Race, socioeconomic status, and response to methotrexate treatment of ectopic pregnancy in an urban population

On the basis of the documented racial disparities in ectopic pregnancy incidence and mortality we hypothesized that African-American women with ectopic pregnancy would be more likely than white women to have treatment failure with methotrexate. In this retrospective cohort study, a racial disparity in methotrexate effectiveness was not found, but a significant relationship between low socioeconomic status and methotrexate failure was demonstrated.

Key Words: Ectopic pregnancy, methotrexate, diagnosis, race, health disparity, socioeconomic status

The incidence of ectopic pregnancy (EP) and its associated mortality represent a persistent racial health disparity in gynecology. According to the most recent estimates from the Centers for Disease Control and Prevention, minority women have a nearly twofold increased incidence of EP and a nearly fourfold greater risk of EP-related mortality than white women (1, 2). This racial divide has been attributed to differential health care access that allows for elaboration of risk factors for EP and delays the diagnosis of incident EPs (1, 3–8). Both gonorrheal and chlamydial infections are more prevalent in samples of African-American women than whites (3–8); the fact that these infections are often asymptomatic (9) suggests that African-American women are likely undertreated relative to whites. The sequelae of increased pelvic infections are reflected in the assisted reproductive technology literature, with numerous reports demonstrating higher proportions of tubal factor infertility in African-American women seeking care and more EPs resulting from treatment compared with white patients (2, 10–12). In addition, population-based studies have demonstrated that self-reported infertility is up to twofold higher in African-American women than whites, which may be attributable in part to tubal damage from pelvic infections (10, 13–15).

Despite the well-documented racial disparities in EP incidence and mortality, there is little extant literature specifically comparing outcomes of medical management of EP by race or ethnicity. Although extensive research has demonstrated methotrexate (MTX) to be highly effective, failure rates have been variable from as low as 4% to as high as 36% depending on the treatment protocol used (16–20). Anticipated poor patient follow-up is a notable contraindication to the administration of MTX for EP treatment (19, 20). Thus, it is plausible to consider that the documented association between race and barriers to health care access (1, 3, 4, 17, 18, 21–24) may increase the risk of MTX failure of EP treatment.

The primary objective of this investigation was to test the hypothesis that African Americans have a higher risk of MTX treatment failure of EP than whites. Socioeconomic status (SES) is known to differ across racial strata and to contribute to health disparities, at times predicting health outcomes more powerfully than race (21, 22, 25). Therefore, an additional aim of this study hypothesis that African Americans have a higher risk of MTX treatment failure of EP than whites. Socioeconomic status (SES) is known to differ across racial strata and to contribute to health disparities, at times predicting health outcomes more powerfully than race (21, 22, 25). Therefore, an additional aim of this study was to test the association between low SES and risk of MTX failure. This investigation focused on patients treated with the two-dose MTX protocol, which was the predominant method of MTX administration in our center during the period studied.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Pennsylvania. Patients evaluated for an EP at the Hospital of the University of Pennsylvania have their clinical data entered into a computerized database (26). Patients treated with MTX were identified through this database, as was clinical information pertinent to our investigation. Additional data were abstracted through queries of electronic medical records (using appropriate ICD-9 codes 633.0–633.9), billing records, and pharmacy data. Data from January 2001 through December 2007 were included.
Self-reported race was captured from all patients registering for medical care. Only those who identified themselves as “African-American/Black” or “White/Caucasian” were included in the investigation. An EP was defined either as an extrauterine pregnancy confirmed on ultrasound examination or as lack of products of conception following dilation and curettage for evaluation of an abnormal pregnancy followed by a postoperative rise in hCG level. Patients receiving intramuscular MTX as a two-dose protocol for treatment of confirmed EP were studied; this protocol is described in detail elsewhere (27). Treatment failure was defined as the need for surgical treatment of EP after the initiation of MTX. Socioeconomic status was captured by insurance status; patients who were confirmed as uninsured or receiving public assistance at the time of treatment were classified as low SES.

Bivariate associations were evaluated with use of relative risks (RRs), Pearson’s χ², or Fisher’s exact test where appropriate. Continuous variables were compared with use of the Wilcoxon rank sum test. Logistic regression was used to create an explanatory model for MTX failure. All analyses were performed with use of STATA software (version 10; StataCorp, College Station, TX).

