Published in final edited form as:

Fertil Steril. 2010 December ; 94(7): 2789–2792. doi:10.1016/j.fertnstert.2010.06.062.

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

Samantha F. Butts, M.D., M.S.C.E.^{a,b}, Erika Gibson, M.D.^a, Mary D. Sammel, Sc.D.^b, Alka Shaunik, M.D.^a, Brianna Rudick, M.D.^c, and Kurt Barnhart, M.D., M.S.C.E.^{a,b}

^a Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania

^b Center for Clinical Epidemiology and Biostatistics, Philadelphia, Pennsylvania

^c Department of Obstetrics and Gynecology, University of Southern California, Keck School of Medicine, Los Angeles, California

Abstract

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.

Keywords

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).

2010 by American Society for Reproductive Medicine.

Reprint requests: Samantha F. Butts, M.D., M.S.C.E., Penn Fertility Care, Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, 3701 Market St., Suite 810, Philadelphia, PA 19104 (FAX: 215-349-5512; sbutts@obgyn.upenn.edu)..

S.F.B. has nothing to disclose. E.G. has nothing to disclose. M.D.S. has nothing to disclose. A.S. has nothing to disclose. B.R. has nothing to disclose. K.B. has nothing to disclose.

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 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 after 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 χ^2 , 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 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 resolving the relationship between SES and two-dose MTX effectiveness will be critical in eliminating barriers to optimal treatment outcomes for vulnerable women.

Acknowledgments

Supported by National Institutes of Health grant RO1-HD-36455-01A1.

REFERENCES

1. Goldener TE, Lawson HN, Xia Z, Atrash HK. Surveillance for ectopic pregnancy—United States, 1970–1989. *MMWR Morb Mortal Wkly Rep* 1993;42:73–82.
2. Clayton HB, Schieve LA, Peterson HB, Jamieson DJ, Reynolds MA, Wright VC. Ectopic pregnancy risk with assisted reproductive technology procedures. *Obstet Gynecol* 2006;107:595–604. [PubMed: 16507930]
3. Bernstein J. Ectopic pregnancy: a nursing approach to excess risk among minority women. *J Obstet Gynecol Neonatal Nurs* 1995;24:803–10.
4. Sewell CA, Cundiff GW. Trends in inpatient treatment of tubal pregnancies in Maryland. *Am J Obstet Gynecol* 2002;186:404–8. [PubMed: 11904598]
5. Saraiya M, Berg CJ, Shulman H, Green CA, Atrash HK. Estimates of the annual number of clinically recognized pregnancies in the US. *Am J Epidemiol* 1999;149:1025–9. [PubMed: 10355378]
6. Datta SD, Sternberg M, Johnson RE, Berman S, Papp JR, McQuillan G, et al. Gonorrhea and chlamydia in the United States among persons 14 to 39 years of age, 1999 to 2002. *Ann Intern Med* 2007;147:89–96. [PubMed: 17638719]
7. Laumann EO, Youm Y. Racial/ethnic group differences in the prevalence of sexually transmitted diseases in the United States: a network explanation. *Sex Transm Dis* 1999;26:250–61. [PubMed: 10333277]
8. Racial disparities in nationally notifiable diseases—United States, 2002. *MMWR Morb Mortality Wkly Rep* 2005;54:9–11.
9. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. *Prev Med* 2003;36:502–9. [PubMed: 12649059]
10. Seifer DB, Frazier LM, Grainger DA. Disparity in assisted reproductive technologies outcomes in black women compared with white women. *Fertil Steril* 2008;90:1701–10. [PubMed: 17980873]
11. Seifer DB, Zackula R, Grainger DA. Trends of racial disparities in assisted reproductive technology outcomes in black women compared with white women: Society for Assisted Reproductive Technology 1999 and 2000 vs. 2004–2006. *Fertil Steril* 2010;93:626–35. [PubMed: 19368916]

