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Hepatotoxicity of Erythromycin Estolate During Pregnancy

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Women in the second half of pregnancy, who were infected with genital mycoplasmas and who gave written informed consent, were randomly assigned to receive capsules of identical appearance containing erythromycin estolate, clindamycin hydrochloride, or a placebo for 6 weeks. Levels of serum glutamic oxalacetic transaminase (SGOT) were determined before and during treatment by a fluorometric method. All pretreatment levels of SGOT were normal (<41 units). Participants who received erythromycin estolate had significantly more abnormally elevated levels of SGOT (16/161, 9.9%) than did those who received clindamycin (4/168, 2.4%, $P < 0.01$) or those who received placebo (3/165, 1.8%, $P < 0.01$). Elevated levels of SGOT ranged from 44 to 130 U. Serum bilirubin levels were normal. Gamma-glutamyl transpeptidase activity was abnormal in six of six participants who had abnormal levels of SGOT while receiving erythromycin estolate. There were few associated symptoms, and all levels of SGOT returned to normal after cessation of treatment. The treatment of pregnant women with erythromycin estolate may be inadvisable.

Erythromycin, a macrolide antibiotic produced by the actinomycete *Streptomyces erythreus*, has been used extensively in clinical medicine since its introduction in 1952. Erythromycin base and its salts are not consistently absorbed from the gastrointestinal tract, presumably because they are destroyed by gastric acid. The only preparation of erythromycin that is well absorbed when given orally is the lauryl sulfate salt of the propionyl ester (propionyl erythromycin lauryl sulfate; erythromycin estolate [5]). The estolate is also the only form of erythromycin that has been associated with any reported hepatotoxicity. As reviewed by Braun (1), there have been reports of individuals who have developed hepatic toxicity in association with the administration of erythromycin estolate (8). Even when the propensity of erythromycin to produce hepatic toxicity has been considered to be established, it has been generally considered that this is an unusual idiosyncratic reaction (1, 5). The present report describes a group of pregnant women, over 9% of whom developed subclinical hepatotoxicity while receiving erythromycin estolate.

Investigators in this laboratory have associated the genital mycoplasmas *Mycoplasma hominis* and *Ureaplasma urealyticum* (T-mycoplasmas) with birth weight. In one study (9), these organisms were found to be more prevalent among low-birth-weight infants than among infants of normal birth weight. In another study (3), women who were colonized with these organisms early in pregnancy gave birth to infants that weighed significantly less than infants whose mothers were not colonized. Earlier studies from this laboratory had found that non-bacteriuric pregnant women who were treated with a broad-spectrum antimicrobial agent gave birth to significantly fewer low-birth-weight infants than did women who received a placebo (4; H. A. Elder, R. Smith, and E. H. Kass, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 8th, New York, Abstr. no. 173, 1968). These observations led to the hypothesis that the genital mycoplasmas were an etiological factor in birth weight. The study in which the findings described in this report were noted was established to test this hypothesis.

MATERIALS AND METHODS

Women who were between week 22 and 32 of pregnancy and who were infected with *M. hominis* and/or *U. urealyticum* were asked to participate in this study if they were not bacteriuric and if all of the following laboratory studies were within normal limits: serum bilirubin, alkaline phosphatase, se-

rum glutamic oxalacetic transaminase (SGOT), blood urea nitrogen, creatinine, hemoglobin, and leukocyte count.

Infected women who met all of the above criteria and who gave written informed consent after a detailed explanation of the objectives of the study and the procedures that would be employed were randomly assigned to receive identical capsules that contained either 250 mg of erythromycin estolate, 150 mg of clindamycin hydrochloride, or a placebo. Participants were instructed to take one capsule four times a day for 6 weeks. Compliance was determined by examining a written record on which the patient recorded the time that she took each capsule and by counting the unused capsules. After the completion of 3 and 6 weeks of treatment, participants were specifically asked about the presence or absence of a number of symptoms, and a sample of venous blood was obtained. The laboratory studies listed above were performed on these blood samples. Participants who reported bothersome symptoms that might conceivably be attributed to the antibiotics were told to stop taking their capsules and were dropped from the study. Similarly, participants who had an abnormal value in any of the laboratory studies performed on the sample of blood collected after 3 weeks of treatment were contacted as soon as the abnormal result was available, instructed to discontinue the capsules immediately, and asked to come to the clinic at their earliest convenience so that another blood sample could be obtained.