On the basis of the accrued sample size of 189 subjects, there was 80% power to detect a threefold increase in the risk of MTX failure in African Americans versus whites. This estimate assumes a conservative baseline failure risk of 13% in whites (27) and takes into consideration the assumption that the ratio of African Americans to whites in the study population is 4:1.

RESULTS
One hundred eighty-nine women who received MTX for the treatment of EP were identified. One hundred fifty-one were African American (80%), and 38 (20%) were white. We did not detect an association between race and the decision to pursue medical therapy instead of surgical therapy as primary treatment of EP. Of the patients who received MTX (all protocols considered), 82.6% were African American. Of the patients with EP in our center treated surgically, 90.9% were African American (P = .12).

The overall incidence of MTX treatment failure was 15.3% (29/189). There was no association between African-American race and risk of MTX treatment failure of EP (RR 0.94, 95% confidence interval [CI] 0.76–1.2, P = .56). Compared with insured patients, those with low SES were more likely to have MTX failure (RR 2.4, 95% CI 1.2–4.9, P = .05). Although a higher proportion of African Americans required public assistance than did whites (14.8% and 5.7% respectively), this difference was not statistically significant (P = .25). Nine of the patients treated had a tubal rupture, and the risk was comparable in African-American and white patients (RR 0.88, 95% CI 0.19–4.07, P = .87). The majority of patients with EP received care through the resident clinic service (which treats private, Medicaid, and low-income patients) compared with those who were seen by private practitioners or infertility specialists (78.8%, 2.1%, 19.1% respectively, P < .0001), but this status did not influence risk of treatment failure (P = .7).

Published risk factors for MTX failure were demonstrated in our study population but, in general, were not significantly different across racial or SES strata (Table 1). Higher levels of hCG at the time of MTX administration were associated with MTX failure. History of a prior gestation resulting in EP has been associated with single-dose MTX failure in published reports (28, 29) and was associated with a nearly twofold increased risk of MTX failure in our population (RR 1.94, 95% CI 0.94–3.97, P = .08), a difference that achieved borderline significance. Women with ultrasound evidence of EP were nearly eight times more likely to have MTX fail than those with a nondiagnostic ultrasound examination (RR 7.8, 95% CI 2.8–21.8, P < .0001); African Americans and whites were comparable in the proportions of women with ultrasound confirmation of EP.

A strengthening of the association between low SES and risk of MTX failure (adjusted odds ratio 4.9, 95% CI 1.3–18.3, P = .02), was demonstrated when controlling for race, hCG at the initiation of treatment, history of prior EP, practice type (private, infertility, or resident clinic), and initial ultrasound assessment in a logistic regression model. The association between African-American race and MTX failure remained nonsignificant in the model (adjusted odds ratio 0.46, 95% CI 0.1–2.2, P = .3). There was no evidence of interaction between SES and race on the impact of MTX failure.

DISCUSSION
Our study is the first of which we are aware to specifically compare two-dose MTX effectiveness across racial and SES categories. We demonstrated no disparity in MTX effectiveness by race and found that African Americans and whites in our cohort receiving MTX were comparable with respect to many of the traditional predictors of MTX failure.

We found that patients who were uninsured or required public assistance were nearly five times more likely than those who were insured to have MTX failure. However, low SES was not associated with gestational age at the time of MTX administration, with intervals between follow-up visits after initiation of treatment, or with other predictors of failure (Table 1). It is possible that subtle differences in access were not captured in this analysis or that correlates of low SES other than marginalization from health care resources contributed to the increased risk of failure in this population.

The association of low SES with two-dose MTX failure is novel, contradicting an earlier report by Lewis et al. (30) that did not demonstrate such a relationship. In comparison with our population, the women investigated by Lewis et al. (30) resided in the Southwest and more than 90% of the patients were Latinas, Native American, and non-Hispanic white, primarily receiving single-dose therapy. It is possible that indigent status has differential impact based on the MTX protocol administered, racial and ethnic breakdown of populations treated, and/or geography.

It is possible that we could not detect subtle differences in MTX effectiveness across racial groups because of the sample size of our study. Thus, if there truly is an increased risk of MTX failure in African Americans compared with whites but it is small (less than a threefold increased risk of failure), it could not be appreciated in this sample. Despite this fact, there is consistency between racial groups in predictors of MTX effectiveness, which lends support to our conclusions.

