Abortion, Changed Paternity, and Risk of Preeclampsia in Nulliparous Women

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A prior birth confers a strong protective effect against preeclampsia, whereas a prior abortion confers a weaker protective effect. Parous women who change partners in a subsequent pregnancy appear to lose the protective effect of a prior birth. This study (Calcium for Preeclampsia Prevention Trial, 1992–1995) examines whether nulliparous women with a prior abortion who change partners also lose the protective effect of the prior pregnancy. A cohort analysis was conducted among participants in this large clinical trial of calcium supplementation to prevent preeclampsia. Subjects were nulliparous, had one prior pregnancy or less, delivered after 20 weeks’ gestation, and were interviewed at 5–21 weeks about prior pregnancies and paternity. Women without a history of abortion served as the reference group in logistic regression analyses. Women with a history of abortion who conceived again with the same partner had nearly half the risk of preeclampsia (adjusted odds ratio = 0.54, 95 percent confidence interval: 0.31, 0.97). In contrast, women with an abortion history who conceived with a new partner had the same risk of preeclampsia as women without a history of abortion (adjusted odds ratio = 1.03, 95 percent confidence interval: 0.72, 1.47). Thus, the protective effect of a prior abortion operated only among women who conceived again with the same partner. An immune-based etiologic mechanism is proposed, whereby prolonged exposure to fetal antigens from a previous pregnancy protects against preeclampsia in a subsequent pregnancy with the same father.

AOR, adjusted odds ratio; CI, confidence interval; CPEP, Calcium for Preeclampsia Prevention.

The strongest protective factor for preeclampsia is a prior birth, suggesting that immune tolerance may play an etiologic role in this hypertensive disorder of pregnancy. Over 40 years ago, MacGillivray (1) reported that a prior abortion provided a measure of protection nearing but not equivalent to that of a completed pregnancy. Subsequent studies of the effect of abortion on the risk of preeclampsia were relatively few and provided inconsistent findings (2). More recent studies limited to nulliparous women, however, have been consistent, suggesting that a prior abortion of any type may protect against preeclampsia (3–5).

Preeclampsia has been hypothesized to have an immune-based etiology, whereby prolonged exposure to paternal sperm through sexual intercourse or fetal antigens through a previous pregnancy may be protective (6–8). In support of this hypothesis, studies have found that reproductive practices that minimize exposure to sperm are associated with an increased risk of preeclampsia. These practices include use of barrier contraception (9, 10), nonpartner donor insemination (11, 12), and short duration of sexual cohabitation with the father before conception (13). Moreover, an accumulating and consistent collection of studies suggests that the
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Definitions of hypertension and proteinuria

Blood pressure measurements at all clinic sites were taken according to a standardized published protocol (21), and all urine specimens were assessed for protein by dipstic. Pregnancy-associated hypertension was defined by the occurrence of two or more diastolic blood pressure measurements of at least 90 mmHg, measured 4–168 hours apart, with the first elevated blood pressure occurring after 20 weeks’ gestation up to 24 hours after delivery. Proteinuria was defined by the presence of at least one of the following criteria: ≥300 mg of protein in a 24-hour urine measurement, two or more random urine specimens of at least “1+ protein” (300 mg/liter) taken 4–168 hours apart, or a single urine sample with a protein/creatinine ratio of at least 0.35 mg/mg or containing at least “2+ protein” (1,000 mg/liter) by dipstick. Dipstick measurements of 1+ or greater were confirmed with a clean-catch, midstream urine sample. Urine specimens were collected by catheter after rupture of the membranes or in the presence of vaginitis. Preeclampsia was defined as pregnancy-associated hypertension in the presence of proteinuria. Severe preeclampsia was classified by the presence of severe pregnancy-associated hypertension or severe pregnancy-associated proteinuria. Severe pregnancy-associated hypertension was defined as a diastolic blood pressure of 110 mmHg or greater on at least two occasions at least 4 hours apart or on one occasion if antihypertensive therapy was administered. Hypertension with unexplained oliguria, pulmonary edema, or thrombocytopenia was also classified as severe pregnancy-associated hypertension. Severe proteinuria was defined with a 24-hour urine sample containing ≥3.5 g of protein or two urine samples of “3+ protein” (3,000 mg/liter) or greater taken at least 4 hours apart. The syndrome of hemolysis, elevated liver enzymes, and low platelets and eclampsia was also categorized as severe preeclampsia.