Levels of SGOT in the samples obtained before, during, and after treatment were estimated by employing an automated fluorometric procedure, using an Autoanalyzer (Technicon Corp., Tarrytown, N.Y.). This procedure is adapted from the manual spectrophotometric method of Henry et al. (6) and measures a decrease in the native fluorescence of reduced nicotinamide adenine dinucleotide in a two-step reaction. First, serum samples are diluted with substrate containing aspartic acid and alpha-ketoglutaric acid and incubated for 6.5 min at 37°C. Oxalacetic acid is produced, proportional to the SGOT present. The oxalacetic acid is then dialyzed into a recipient stream containing reduced nicotinamide adenine dinucleotide (fluorescent) and malic dehydrogenase, producing malic acid and nicotinamide adenine dinucleotide (nonfluorescent). Enzyme activity, therefore, is proportional to the decrease in fluorescence as measured in a fluorometer equipped with a 355-nm narrow-pass filter for the primary (activation) wavelength and a 485-nm sharp-cut filter for the secondary (fluorescence) wavelength. Samples with known normal and abnormal levels of SGOT were included in each set of determinations.

The use of the fluorometric procedure for the estimation of SGOT avoids the possibly confounding false elevations of SGOT activity seen when sera from patients receiving erythromycin estolate were examined by using a colorimetric assay (13). The normal range of SGOT for this population was determined by examining sera from the 71 consecutive women attending the prenatal clinic at Boston City Hospital. Their mean level of SGOT was 23.24 Karmen units, with a standard deviation of 5.85 units. The upper limit of normal was set at 3 standard deviations above the mean or 41 units. Total serum bilirubin concentrations were estimated with a Technicon Autoanalyzer.

After it became apparent that there were significantly more abnormally elevated levels of SGOT among one of the groups of patients, selected portions of serum that had been frozen at −20°C were thawed by leaving them at room temperature and examined for gamma-glutamyl transpeptidase activity by a modification of the kinetic photometric method of Szasz (14), utilizing a Beckman DBGT precision spectrophotometer. The upper limit of normal for women in this assay is 27 units. The coefficient of variation is about 10%. Abnormally high levels of gamma-glutamyl transpeptidase appear to be specific for disorders of the liver, biliary tract, and pancreas. Pregnancy does not appear to have any influence on the activity of this enzyme (10).

RESULTS

This report describes the first 539 women who had been enrolled in the study. Of these 539 women, 179, 181, and 179 had been assigned to receive erythromycin estolate, clindamycin hydrochloride, and a placebo, respectively. Table 1 shows the number of participants in each of the groups who had abnormal levels of SGOT in the samples obtained after 3 or 6 weeks of treatment. A total of 45 subjects (18, 13, and 14 from each of the groups) have been excluded because they did not take any of the capsules or because they did not return to the clinic. Participants who received erythromycin estolate had significantly more abnormal SGOT determinations (16 of 161, 9.9%) than did those who received clindamycin hydrochloride (4 of 168, 2.4%, $P < 0.01$) or a placebo (3 of 165, 1.8%, $P < 0.01$).

About 40% of the women who were enrolled in the study failed to complete more than 3 weeks of therapy. Since most of these noncompliant participants stopped taking study capsules after 1 or 2 days, their exposure to the study medications was minimal. Thus, a separate tabulation was made excluding these participants. Table 1 shows that 14 (14.4%) of the 97 women who took erythromycin estolate for more than 3 weeks had abnormally elevated levels of SGOT. This differed significantly ($P < 0.05$) from the clindamycin and placebo groups and is probably more indicative of the actual prevalence of abnormalities of SGOT among pregnant women who receive a relatively prolonged course of therapy with erythromycin estolate.

