for additional provider education and potential creation of best practice alerts in the EMR regarding the risk of ACE inhibitors and ARBs in this population. These next steps are important to prevent the continued prescribing of ACE inhibitors and ARBs in this population. If these medications are unavoidable or strongly indicated, then females should be counseled regarding risks, and effective contraception should be recommended. For females with HTN who become pregnant or are planning to become pregnant, antihypertensive therapy should be changed to methyldopa, nifedipine, and/or labetalol.

Conclusion

Rates of ACE inhibitor or ARB prescribing to females of childbearing age were high despite the teratogenic risk, and less than half of patients had documented protection from pregnancy. Therefore, additional provider education, patient education, and potential creation of best practice alerts in the EMR are warranted for appropriate antihypertensive selection in this population and to inform counseling on and prescribing of effective forms of contraception when ACE inhibitor or ARB use is necessary.

Disclosures

The authors have declared no potential conflicts of interest.

Previous affiliations

At the time of project completion Dr. White was affiliated with Denver Health Medical Center, Denver, CO.

Additional information

Deidentified study data are available upon request.

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