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An estrogen receptor genetic polymorphism and the risk of primary and secondary recurrent spontaneous abortion

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OBJECTIVE: A case-control study was undertaken to assess the association between an estrogen receptor gene variant and the risk of recurrent spontaneous abortions.
STUDY DESIGN: The frequency of the estrogen receptor gene variant in blood lymphocyte deoxyribonucleic acid and other selected maternal characteristics was compared among 60 primary recurrent aborters, 61 secondary recurrent aborters, and 43 women who had had at least two live births but no spontaneous abortions.
RESULTS: No association was evident between the estrogen receptor gene variant and the risk of either primary or secondary recurrent abortion. There were data suggesting that primary recurrent aborters in particular were more likely to report a family history of recurrent abortion and a family history of breast cancer.
CONCLUSIONS: These findings indicate that the estrogen receptor polymorphism is not a genetic marker for recurrent spontaneous abortions. Therefore, as suggested by previous investigations, this polymorphism appears to be a marker for breast cancer risk only among the subgroups who have had a history of repeated abortions. (Am J Obstet Gynecol 1994;171:1579-84.)

Key words: Abortion, polymorphism, receptors, estrogen

The risk factors for primary and secondary recurrent abortions are largely unknown.[1, 2] Lehrer et al.[3] recently reported that among women with estrogen receptor–positive breast cancer those carrying an estrogen receptor gene variant had a significantly higher frequency of previous spontaneous abortions than did those without the genetic variant. A subsequent study showed that this association was not present among women with estrogen receptor–negative breast cancer or in older women without breast cancer.[4] To confirm that this association is not independent of breast cancer, we conducted a case-control study comparing the frequency of the estrogen receptor variant among women who were primary recurrent aborters, secondary recurrent aborters, and controls. In this investigation we also evaluated other potential risk factors for repeated abortions.

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Material and methods

The study population was drawn from patients seen at four private physician offices affiliated with Mount Sinai Medical Center from September 1991 through

Table I. Distribution of variant estrogen receptor gene and selected maternal characteristics for primary and secondary recurrent aborters and controls

	Primary recurrent aborters (n = 60)		*Secondary recurrent aborters (n = 61)*		*Controls (n = 43)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Variant estrogen receptor gene	6	10.0	6	9.8	6	14.0
Race or ethnicity						
Non-Hispanic white	55	91.7	55	90.2	34	79.1
Other	5	8.3	6	9.8	9	11.9
Maternal age						
< 30 yr	10	16.7	11	18.0	15	34.9
30-34 yr	20	32.5	21	36.2	17	39.5
≥ 35 yr	30	50.0*	29	47.5†	11	25.6
Age at menarche						
< 12 yr	6	10.2	6	10.5	3	7.1
12-13 yr	38	64.4	43	75.4	30	71.4
≥ 14 yr	15	25.4	8	14.0	9	21.4
Family history of recurrent abortion	12	20.0	11	18.0	4	9.3
Family history of breast cancer	11	18.3	8	13.1	3	7.0
Cigarette smoking‡						
No	55	94.8	59	98.3	42	100.0
Yes	3	5.2	1	1.7	0	0.0
Coffee consumption‡						
No	45	77.6	42	70.0	29	69.0
Yes	13	22.4	18	30.0	13	31.0
Intake of caffeinated soda‡						
No	55	94.8	49	81.7	33	80.5
Yes	3	5.2	11	18.3	8	19.5

*$p = 0.007$, compared with controls.
†$p = 0.014$, compared with controls.
‡Information was missing from a few participants.

March 1993. The primary recurrent aborter group comprised women who had had two or more clinically recognized spontaneous abortions but no live births. Secondary recurrent aborters represented women who had had two or more spontaneous abortions and one or more live births. The controls were women who had had at least two live births and no spontaneous abortions. A total of 60 primary recurrent aborters, 61 secondary recurrent aborters, and 43 controls agreed to provide an extra blood sample at the time of routine blood drawing and to respond to a brief telephone interview. This study was approved by the Institutional Review Board of our medical center, and informed consent was obtained from all patients.

