

Outpatient Penicillin Allergy Testing in Pregnant Women Who Report an Allergy

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OBJECTIVE: To estimate the feasibility, acceptability, and safety of outpatient penicillin allergy testing among pregnant women.

METHODS: We conducted a prospective cohort study at a large academic hospital from March 2019 to March 2020. We recruited pregnant women with a self-reported penicillin allergy who underwent allergy testing between 14 0/7 and 36 6/7 weeks of gestation.

RESULTS: Of 127 eligible women pregnant women, 74 (58%, 95% CI 4–67%) accepted allergy testing. Fifty completed or intended to complete allergy testing, yielding a feasibility rate of 68% (95% CI 56–78%). Among the 46 women actually tested (who ranged in age from 18 to 42), 93% (95% CI 68–100%) had a negative test result. A systemic reaction (symptoms consistent with anaphylaxis) occurred in only 2 women (4%, 95% CI 0.5–15%) despite 20 (43%) reporting a severe allergy. No woman suffered an adverse event as a result of allergy testing. In multivariate analysis adjusting for age and parity, women with

public insurance had decreased odds of undergoing penicillin allergy testing (adjusted odds ratio 0.24, 95% CI 0.08–0.69).

CONCLUSION: Outpatient penicillin allergy testing is acceptable and feasible in pregnancy.

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Balancing drug allergy with antibiotic stewardship is difficult and an ever-present challenge for the obstetrician. Antibiotics are administered to 30–74% of women during pregnancy, for a wide variety of indications.^{1–5} The most commonly used antibiotics include penicillin and other beta lactams, clindamycin and other macrolides, and aminoglycosides.^{4,6}

Pregnant women with a self-reported penicillin allergy typically receive alternative antibiotics that are broader spectrum (eg, cefazolin, clindamycin, vancomycin), which increases risk for antibiotic resistance and maternal morbidity.^{1,6–8} In the general population, self-reported penicillin allergy occurs in 10% of patients, however when tested, fewer than 2% have a proven (or true) allergic reaction.^{9,10} Penicillin allergy also decreases over time, with up to 80% of patients with a confirmed penicillin allergy losing sensitization 10 years later.^{11,12,13}

The American College of Obstetrics and Gynecology encourages the consideration of allergy testing in women who self-report a penicillin allergy.^{3,4} Penicillin allergy can be confirmed through skin testing but there are limited data to inform allergy testing in pregnancy.^{13,14} Two studies using skin testing with 27 and 56 pregnant women reported only 3% and 7% of women, respectively, had a true penicillin allergy, and none had anaphylaxis.^{7,15} Neither of these studies in pregnant women included a graded oral challenge, which is important because oral drug challenge is the gold standard for determining true drug allergy.¹⁶

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The authors did not report any potential conflicts of interest.

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Our aim was to estimate the feasibility, acceptability and safety of outpatient penicillin allergy testing in pregnancy.

METHODS

Inclusion criteria at enrollment for this prospective cohort study were a self-reported penicillin allergy, age between 18 and 55 years, singleton or multifetal pregnancy with no known fetal anomalies, gestational age between 14 0/7 and 36 6/7 weeks, and planned delivery within our health care system. The women had a self-reported penicillin allergy documented in their electronic medical record and spoke English or Spanish. Exclusion criteria included history of poorly controlled asthma, beta-blocker use, contraindication to allergy testing (eg, history of Stevens-Johnson syndrome), inability or unwillingness to undergo allergy testing, and prior positive penicillin allergy test results. The University of North Carolina Chapel Hill Institutional Review Board approved this study.

We obtained informed written consent in the woman's preferred language. Study staff administered a written allergy questionnaire administered to enrolled women. We collected a detailed allergy history, including previous allergic reactions to penicillin or other beta-lactams, timing of reactions, and subsequent exposures to penicillin or other beta-lactams. We excluded women from participating if, on detailed allergy history, they reported a recent (defined as within 1 year) history of anaphylaxis, symptoms consistent with a type I immunoglobulin E-mediated allergy reaction after recent penicillin exposure (eg, respiratory compromise including dyspnea, stridor or hypoxemia), or a reaction history consistent with a severe cutaneous adverse reaction (including Stevens-Johnson syndrome, drug rash with eosinophilia and system symptoms, and toxic epidermal necrolysis).