Study subjects

Each subject was interviewed in person to obtain data on demographics, anthropometric characteristics, and pregnancy history of induced abortion, spontaneous abortion, and ectopic and molar pregnancies. Paternity of the prior pregnancy was ascertained as being the same or different from the index pregnancy with the question, “Is this the first pregnancy with this father?” Data on the gestational length (completed weeks) and outcome of each prior pregnancy were also obtained from the study subjects.

Information on the interpregnancy interval was not collected. In addition, the paternity of previous pregnancies beyond the first was not ascertained; therefore, we restricted our analysis to subjects who had no more than one pregnancy prior to the index pregnancy.

In the CPEP Trial, daily maternal calcium supplementation did not alter blood pressure or the occurrence of preeclampsia or gestational hypertension (21); therefore, for this secondary analysis we combined women who had received either calcium or placebo supplements. Analysis for the present study was restricted to the 4,314 women followed to at least 20 weeks’ gestation and for whom complete
outcome data were available. Of these, 247 subjects had had two or more prior abortions, and paternity information was missing for three women, leaving a total of 4,064 eligible study subjects for the present analysis (3,242 primigravidas and 822 women with one prior pregnancy).

Statistical analyses

The present analysis was designed to determine if subjects with a history of one abortive pregnancy outcome (i.e., induced or spontaneous abortion, molar or ectopic pregnancy) are at decreased risk of preeclampsia or pregnancy-associated hypertension in the subsequent pregnancy compared with primiparous women, according to whether paternity changed. Not infrequently, preeclampsia is misclassified as pregnancy-associated hypertension and vice versa, particularly in studies utilizing birth registry or hospital discharge diagnosis data (23). Because the CPEP Trial conducted active surveillance to identify women with these two diagnoses and utilized standard case definitions, it is of value to present the results for both outcomes.

Univariate analyses were performed to examine the frequency distributions of maternal characteristics (e.g., age, body mass index, smoking status) stratified by the occurrence and type of hypertension during pregnancy, abortion history (yes, no), and change in paternity (yes, no). Maternal characteristics among women in the three exposure groups (i.e., primigravidas, history of abortion with same father, history of abortion with a different father) were compared using the Wilcoxon two-sample test (for continuous variables) or the chi-square test (for categorical data). Crude odds ratios and 95 percent confidence intervals for the risk of preeclampsia and pregnancy-associated hypertension, with respect to history of abortion or paternity status, were computed using a reference group composed of women pregnant for the first time.

Adjusted odds ratios were computed using a multiple logistic regression model, which included potential confounding factors. The variables evaluated for confounding included the following: clinical center (Albuquerque, Birmingham, Cleveland, Memphis, Portland); maternal age at enrollment (<17, 18–19, 20–22, 23–24, 25–29, ≥30 years); prepregnancy body mass index (<19.8, 19.8–25.9, 26.0–29.9, 30.0–34.9, ≥35.0 kg/m²); race/ethnicity (non-Hispanic White, Hispanic White, Black, other/unknown races); private insurance status (yes, no); smoked cigarettes during pregnancy (yes, no); type of pregnancy loss (induced abortion or spontaneous pregnancy loss, i.e., spontaneous abortion, ectopic (n = 26), or molar pregnancy (n = 4)); and gestational length of the prior pregnancy (completed weeks).

Confounding factors were identified as variables having at least a marginally significant association (p < 0.2 by chi-square test) with preeclampsia or pregnancy-associated hypertension separately and with history of abortion and paternity status (no prior pregnancy, one prior pregnancy with the same father, and one prior pregnancy with a change in paternity).

As an indirect means of evaluating for an effect of interpregnancy interval, we stratified the final logistic regression model by median maternal age (19.735 years) to determine if older subjects, who are more likely to have longer interpregnancy intervals than the teenaged subjects, were at higher risk of preeclampsia or pregnancy-associated hypertension. All statistical analyses were performed using SAS for Windows, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Shown in table 1 are the demographic and reproductive characteristics of the participants according to the outcome of the pregnancy (i.e., normotensive, preeclampsia, and pregnancy-associated hypertension) and history of abortion. Of the 4,064 subjects eligible for this analysis, 80 percent were primigravidas and 20 percent had had one prior abortion. Among the 822 women with a history of abortion, nearly two thirds (63 percent) conceived the index pregnancy with a different father compared with just over a third (37 percent) who conceived again with the same father. The average subject was 20–22 years of age, unmarried, and non-Hispanic White or African American; had a high normal body mass index of 25.2 among primigravidas with normotensive pregnancies and no more than a high school education; and lacked private health insurance. CPEP subjects who had had a prior abortion averaged 22 years of age, just 1 year more than primigravidas. The average age of women who had had a prior abortion with a different father was only 0.1 year greater than the average age of women with a prior abortion with the same father (22.2 vs. 22.1 years). Normotensive primigravidas were also less likely to have smoked during pregnancy (20 percent) than women who had had a prior abortion (31 percent). The average gestational age at termination of the aborted pregnancies was about 9 weeks. Notably, among normotensive women, spontaneous abortions were more frequent among those who remained with the same partner (70 percent), whereas induced abortions were more common among women who changed paternity (60 percent).