Deoxyribonucleic acid (DNA) was extracted from the blood samples by standardized techniques, as previously described.[5] The polymerase chain reaction was used to amplify genomic DNA around the polymorphic region of the estrogen receptor gene on chromosome 6q, followed by allele-specific oligonucleotide hybridization. The synthetic oligonucleotides used for hybridization were the wild type sequence 5′tctgaggCtgcGgcgttcgg3′ and the variant sequence 5′ctgaggTtgcCgcgttcgg3′, using hybridization and washing conditions previously described.[5] Because the variant allele was located in the B domain of the protein, this variant is referred to as the B′ allele to distinguish it from the more common allele (the B allele). In the course of these studies we[6] and others[7] determined that our originally reported sequence for the B′ allele[8] was in error in that the correct sequence lacked the C-T change and had only the G-C change. This meant that our screening with the oligonucleotide probes could correctly identify individuals carrying the B′ allele, because the variant oligo differed from the wild type by two nucleotides and could therefore easily be separated from DNA of BB homozygotes. However, this combination of probes would not allow us to distinguish BB′ heterozygotes from B′B′ homozygotes. Therefore polymerase chain reaction amplification products from individuals originally scored as having the B′ allele were reevaluated by means of an oligonucleotide probe with the corrected sequence 5′tctgaggctgcCcgcgttcgg3′. Hybridization and washing conditions were similar to those previously described,[5] except that the final stringent wash used 6 × saline–sodium citrate buffer at 65° C for 30 minutes.

Information obtained from the telephone interview included sociodemographic characteristics; obstetric, gynecologic, and medical history; height and prepregnancy or current weight if the patient was not pregnant or had not been recently delivered; family history of recurrent abortions; breast and reproductive cancers; substance use and abuse; and employment. The medi-

cal data were confirmed by review of the patients' medical records. The distribution of discrete variables among the three groups was assessed by χ^2 test. Where differences among the three groups were discerned, each abortion group was compared with the controls. Fisher's exact test was used instead of the χ^2 test in the case of small cell counts. Analysis of variance, Student t test, or, where applicable. Wilcoxon rank-sum test was used to assess continuous variables. A p value <0.05 was considered statistically significant. Odds ratios and 95% confidence intervals were also calculated, and logistic regression analysis was used to adjust for possible confounding variables.

Results

Table I shows the distribution of the variant estrogen receptor gene and selected maternal characteristics for the primary and secondary recurrent aborters and the controls. It may be seen that the frequency of the variant estrogen receptor gene (B′ allele) did not differ among the three groups. Because the frequency of women carrying the B′ allele was slightly higher among the controls (14.0%) than among either the primary (10.0%) or the secondary recurrent aborters (9.8%), the odds ratios were <1.0 (0.69 and 0.67, respecitvely). All those with the variant gene were heterozygous except for one control woman who was homozygous for the variant. The identification of DNA samples with each of the three genotypes (BB, BB′, and B′B′) is shown in Fig. 1.

When the characteristics of the three groups of women were compared irrespective of the estrogen receptor B genotype, the two case groups had a slightly higher proportion of non-Hispanic whites than did the controls, but none of the comparisons was significant. The cases were, however, significantly older than the controls. No consistent differences were seen for age at menarche. Both case groups reported a higher frequency of family history of recurrent abortions, but the differences were not significant (odds ratio 2.4, 95% confidence interval 0.7 to 8.1 when primary recurrent aborters were compared with the controls). A family history of breaast cancer was also more common among the case groups than the controls, but the association did not reach significance (odds ratio 3.0, 95% confidence interval 0.8 to 11.7 for primary recurrent aborters vs controls). These odds ratios were not materially changed in logistic regression analysis controlling for age and race and ethnicity. No differences were observed for a family history of either ovarian or uterine cancer, but the reported numbers were small (data not shown). Cigarette smoking was uncommon in all three groups, whereas caffeine consumption was lower among the primary recurrent aborters than among either the secondary recurrent aborters or the controls. Analysis based on number of cups of caffeinated coffee and cans of caffeinated soda consumed showed similar results.