The study allergist (J.W.) performed penicillin allergy testing on all women, which consisted of a

single in-person outpatient visit lasting approximately 3–4 hours at a free-standing outpatient allergy clinic. She used commercially available penicillin skin testing reagents (benzylpenicilloyl polylysine, penicillin G and amoxicillin), as approved by the U.S. Food and Drug Administration for this indication.¹⁷ Penicillin allergy testing was a three-part test composed of skin prick and intradermal testing with controls (saline and histamine), benzylpenicilloyl polylysine (Prepen), penicillin G, followed by a graded oral amoxicillin drug challenge.

Figure 1 illustrates the schema for our three-part allergy testing protocol. A woman who had a positive test result at any step of the procedure (including positive skin prick or intradermal testing) was confirmed to have a penicillin allergy and did not proceed to any subsequent testing. We labeled women with systemic reaction consistent with anaphylaxis as having “anaphylaxis” for their penicillin allergic reaction. After testing, the results were discussed with the woman and were recorded in the electronic medical record. Allergy status was updated as indicated. For this study, we used the phrase “penicillin allergy testing” to represent this three-part test; the phrase “skin testing” signifies the two-step process composed of skin prick and intradermal testing.

We prospectively monitored for adverse events (untoward medical occurrences associated with study procedures and agents) and serious adverse events (death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions). We planned, a priori, that the study would be stopped if more than 10% of women experienced a serious adverse event or anaphylaxis during the study procedures.

After penicillin allergy testing, the women underwent routine prenatal care. Maternal characteristics collected included age, race or ethnicity (as noted in the electronic health record), marital status, insurance

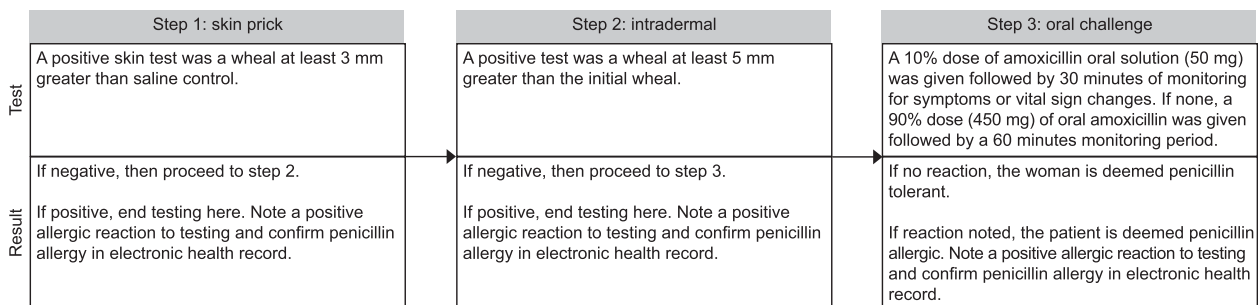


Fig. 1. Three-step testing protocol in the evaluation of penicillin allergy in pregnancy.

Desravines. *Penicillin Allergy Testing in Pregnancy*. *Obstet Gynecol* 2020.

type, preferred language, prenatal care site, gravidity and parity, medical comorbidities, and details of penicillin allergy history (including drug and reaction symptoms). We collected race and ethnicity, as noted within the electronic health record, in this study to assess feasibility and acceptability among our diverse patient population.

The primary outcome was feasibility of penicillin allergy testing, defined as the number of women who completed testing divided by the number of women enrolled into the study. Secondary outcomes were acceptability and safety of allergy testing. Acceptability was defined as the number of women enrolled into the study divided by the number of women approached to participate. Safety was measured as the number of serious adverse events and anaphylaxis. Enrollment of 50 women provided ability to detect 80% feasibility with a 95% CI of 68–89% at alpha error of 5%.

We compared maternal characteristics between the tested women and the nontested women using χ^2 test for categorical variables and Student's *t* test for continuous variables. Variables were selected for inclusion in the multivariable model a priori and based on statistical significance, with $P < .1$. Analyses were performed using STATA 16.0 software.