The incidence of preeclampsia among primigravidas was essentially the same as the rate among women with a history of abortion with a different partner (8.0 percent and 7.9 percent, respectively) (table 2); however, the rate of preeclampsia was substantially lower among women with a history of abortion who conceived again with the same father (4.3 percent). For pregnancy-associated hypertension, the incidence rates were very similar among primigravidas (17.7 percent) and women with changed paternity (17.1 percent); the corresponding rate was somewhat lower among women with a history of abortion who conceived again with the same father (15.3 percent).

Final logistic regression models, constructed to estimate the risks of preeclampsia and pregnancy-associated hypertension associated with changed paternity, included five covariables, which satisfied study criteria for confounding. These variables included clinical center (Albuquerque, Birmingham, Cleveland, Memphis, Portland), smoked during the index pregnancy (yes, no), body mass index (<19.8, 19.8–25.9, 26.0–29.0, 30.0–34.9, ≥35.0 kg/m²),
TABLE 1. Selected demographic characteristics of subjects by hypertension category, gravidity, and change in paternity, Calcium for Preeclampsia Prevention Trial, 1992–1995

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Preeclampsia</th>
<th>Pregnancy-associated hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primigravida</td>
<td>Same father</td>
<td>Different father</td>
</tr>
<tr>
<td></td>
<td>(n = 2,411)</td>
<td>(n = 242)</td>
<td>(n = 391)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>20.4</td>
<td>22.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White, non-Hispanic</td>
<td>34</td>
<td>807</td>
<td>45</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>19</td>
<td>451</td>
<td>15</td>
</tr>
<tr>
<td>Black</td>
<td>45</td>
<td>1,092</td>
<td>36</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>3</td>
<td>61</td>
<td>4</td>
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<tr>
<td>Mean education (years)</td>
<td>11.4</td>
<td>11.9</td>
<td>12.1</td>
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<tr>
<td>Ever married (%)</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>21</td>
<td>508</td>
<td>36</td>
</tr>
<tr>
<td>No</td>
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<td>0</td>
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<tr>
<td>Private insurance (%)</td>
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<tr>
<td>Yes</td>
<td>11</td>
<td>275</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>89</td>
<td>2,133</td>
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<td>Body mass index (%)</td>
<td></td>
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<tr>
<td>&lt;19.8 kg/m²</td>
<td>10</td>
<td>245</td>
<td>10</td>
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<tr>
<td>19.8–25.9 kg/m²</td>
<td>57</td>
<td>1,371</td>
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<td>26.0–29.9 kg/m²</td>
<td>17</td>
<td>403</td>
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<tr>
<td>30.0–34.9 kg/m²</td>
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<tr>
<td>≥35.0 kg/m²</td>
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<tr>
<td>Mean body mass index (kg/m²)</td>
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<td>Ever smoked (%)</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Outcome of first pregnancy (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Spontaneous loss</td>
<td>70</td>
<td>167</td>
<td>40</td>
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<tr>
<td>Induced abortion</td>
<td>30</td>
<td>70</td>
<td>60</td>
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<tr>
<td>Mean length of first pregnancy (weeks)</td>
<td>9.6</td>
<td>9.5</td>
<td>9.2</td>
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As shown in table 2, women with a history of abortion who conceived again with the same partner had approximately half the risk of developing preeclampsia as did women pregnant for the first time (adjusted odds ratio (aOR) = 0.55, 95 percent confidence interval (CI): 0.31, 0.97). In contrast, women with a history of abortion who conceived again with a new partner had essentially the same risk of preeclampsia as did women who were pregnant for the first time (aOR = 0.99, 95 percent CI: 0.77, 1.27).