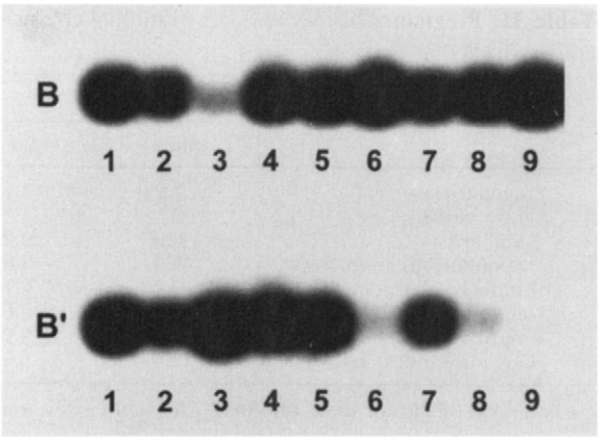

Fig. 1. Identification of BB, BB′, and B′B′ genotypes by allele-specific oligonucleotide hybridization of polymerase chain reaction–amplified DNA. Polymerase chain reaction–amplified genomic DNA samples from women who were found to carry B′ allele by our previous method of analysis[3] (see Material and methods) were tested for homozygosity of B′ allele. After polymerase chain reaction amplification around the polymorphic region[3] replicate aliquots of DNA were electrophoretically fractionated on 2% agarose gels. Ethidium bromide staining was used to confirm equal loading of replicate samples (data not shown). Samples were transferred to nylon membranes and probed with phosphorus 32–labeled oligonucleotides for B and corrected B′ sequence (see Material and methods). After hybridization and stringent washing filters were exposed to x-ray film and intensifying screens for several hours. Upper filter was tested with B probe and lower filter with B′ probe. *Lanes 1, 2, 4, 5,* and 7, BB′ heterozygotes; *lane 3,* B′B′ homozygote; *lanes 6, 8,* and *9* samples known to be BB homozygotes by previous analysis.

When compared with controls (Table II), the mean number of pregnancies was only marginally higher for the primary recurrent aborters ($p = 0.08$) but significantly higher for the secondary recurrent aborters ($p < 0.001$). Of the primary recurrent aborters, 24 reported two spontaneous abortions, 18 reported three, nine reported four, and another nine reported five or more. Of the secondary recurrent aborters, 29 reported two, 16 reported three, nine reported four, and seven reported five or more spontaneous abortions. As a result, the mean number of spontaneous abortions was slightly higher for the primary compared with the secondary recurrent aborters. The number of stillbirths and induced abortions did not differ markedly among the three groups. The primary and to a lesser extent the secondary recurrent aborters tended to be shorter and to weigh less than the controls, but no significant differences were observed in body mass index.

Various gynecologic and medical complications, including in utero diethylstilbestrol exposure and history of pelvic inflammatory disease, hypothyroidism, or infertility, and in vitro fertilization in the most recent

Table II. Pregnancy history and constitutional characteristics of primary and secondary recurrent aborters and controls

	Primary (n = 60)		*Secondary (n = 61)*		*Controls (n = 43)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Pregnancies	3.9	2.7	5.6	3.1	3.1	1.7
Live births	0		2.4	2.8	2.7	1.7
Stillbirths	0.05	0.2	0.03	0.2	0	
Spontaneous abortions	3.5	2.6	3.0	1.4	0	
Induced abortions	0.2	0.7	0.2	0.5	0.4	0.8
Height	63.5	2.6	63.8	2.5	64.5	3.0
Weight*	128.4	19.2	136.1	23.4	139.1	29.6
Body mass index (kg/m^2)	22.5	3.1	23.5	4.1	23.5	4.8

*Pregravid weight for those who were pregnant or who were recently delivered at time of blood sampling.