RESULTS

We conducted this study from March 2019 through March 2020, during which time we screened 175 women who were eligible to participate based on our inclusion criteria by prospectively reviewing the prenatal clinic schedule. We failed to approach 42 women, and others were either deemed not to have penicillin allergy by their obstetrician, had duplicate records, had an incorrect medical record number, or had a spontaneous abortion outside of the gestational age window (Fig. 2). Effectively, we approached 127 women for participation and enrolled 74. Twenty-four of these women failed to present for testing or withdrew from the study. The remaining 50 intended to undergo allergy testing, but only 46 were able to successfully undergo testing. Four women were scheduled for testing, but testing was prematurely halted because of coronavirus disease 2019 (COVID-19) pandemic restrictions. In all, 74 of 127 (58%, 95% CI 49–67%) women accepted allergy testing, and 50 of 74 (68%, 95% CI 56–78%) underwent testing. We included the 4 women who were impeded by the pandemic women based on their intent. The 24 women who enrolled but did not have allergy testing or withdrew cited difficulty with scheduling or time constraints or simply failed to present for their testing.

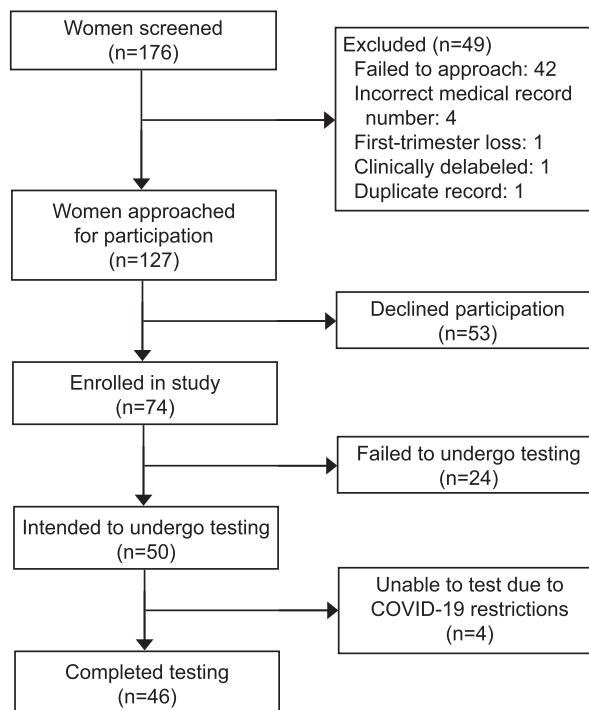


Fig. 2. Schematic of women undergoing penicillin allergy testing in pregnancy at an academic medical center. COVID-19, coronavirus disease 2019.

Desravines. Penicillin Allergy Testing in Pregnancy. Obstet Gynecol 2020.

In multivariate analysis adjusting for age and parity, women with public insurance had decreased odds of undergoing penicillin allergy testing (adjusted odds ratio 0.24, 95% CI 0.08–0.69).

Compared with the nontested group, women who underwent testing were significantly more likely to be married and have private insurance (Table 1). Of the 46 women who underwent testing, the majority (52%, 95% CI 37–67%) did so in the second trimester, between 14 0/7 and 27 6/7 weeks of gestation. Most women (85%, 95% CI 71–94%) had their initial allergic reaction to penicillin more than 10 years previously. As shown in Figure 3, 43 of the 46 women tested (93%, 95% CI 68–100%) had negative results for a penicillin allergy despite 20 (43%) reporting a severe allergy. Of the three women with confirmed penicillin allergies, two failed the 10% oral drug challenge and one had a positive intradermal test result for penicillin G (Table 2).