To determine if maternal age modifies the association of paternal change with the risk of preeclampsia and pregnancy-associated hypertension, we stratified the final logistic regression models according to the median age of CPEP subjects (19.735 years) (table 2). Crude and adjusted odds ratios were computed using primigravidas as the referent group. Among women who had had a prior abortion with the same father, the odds ratios for preeclampsia and pregnancy-associated hypertension were changed only slightly after stratification by median maternal age. Some mild variation in the age-stratified odds ratios occurred.

maternal race (White, non-White), and private health insurance (yes, no).
among women who had had a prior abortion with a different father. Women below the median age had a mild increased risk of preeclampsia (aOR = 1.29) and pregnancy-associated hypertension (aOR = 1.23), whereas subjects older than the median age had a mild decreased risk (aOR = 0.92 and aOR = 0.82, respectively), although the 95 percent confidence limits for these odds ratios included unity. To determine if the effect of abortion and changed paternity differed by the randomized intervention category, we tested for the interaction of calcium supplementation (yes, no) and exposure group (primiparous, pregnancy loss with the same father, pregnancy loss with a different father). This interaction was not statistically significant, suggesting that the protective effect of same paternity was consistent among women in the two randomized treatment arms.

When the outcomes of mild and severe preeclampsia were evaluated separately, the risks associated with a history of abortion with the same partner were essentially unchanged (aOR = 0.55, 95 percent CI: 0.28, 1.10 for mild preeclampsia; aOR = 0.52, 95 percent CI: 0.19, 1.43 for severe preeclampsia). Likewise, the risks of mild and severe preeclampsia associated with a history of abortion with a different father were similar to those among women pregnant for the first time (aOR = 0.94, 95 percent CI: 0.61, 1.47 for mild preeclampsia; aOR = 1.19, 95 percent CI: 0.68, 2.07 for severe preeclampsia).

**DISCUSSION**

Our analysis of nulliparous women enrolled in the CPEP study suggests that a prior abortion reduces the risk of preeclampsia by one half, providing significant protection, but only among women who conceive again with the same partner. Women who had had a prior abortion but conceived the index pregnancy with a new partner assumed the same risk of preeclampsia as women pregnant for the first time. These findings were unchanged after stratification by median age and by mild and severe preeclampsia. To our knowledge, this study is the first to demonstrate the effect of changed paternity on the risk of preeclampsia in nulliparous women with an abortion history, lending further support for an immune-based etiology of preeclampsia. Our findings are consistent with those from studies of multiparous women, which have noted a similar effect of changed paternity on the risk of preeclampsia (16, 17).

Findings from the present study and an accumulating body of literature suggest that paternal and fetal factors (genetic, immune based, or both) play a key role in the complex etiology of preeclampsia. A recent Norwegian study linked birth records of different women who had children fathered by the same man (18). Women who conceived with men who had previously fathered a preeclamptic pregnancy with another woman were at significantly increased risk of preeclampsia compared with women whose partners had sired a normotensive pregnancy with a different woman (18). A California study, which linked state birth certificates belonging to women who had had two consecutive births over the period 1989–1991, examined the effect of changed paternity on the risk of preeclampsia in the second pregnancy according to whether preeclampsia complicated the first pregnancy (17). Among women who changed partners, the preeclampsia risk was increased only for those who were normotensive during the prior pregnancy. In contrast, changed paternity was associated with a reduced risk among women who had had preeclampsia during their first birth (17). The authors proposed that parental human leukocyte antigen sharing or other paternal factors could be responsible. Human leukocyte antigen sharing between the mother and father has been hypothesized to impair maternal recognition of the fetal allograft and to promote immune tolerance, which is required in normal, successful pregnancy (24).

Repeated and prolonged exposure to the father’s sperm prior to conception of the index pregnancy has been consistently associated with decreased risk of preeclampsia, suggesting that maternal sensitization to paternal or fetal antigens may be operating. Robillard et al. (13) found an inverse association of risk of pregnancy-induced hypertension with length of sexual cohabitation with the baby’s father.
prior to conception. This association was observed among both primigravids and multigravids. Women with longer periods of sexual cohabitation also have an increased opportunity (i.e., more cycles at risk) of clinically undetected spontaneous abortion(s), which would confer additional protection against preeclampsia in subsequent gestations. An increased risk of preeclampsia has also been reported among users of barrier contraception (9, 10) and recipients of nonpartner donor inseminations (11, 12, 25), suggesting a detrimental effect of limited exposure to sperm before conception. Wang et al. (26) recently conducted a study of Australian women who used assisted reproductive technology to determine if the risk of preeclampsia differed among women who conceived through in vitro fertilization or intracytoplasmic sperm injection using partners’ ejaculated sperm and those who conceived through intracytoplasmic sperm injection with partners’ surgically obtained sperm. Presumably, partners whose sperm was obtained surgically had insufficient sperm at ejaculation. Women who conceived using surgically obtained sperm had a threefold increased risk compared with women who conceived through in vitro fertilization with their partners’ ejaculated sperm. This suggests that the protective effect of semen exposure on the risk of preeclampsia is associated with exposure to sperm cells or a factor closely linked with sperm in the ejaculate (26).