Table III. Frequency of variant estrogen receptor gene by selected characteristics among cases and controls

	Primary recurrent aborters		*Secondary recurrent aborters*		*Controls*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Race or ethnicity						
Non-Hispanic white	5	9.1	6	10.9	5	14.7
Other	1	20.0	0	0.0	1	11.1
Maternal age						
< 35 yr	0	0.0	4	12.5	5	15.6
≥ 35 yr	6	20.0*	2	6.9	1	9.1
History of infertility						
No	4	8.2	5	9.3	5	12.5
Yes	2	18.2	1	14.3	1	33.3
In vitro fertilization						
No	5	8.8	6	9.8	5	11.9
Yes	1	50.0	0	0.0	1	100.0
Family history of recurrent abortion						
No	4	8.7	4	8.2	6	16.2
Yes	2	16.7	2	18.2	0	0.0
Family history of breast cancer						
No	5	10.6	5	9.4	6	15.4
Yes	1	9.1	1	12.5	0	0.0
Family history of ovarian or uterine cancer						
No	6	10.5	6	10.2	5	12.2
Yes	0	0.0	0	0.0	1	16.7
Overall	6	10.0	6	9.8	6	14.0

*$p < 0.05$.

pregnancy tended to be more common among the primary recurrent aborters compared with the controls, but none of the differences reached statistical significance (data not shown). A history of gestational diabetes ($n = 5$) was only reported among the secondary recurrent aborters.

The association between the various maternal characteristics and the presence of the B′ allele was also assessed. The women with the B′ allele were taller ($p = 0.052$) and slightly heavier ($p = 0.08$) than those who did not carry the variant. As a result, no association was evident for the body mass index. A higher proportion of those with the B′ allele, compared with those with the BB allele, had conceived as a result of in vitro fertilization (odds ratio 18.0, 95% confidence interval 1.5 to 209.7), but this finding was based on only three in vitro fertilization pregnancies. Those with the B′ allele also tended to be more likely to consume coffee (odds ratio 2.4, 95% confidence interval 0.9 to 6.4). None of the other characteristics assessed, including the trimester of the spontaneous abortion, varied according to the status of the estrogen receptor gene polymorphism.

When the association between the estrogen receptor B′ allele and maternal characteristics were stratified by case-control status (Table III), the frequency of the B′ allele was significantly increased among the primary recurrent aborters ≥35 years old compared with younger women ($p = 0.02$). Those among the primary recurrent aborters who had the variant allele were also significantly older than those among the controls who had the variant ($p = 0.015$). No significant age difference ($p = 0.09$) was seen among the women with the BB allele when the primary recurrent aborters were

compared with the controls. This suggests that there may be an interaction among maternal age, the presence of the B′ allele, and the risk of primary recurrent abortion. However, this is based on small numbers, and a similar interaction was not evident among the secondary recurrent aborters. The frequency of the B′ allele was also higher among the primary and secondary recurrent aborters who had a family history of recurrent abortions compared with those who did not have such a history, but these differences did not reach statistical significance.

Comment

These data provide no convincing evidence that the variant genotype increases the risk of either primary or secondary recurrent abortions. Taylor et al.[9] recently reported the results of a case-control study of 29 women who had had two or more spontaneous abortions and 29 women with no spontaneous abortions. Although the reported odds ratio was elevated (1.8), it was not significant (95% confidence interval 0.3 to 11.0) and was substantially lower than the fivefold relative risk based on the original report for breast cancer patients by Lehrer et al.[3] Taylor et al.[9] also calculated that a fivefold relative risk would have appeared as an odds ratio of 25 in their case-control study. Power calculations for our study indicated that we had 80% power for detecting an odds ratio of 3.0 in comparing either of the case groups with the controls. In addition to the larger sample size, our study incorporated both primary and secondary recurrent aborters, whereas the findings by Taylor et al.[9] were restricted to secondary recurrent aborters.