Two of 46 women (4%, 95% CI 0.5–15%) tested were proven to have a severe penicillin allergy by meeting criteria for anaphylaxis after receiving the 10% amoxicillin drug challenge. Within 30 minutes of receiving amoxicillin, both women initially experienced coughing and chest tightness, with pruritus of

Table 1. Baseline Demographics of Approached Women With Self-Reported Penicillin Allergy From March 2019 to March 2020 at a Single Health Care System

| | Whole Cohort (N=127) | Nontested Group (n=77) | Allergy Tested in Pregnancy (n=50) | P |
|-------------------|----------------------|------------------------|------------------------------------|-------|
| Age (y) | 30 (18–42) | 30 (18–42) | 31 (21–42) | .09 |
| Nulliparous | 55 (44) | 34 (45) | 21 (42) | .71 |
| Married | 73 (57) | 37 (48) | 36 (72) | .02 |
| Private insurance | 83 (66) | 40 (53) | 43 (86) | <.001 |

Data median (range) or n (%) unless otherwise specified.

skin and oropharynx; both experienced an episode of vomiting (at 1 hour and 2 hours postingestion, respectively). Epinephrine (0.3-mg intramuscular injection) and cetirizine (20 mg orally) were promptly administered with initial symptomatic development. One of the two women received an albuterol updraft owing to a history of well-controlled asthma. Vital signs were measured throughout clinical course and remained stable; both women exhibited resolution of symptoms with no further symptomatic development noted on continued monitoring. Both women were discharged home from clinic without additional intervention.

One woman had penicillin allergy confirmed through a positive intradermal test result for penicillin G; owing to associated symptoms of pruritis, she received cetirizine (20 mg orally) and topical hydrocortisone application, with resolution of symptoms. All three women with confirmed penicillin allergies had their initial allergic reaction more than 10 years ago, and all had isolated cutaneous symptoms as their

previous reaction; one reported “rash,” and two noted “hives” as their previous allergic reaction symptoms. In all three women, there were no adverse events noted in subsequent prenatal visits and no need for further monitoring beyond our allergy outpatient visit, including no subsequent need for emergency department visit or hospital admission.

DISCUSSION

We found that 58% of pregnant women with a self-reported penicillin allergy who were approached were willing to undergo penicillin allergy testing. The women who declined participation in the study most often cited difficulty in scheduling the additional visit required or fear of adverse event. In a previously published study, we examined 190 pregnant women who tested positive for group B streptococcus infection over a 3-year period who delivered at term who also had a self-reported penicillin or cefazolin allergy.⁸ Women with low risk allergic-reaction (rash, itching or unknown reaction) represented 58% (99/171) of our penicillin-allergic group and would have been suitable candidates for confirmatory allergy testing.⁸ Penicillin allergy testing during pregnancy is recommended for moderate risk groups too, inclusive of women reporting urticaria.¹⁸ This suggests that up to 94% of women would have been eligible for penicillin allergy testing. Another recent retrospective study of 447 women with a reported penicillin allergy stratified patient allergies to undocumented, low, moderate or high risk.¹ The authors found that 81% of women were candidates for penicillin allergy testing.¹ The implementation of penicillin allergy testing in pregnancy would affect a large proportion of reported allergic women.

We observed systemic reactions (symptoms consistent with anaphylaxis) in 4% (0.5–15%) of women, which is lower than reported in the general population.⁹ We acknowledge that, with a low prevalence of proven (true) penicillin allergy, our sample size may underestimate the true prevalence of systemic reactions. Our participants with positive test results were

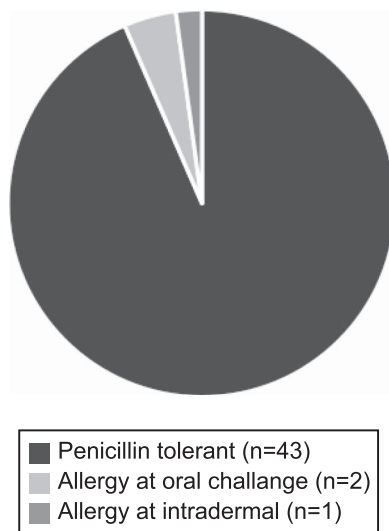


Fig. 3. Testing outcomes in 46 women with a history of self-reported penicillin allergy who underwent allergy testing during pregnancy.