Moreover, pregnancies characterized by increased placental mass (e.g., multiple gestations, molar pregnancies) are consistently shown to be at increased risk of preeclampsia, suggesting that greater trophoblastic volume and fetal antigen load may be responsible (27).

Three recent registry-based studies from Scandinavia examined the effect of partner change on preeclampsia risk among multiparous women, while taking into account the effect of interbirth interval (28, 29) or the interval between birth and the estimated conception date of a following birth (30), used as proxies for interpregnancy interval. These studies utilized hospital discharge diagnoses rather than medical chart audits to identify cases of preeclampsia and are among the first to identify birth interval as a strong risk factor for preeclampsia. After adjustment for birth interval, a change in partner was no longer a risk factor for preeclampsia. None of these studies, however, considered the effect of history of abortions, particularly induced abortions. Because induced abortions protect against preeclampsia (3, 5) and are obtained more frequently by unmarried, separated, or divorced women than by women in stable unions (31), failure to account for terminations of pregnancies conceived between registered births would result in erroneously long interbirth intervals attributed to women who change partners. Moreover, adjustment for induced abortions would decrease the relative risk associated with interbirth interval and increase the relative risk associated with changing partners.

Although the interpregnancy interval was not ascertained directly in the CPEP Trial, which enrolled only nulliparous women (median age, 19.735 years), the average interpregnancy interval may approximate 1 year, given that the average age of primigravidas is 1 year less than that for women who had one previous pregnancy. Confounding by interpregnancy interval is also unlikely because the odds ratios for women above or below the median age were virtually identical, despite the fact that the interpregnancy interval was, of necessity, shorter for women below than above the median age. In addition, the average age of women who changed partners was only about a month more than that of women who remained with the same partner. However, because we used maternal age as a proxy to examine for a potential effect of interpregnancy interval on our analyses, further studies using high quality diagnostic and exposure documentation are needed.

The rate of preeclampsia in the CPEP study is somewhat higher than that reported by some other studies; however, this can be explained, at least in part, by the fact that clinic and hospital staff conducted intensive, active surveillance for preeclampsia among the CPEP subjects. The protocol for the CPEP Trial required blood pressure measurements and urine protein assessments in situations where these would not have ordinarily been obtained. Moreover, CPEP subjects tended to be young, nulliparous, ethnically diverse, and more likely to be obese than women of reproductive age in the general population, possibly placing them at increased risk of preeclampsia.

The follow-up rate in the CPEP population was very high (94.5 percent) and showed little variation among the three groups of women who were the focus of this analysis. Loss to follow-up was 5.6 percent among the primiparous, 5.9 percent among women who had one prior pregnancy with the same father, and 5.2 percent among women who had one prior pregnancy with a different father, suggesting that selection bias is unlikely to influence study findings.

The major strengths of the present study are the large number of preeclampsia patients identified by the CPEP Trial and its application of standard methodologies, including standardized protocols for blood pressure and proteinuria measurements, a uniform schedule for patient follow-up, and detailed diagnostic criteria to classify preeclampsia and pregnancy-associated hypertension. The CPEP Trial may be the largest existing database permitting analysis of preeclampsia and pregnancy-associated hypertension risk associated with changed paternity in nulliparous women. Moreover, our findings are unlikely to be influenced by recall bias, as women tend not to forget previous pregnancies and their paternity. Nonetheless, our study would have been strengthened by a larger number of preeclamptic subjects, particularly those with a history of abortion, and by information on the duration of sexual cohabitation with the baby’s father, frequency of coitus, contraceptive practices with the baby’s father, and the interbirth interval.

In summary, this analysis of the effect of abortion on subsequent risk of preeclampsia in nulliparous women provides further evidence to support an immune-based etiology of preeclampsia in which paternal and fetal factors play a key role. Epidemiologic studies, which use comprehensive immunologic and genetic components for the analysis of biologic specimens from mother, father, and baby triads, are needed to elucidate further the etiologic mechanisms of preeclampsia.
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