Table 2 lists some of the laboratory determinations for the individuals who had an abnormal level of SGOT. Women who failed to com-

TABLE 1. *Abnormal SGOT values among pregnant women who were taking erythromycin estolate, clindamycin hydrochloride, or a placebo*

Drug group	All participants			Participants who completed more than 3 weeks of treatment		
	No. tested	Abnormal levels of SGOT during treatment		No. tested	Abnormal levels of SGOT during treatment	
		No.	%		No.	%
Erythromycin estolate	161	16	9.9	97	14	14.4
Clindamycin hydrochloride	168	4	2.4	97	4	4.1
Placebo	165	3	1.8	104	3	2.9

TABLE 2. *Laboratory values in participants who developed abnormal levels of SGOT*

Study no.	SGOT levels (units)			Serum bilirubin level during treatment (mg/100 ml)
	Before treatment	During treatment	After treatment	
Participants who received erythromycin estolate				
11	20	74 (3)[a]	32 (0)[b]	0.5
32	28	55 (3)	Not done	0.6
63	28	59 (3)	34 (5)	0.5
107	27	58 (3)	36 (6)	0.6
119	20	46 (3)	10 (62)	1.0
281	12	88 (3)	36 (10)	0.7
322	16	44 (3)	28 (3)	0.5
338	18	46 (3)	36 (1)	0.5
339	20	82 (3)	42 (2)	0.9
438	22	130 (3)	28 (1)	0.8
465	22	46 (3)	22 (1)	0.5
483	40	44 (3)	40 (2)	0.4
515	24	50 (6)	24 (6)	0.6
523	18	44 (3)	16 (2)	0.5
Participants who received clindamycin hydrochloride				
59	35	42 (6)	Not done	0.5
85	38	42 (6)	22 (?)	0.6
123	30	42 (6)	28 (?)	0.7
159	28	44 (3)	96 (0)	0.9
Participants who received a placebo				
83	41	55 (6)	50 (?)	0.7
133	30	42 (3)	30 (13)	0.9
379	22	88 (6)	10 (?)	0.5

[a] Week of treatment after which serum with abnormal level of SGOT was obtained.
[b] Number of days between cessation of treatment and post-treatment blood sample.

plete more than 3 weeks of treatment have been excluded. The abnormal levels of SGOT among the participants who received erythromycin estolate ranged from 44 to 130 units. The levels of SGOT returned to or toward normal in serum examined shortly after cessation of treatment. Abnormal levels of SGOT were not associated with abnormalities in serum bilirubin levels. Three of the four patients with abnormal levels of SGOT in the group that received clindamycin hydrochloride had levels of 42 units, just above the upper limits of normal. The fourth patient (no. 159) was subsequently shown to have alcoholic liver disease. All but one of the women who received erythromycin estolate had their abnormal level of SGOT recorded at the visit that followed 3 weeks of therapy. In contrast, five of the seven women in the other two groups had their abnormal values noted at the visit that followed 6 weeks of treatment.

The symptoms reported by the 14 participants listed in Table 2 who had abnormal levels of SGOT while receiving erythromycin estolate were compared with those reported by 179 patients who were assigned to receive a placebo.

There were no significant differences between these groups in the reported incidence of abdominal pain, dark urine, nausea, vomiting, or pruritus.

When it became apparent that there were significantly more abnormal levels of SGOT among the patients who had received erythromycin estolate, portions of selected sera that had been frozen at −20°C were examined for gamma-glutamyl transpeptidase, an enzyme that is thought to be a more specific indicator of hepatic damage than is SGOT (10). The results of these determinations are summarized in Table 3. Levels of gamma-glutamyl transpeptidase were abnormal before treatment in 2 of the 6 women who received erythromycin estolate and developed elevations of SGOT, in 0 of 7 participants who received erythromycin estolate and whose levels of SGOT remained normal, and in 1 of 9 and 1 of 12 participants who received clindamycin hydrochloride and placebo, respectively. All of the participants in the last three groups had completed 6 weeks of treatment.

Abnormal levels of gamma-glutamyl transpeptidase were noted in serum samples collected during treatment from 6 of 6 women who received erythromycin estolate and had abnormal levels of SGOT and in 2 of 7, 1 of 9, and 3 of 12 women in each of the other three groups.

As soon as it was noted that there were significantly more abnormal levels of SGOT among the women who were receiving erythromycin estolate, we stopped assigning patients to this group. We have subsequently formulated new capsules that contain the stearate salt of erythromycin. Of the first 97 patients who received erythromycin stearate, 3 (3.0%) had abnormal levels of SGOT. Sera obtained after 3 weeks of treatment from five patients who received erythromycin stearate were examined for gamma-glutamyl transpeptidase activity. All five were normal.