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Table 2. History and Allergy Reaction for Women Who Had Positive Test Results After Undergoing Penicillin Allergy Testing in Pregnancy (n=3/46)

| ID | Gestational Age Range at Testing (wk) | Allergy per Medical Record | Previous Reaction* | Timing of Previous Allergy* | Testing Component When Positive | Intervention Performed | Delivery Type | GBS Status | Antibiotics Administered at Delivery |
|----|---------------------------------------|----------------------------|--------------------|-----------------------------|---------------------------------|----------------------------|---------------|------------|--------------------------------------|
| 1 | 28 0/7–33 6/7 | Amoxicillin | Hives | More than 10 y ago | Oral challenge | Epinephrine and cetirizine | Vaginal | Positive | Vancomycin |
| 2 | 34 0/7–36 6/7 | Amoxicillin | Hives | More than 10 y ago | Skin prick | Cetirizine | Vaginal | Negative | None |
| 3 | 14 0/7–23 6/7 | Penicillin | Rash | More than 10 y ago | Oral challenge | Epinephrine and cetirizine | Vaginal | Positive | Cefazolin |

GBS, group B streptococcus.

* As stated in the allergy questionnaire.

promptly treated by the allergist without apparent negative ramifications for their pregnancies. Under the supervision of an allergist, the rare patient with reactions can be adequately treated to prevent ill-effects of anaphylaxis and maintain safety of this penicillin allergy testing during pregnancy. The primary factor in safely conducting allergy testing in pregnancy is an outpatient facility that is appropriately outfitted with trained personnel and medications for possible serious reaction. As demonstrated in previous studies, our findings suggest that penicillin allergy testing is safe in pregnancy.^{7,15}

Our allergy testing protocol included a graded oral drug challenge that has not been used in previous studies of outpatient-based penicillin allergy testing during pregnancy. This is notable because two of our three participants with positive test results had penicillin allergy confirmed based on reaction to the first step (10% dose) of oral challenge to amoxicillin. In another study, 28 women were referred for allergy testing; 25 (89%) had negative results on skin testing and two had positive results on skin testing (7%).⁷ This protocol may have been insufficient to detect a reaction in our cohort given its lack of an oral challenge. Similarly, in another study of skin testing only, 90% (53/59) of women had negative test results but later, at the time of delivery, two women reported delayed-onset rashes. Applied to our study cohort, this may not have been sufficient to detect 2 of the 3 women who were ultimately deemed allergic. The addition of the oral challenge allows for the confirmation of penicillin tolerance.

This study has its strengths and limitations. An outpatient protocol that could easily be implemented in an obstetrics or allergy clinic serves as strength of this study. A limitation of this study is the observed

rate of systemic reaction in this patient population. Given the rarity of a diagnosis of “anaphylaxis” in this study, we had a wide CI, indicating that rates of anaphylactic allergic reaction may be as high as 15%. Given the small sample size of the study, our safety analysis is limited for rare outcomes such as death. Although no deaths were observed among 46 women, the corresponding 95% CI is 0–8%, which would be an unacceptably high threshold to deem our intervention safe. Larger studies are needed to better understand the contemporary rates of an anaphylactic allergy.

Women reported several barriers over the course of this study. The time commitment of the penicillin allergy testing visit was a deterrent for many of our women, despite the ability to schedule this visit anytime between 14 and 36 weeks of gestation. Owing to constraints of time and distance, we were unable to enroll rural women or those who received prenatal care from health departments or community health centers. Despite the availability of bilingual staff and interpreters, we were able to enroll only one Spanish-speaking woman.

The potential benefits of penicillin allergy testing in pregnant women with a suspected allergy include adherence to guideline-directed antibiotic therapy in the setting of group B streptococcus prophylaxis or cesarean delivery infection prophylaxis and reduction in exposure to broad-spectrum antibiotics. Penicillin allergy testing to document those who truly require alternative treatments supports antibiotic stewardship to mitigate emerging drug resistance. Penicillin allergy testing should ideally occur preconception or at the time of initial allergy reaction. Obstetricians can also use preconception encounters as well as postpartum visits to counsel women regarding the benefits of

penicillin allergy testing. Recent publications as well as the latest Committee Opinion from the American College of Obstetricians and Gynecologists advocate for the consideration of penicillin allergy testing in pregnancy.^{2,3} Given the low incidence of anaphylaxis, this study highlights the ability to perform allergy testing in the outpatient setting. In light of the potential to improve antibiotic stewardship and demonstrated acceptability and feasibility of testing, women with a reported penicillin allergy can undergo allergy testing in pregnancy.

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