We found some suggestive data that recurrent aborters were more likely to report a family history of recurrent abortion. Although this finding may reflect greater knowledge of the pregnancy histories of relatives among women with recurrent abortions, it is consistent with the findings of two previous studies.[2, 10]

The finding that the primary recurrent aborters in particular were more likely to report a family history of breast cancer was more unexpected. We are unaware of any studies of a family history of breast cancer as a risk factor for spontaneous abortion. However, several studies have examined the occurrence of spontaneous abortion as a risk factor for breast cancer. Although these studies have not produced any consistent findings,[11, 12] two recent studies that examined the combination of a family history of breast cancer and history of spontaneous abortions found an elevated risk of breast cancer.[13, 14] More specifically, Andrieu et al.[13] found that the odds ratio for breast cancer was 1.4 for women with a family history of breast cancer and no spontaneous abortions but 3.8 for women with a family history and two or more spontaneous abortions. It is possible that familial breast cancer and the occurrence of spontaneous abortion may involve the same biologic pathways. Alternatively, term pregnancies may be protective against the development of breast cancer in women who have a family history of breast cancer.

With regard to other risk factors for recurrent abortion, it is not surprising that the cases were significantly older than the controls, because it is well established that the risk of spontaneous abortion increases with maternal age.[15] No associations were apparent for age at menarche, body mass index, cigarette smoking, and caffeine consumption. Although some previous studies found an increased risk of spontaneous abortion with early age at menarche,[2, 16] others found an association with both early and late menarche,[17] inconsistent results,[18] or no association.[19] More consistent are previous reports of a positive association between cigarette smoking and risk of spontaneous abortion. However, the overall frequency of cigarette smoking was very low in the current study. Previous studies found no association for body mass index.[13] A recent study found a strong association between caffeine intake during pregnancy and fetal loss,[20] but other studies have reached inconsistent results.[2, 21-24]

Although the current sample size was insufficient for ruling out a moderate association with the estrogen receptor gene variant, selection bias is unlikely to have affected our results, because the study participants were unaware of their estrogen receptor status at recruitment. These findings, and those by Taylor et al.,[9] indicate that the estrogen receptor B′ allele is not a genetic marker for an increased risk of recurrent spontaneous abortion. Rather, as suggested by previous investigations by Lehrer et al.,[3, 4] this polymorphism appears to be a marker for breast cancer risk among the subgroup with a history of repeated abortions.

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Single injection of methotrexate for treatment of ectopic pregnancies

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OBJECTIVE: Our purpose was to evaluate the efficacy of single-dose methotrexate as a treatment option for ectopic pregnancies.

STUDY DESIGN: Patients were recruited from a tertiary teaching hospital setting. They had (1) a gestational sac <3.5 cm, (2) no fetal cardiac activity, and (3) no significant pelvic pain or signs consistent with hemoperitoneum. Patients excluded were those who did not desire future fertility or who had evidence of renal or liver disease. Sixty-one patients meeting these criteria were selected and treated with a single intramuscular injection of methotrexate at a dosage of 50 mg/m^2.

RESULTS: Of the 61 patients treated, 16 required a second injection and nine required surgical intervention. Fifty-two (85%) were successfully treated as outpatients with methotrexate alone.

CONCLUSION: Nonsurgical treatment of ectopic pregnancies with single-dose methotrexate is an option for some patients, but more studies are needed to establish the safety, efficacy, and effect on fertility. (Am J Obstet Gynecol 1994;171:1584-7.)

Key words: Ectopic pregnancy, methotrexate, single injection

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Ectopic pregnancy is a leading cause of infertility and pregnancy-related morbidity in the United States, and its occurrence continues to be on the rise. In 1980 there were 52,200 cases of ectopic gestation in the United States, and in 1987 the number reached 88,000 cases (equivalent to 1 in 60 reported pregnancies) as reported to the Centers for Disease Control.[1, 2] With this increasing incidence comes increasing infertility, mor-