12. Fujimoto VY, Luke B, Brown MB, Jain T, Armstrong A, Grainger DA, Hornstein MD. Racial and ethnic disparities in assisted reproductive technology outcomes in the United States. *Fertil Steril* 2010;93:382–90. [PubMed: 19081561]
13. Bitler M, Schmidt L. Health disparities and infertility: impacts of state-level insurance mandates. *Fertil Steril* 2006;85:858–65. [PubMed: 16580365]
14. Stephen EH, Chandra A. Declining estimates of infertility in the United States 1982–2002. *Fertil Steril* 2006;86:516–23. [PubMed: 16952500]
15. Butts SF, Seifer DB. Racial and ethnic differences in reproductive potential across the lifecourse. *Fertil Steril* 2010;93:681–90. [PubMed: 19939362]
16. Barnhart KT. Ectopic pregnancy. *N Engl J Med* 2009;361:379–87. [PubMed: 19625718]
17. Thoen LD, Crenin MD. Medical treatment of ectopic pregnancy with methotrexate. *Fertil Steril* 1997;68:727–30. [PubMed: 9341620]
18. Bixby S, Tello R, Kulihowska E. Presence of a yolk sac on transvaginal sonograph is the most reliable predictor of single-dose methotrexate treatment failure in ectopic pregnancy. *J Ultrasound Med* 2005;24:591–8. [PubMed: 15840789]
19. Practice Committee of the American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy. *Fertil Steril* 2008;90:S206–12. [PubMed: 19007632]
20. Medical management of ectopic pregnancy. ACOG Practice Bulletin No. 94. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2008;111:1479–85. [PubMed: 18515537]
21. Williams DR. Race and health: basic questions, emerging directions. *Ann Epidemiol* 1997;7:322–33. [PubMed: 9250627]
22. Williams DR, Rucker TD. Understanding and addressing racial disparities in health care. *Health Care Financ Rev* 2000;21:75–90. [PubMed: 11481746]
23. Kelley E, Moy E, Dayton E. Health care quality and disparities: lessons from the first national reports. *Med Care* 2005;43:11–2. [PubMed: 15746585]
24. US Department of Health and Human Services. Healthy People 2010: National Health Promotion and Disease Prevention Objectives, January 2000. [July 26, 2010]. Available at: <http://www.healthypeople.gov/>.
25. Duncan GJ, Daly MC, McDonough P, Williams DR. Optimal indicators of socioeconomic status for health research. *Am J Public Health* 2002;92:1151–7. [PubMed: 12084700]
26. Barnhart KT, Mennuti MT, Benjamin I, Jacobson S, Goodman D, Coutifaris C. The prompt diagnosis of ectopic pregnancy in an emergency department setting. *Obstet Gynecol* 1994;84:1010–5. [PubMed: 7970455]
27. Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of “2-dose” regimen of methotrexate to treat ectopic pregnancy. *Fertil Steril* 2007;87:250–6. [PubMed: 17097649]
28. Laibl V, Takacs P, Kang J. Previous ectopic pregnancy as a predictor of methotrexate failure. *Int J Gynecol Obstet* 2004;85:177–8.
29. Lipscomb GH, Givens VA, Meyer NL, Bran D. Previous ectopic pregnancy as predictor of failure of systemic methotrexate therapy. *Fertil Steril* 2003;81:1221–4. [PubMed: 15136080]
30. Lewis C, Martinez C, Rogers R. Barriers to healthcare and protocol based treatment of ectopic pregnancy. *J Reprod Med* 2005;50:8–12. [PubMed: 15730166]

TABLE 1

Demographics and predictors of two-dose MTX failure across race and SES.

	All subjects			Race		SES ^a	
	Failure (n = 29)	Success (n = 160)	P value	African American (n = 151)	White (n = 38)	Public assistance (n = 20)	Insured (n = 137)
Median age, y (range)	27 (15–43)	27 (16–39)	.7	26 (15–43)	34 (19–43)	27.5 (18–37)	27 (15–43)
Median gravidity (range)	3 (0–7)	3 (0–8)	.95	3 (1–7)	1 (1–14)	3 (1–6)	2 (0–8)
Resident clinic patients, % (n)	2.7 (24/29)	78.1 (125/160)		91.4 (138/151)	28.9 (11/38)	100 (20/20)	74.4 (102/137)
Infertility patients, % (n)	3.5 (1/29)	1.9 (3/160)		7.9 (12/151)	63.2 (24/38)	0 (0/20)	2.2 (3/137)
Private patients, % (n)	13.8 (4/29)	20 (32/160)	.7 ^b	0.7 (1/151)	7.9 (3/38)	0 (0/20)	23.4 (32/137)
Prior diagnosis of EP, % (n)	27.6 (8/29)	14.4 (23/160)	.08	18.5 (28/123)	7.9 (3/35)	25 (5/20)	16.8 (23/137)
Ultrasound evidence of EP, % (n)	89.3 (25/28)	44.5 (65/146)	< .0001	52.1 (76/146)	50 (14/28)	57.9 (11/19)	50.8 (63/124)
Median hCG (mIU/mL) at MTX (range)	3,487 (115–16,167)	623 (32–13,041)	< .0001	891 (14–13,041)	483 (30–13,611)	888 (35–6,204)	769 (14–13,611)
Median estimated gestational age at start of MTX, d (range)	41 (19–90)	40.5 (10–87)	.8	40 (10–90)	42 (11–80)	37 (14–61)	40.5 (10–90)
Median days between initial MTX dose and second dose (range)	4 (1–32)	4 (1–21)	.2	4 (1–21)	4 (1–29)	4 (2–29)	4 (1–15)
Median days between initial MTX dose and second follow-up visit (range)	7 (2–35)	7 (3–30)	.2	7 (3–35)	7 (3–15)	7 (3–21)	7 (3–35)

^aComparisons do not include women with missing SES data (n = 32).

^bComparisons of proportions across multiple categories made with use of Fisher's exact test.

^cComparisons of categorical variables made with use of Fisher's exact test.

^dComparisons do not include women with missing ultrasound data (n = 15).

^eComparisons of continuous variables made with use of Wilcoxon rank sum test.