The modern use of MTX for treatment of EP has shifted the paradigm of care dramatically to one that focuses on outpatient...
# TABLE 1
Demographics and predictors of two-dose MTX failure across race and SES.

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Race</th>
<th>SES^a</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Failure (n = 29)</td>
<td>Success (n = 160)</td>
<td>P value</td>
<td>African American (n = 151)</td>
<td>White (n = 38)</td>
<td>P value</td>
<td>Public assistance (n = 20)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>27 (15–43)</td>
<td>27 (16–39)</td>
<td>.7</td>
<td>26 (15–43)</td>
<td>34 (19–43)</td>
<td>.0001</td>
<td>27.5 (18–37)</td>
</tr>
<tr>
<td>Median gravidity (range)</td>
<td>3 (0–7)</td>
<td>3 (0–8)</td>
<td>.95</td>
<td>3 (1–7)</td>
<td>1 (1–14)</td>
<td>&lt;.0001</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Resident clinic patients, % (n)</td>
<td>2.7 (24/29)</td>
<td>78.1 (125/160)</td>
<td>.95</td>
<td>91.4 (138/151)</td>
<td>28.9 (11/38)</td>
<td>&lt;.0001</td>
<td>100 (20/20)</td>
</tr>
<tr>
<td>Infertility patients, % (n)</td>
<td>3.5 (1/29)</td>
<td>1.9 (3/160)</td>
<td>.7b</td>
<td>7.9 (12/151)</td>
<td>63.2 (24/38)</td>
<td>.0001b</td>
<td>0 (0/20)</td>
</tr>
<tr>
<td>Private patients, % (n)</td>
<td>13.8 (4/29)</td>
<td>20 (32/160)</td>
<td>.7b</td>
<td>0.7 (1/151)</td>
<td>7.9 (3/38)</td>
<td>&lt;.0001b</td>
<td>0 (0/20)</td>
</tr>
<tr>
<td>Prior diagnosis of EP, % (n)</td>
<td>27.6 (8/29)</td>
<td>14.4 (23/160)</td>
<td>.08</td>
<td>18.5 (28/123)</td>
<td>7.9 (3/35)</td>
<td>.14</td>
<td>25 (5/20)</td>
</tr>
<tr>
<td>Ultrasound evidence of EP, % (n)</td>
<td>89.3 (25/28)</td>
<td>44.5 (65/146)</td>
<td>&lt;.0001</td>
<td>52.1 (76/146)</td>
<td>50 (14/28)</td>
<td>1.0</td>
<td>57.9 (11/19)</td>
</tr>
<tr>
<td>Median hCG (mIU/mL) at MTX (range)</td>
<td>3,487 (115–16,167)</td>
<td>623 (32–13,041)</td>
<td>&lt;.0001</td>
<td>891 (14–13,041)</td>
<td>483 (30–13,611)</td>
<td>.2</td>
<td>888 (35–6,204)</td>
</tr>
<tr>
<td>Median estimated gestational age at start of MTX, d (range)</td>
<td>41 (19–90)</td>
<td>40.5 (10–87)</td>
<td>.8</td>
<td>40 (10–90)</td>
<td>42 (11–80)</td>
<td>.3</td>
<td>37 (14–61)</td>
</tr>
<tr>
<td>Median days between initial MTX dose and second follow-up visit (range)</td>
<td>7 (2–35)</td>
<td>7 (3–30)</td>
<td>.2</td>
<td>7 (3–35)</td>
<td>7 (3–15)</td>
<td>.3</td>
<td>7 (3–21)</td>
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^a Comparisons do not include women with missing SES data (n = 32).
^b Comparisons of proportions across multiple categories made with use of Fisher’s exact test.
^c Comparisons of categorical variables made with use of Fisher’s exact test.
^d Comparisons do not include women with missing ultrasound data (n = 15).
^e Comparisons of continuous variables made with use of Wilcoxon rank sum test.

therapy. The doctrine of early and rigorous intervention reflects the efforts that have been successful in reducing EP-related morbidity and mortality for all women. Future studies aimed at further re-
solving the relationship between SES and two-dose MTX effectiveness will be critical in eliminating barriers to optimal treatment outcomes for vulnerable women.

REFERENCES