Diarrhea was reported by a significantly greater proportion of participants who received clindamycin hydrochloride (21%) than by participants who received erythromycin estolate (13%) or a placebo (14%) ($P < 0.05$). In most instances, the diarrhea was mild and transient, disappearing while the study medications were continued. Although we did not perform colonoscopy or other extensive evaluations of the patients who reported diarrhea, none of the participants reported bloody stools, were hospitalized because of diarrhea, or were noted to have colitis. Because of these data and because of the reports of clindamycin-associated colitis that began to appear after this study had been initiated, patients who participate in this study are no longer being assigned to receive clindamycin hydrochloride.

TABLE 3. *Gamma-glutamyl transpeptidase values in serum from pregnant women who were receiving erythromycin estolate, clindamycin hydrochloride, or a placebo*

Patient no.	Gamma-glutamyl transpeptidase level[a] (units)		
	Before treatment	After 3 weeks of treatment	After treatment
Erythromycin estolate (abnormal SGOT)			
339	11	*46*	15
438	25	*345*	*30*
465	11	*36*	13
483	*83*	*66*	*96*
515	*42*	*31*	20
523	14	*73*	14
Erythromycin estolate (normal SGOT)			
393	22	27	11
421	24	24	*34*
467	15	*70*	18
482	14	*40*	18
489	8	9	17
514	21	14	7
537	11	5	*32*
Clindamycin hydrochloride			
406	12	8	8
409	21	6	24
480	*32*	*42*	24
521	14	17	*48*
536	34	14	11
1006	9	8[b]	10
1029	18	9	13
1036	16	16	10
1044	25	15[b]	22
Placebo			
419	22	11	16
432	15	14	11
436	21	*35*	*57*
443	*29*	*33*	*34*
452	10	10	18
477	12	4	11
524	12	10	11
1026	16	9	9
1030	18	9	13
1037	24	13	12
1054	14	14	*31*
1066	11	*65*	Not done

[a] Upper limit of normal for women is 27 units. Abnormal values in italics.

[b] Serum samples were collected after 6 weeks, rather than after 3 weeks, of treatment.

DISCUSSION

We decided to undertake this study because we felt that the epidemiological evidence associating the genital mycoplasmas with birth weight was compelling (3, 9) and because low

birth weight is such a significant problem in contemporary medical practice that we felt that direct evaluation of a potentially treatable cause of this condition was necessary. We chose drugs that were effective against the genital mycoplasmas in vitro (2) (clindamycin against *M. hominis*; erythromycin against *U. urealyticum*) and that were thought to be safe for use during pregnancy. Infected patients were asked to participate in this study only after base-line tests of renal and hepatic function were shown to be normal. To minimize the potential risk of teratogenicity, no patient was enrolled in the study prior to week 22 of pregnancy.

We chose erythromycin estolate because it is the form that is best absorbed (5). We were, of course, aware that erythromycin estolate had been associated with hepatic toxicity. A detailed review (1) of the problem, however, concluded that "there is a syndrome of hepatic disorder peculiar to triacetyl oleandomycin and erythromycin estolate," probably involving a sensitization phenomenon, but that there were "no quantitative data on the expected incidence of the syndrome." Properly designed controlled studies had not been carried out. Some authors of prospective studies attributed hepatic abnormalities to erythromycin estolate; others found no evidence of toxicity (1).

It is clear from the data presented in this report that a significant proportion, about 10 to 15%, of pregnant women who receive erythromycin estolate for 3 weeks or longer will develop subclinical, reversible hepatic toxicity. It is not clear whether this represents a subclinical form of the less common clinically apparent syndrome resembling acute cholecystitis, which has been associated with erythromycin estolate (1, 11), or whether a different mechanism is involved. Also unclear is the extent to which men and nonpregnant women share in this increased risk. In an uncontrolled study that is comparable in terms of dosage and length of treatment, Robinson (12) described hepatotoxicity in 15 (16.1%) of 93 patients who received 1 g of erythromycin estolate per day for 14 days or longer, suggesting that this phenomenon might not be limited to pregnant women.

The aforementioned uncertainties notwithstanding, there is one conclusion that can be drawn from these data. Erythromycin estolate should not be administered to pregnant women if alternative antibiotics are available. Furthermore, since it is difficult to conceive of a clinical situation in which an alternative antibiotic would not be available, erythromycin estolate probably ought to join the growing list of drugs whose use is contraindicated during pregnancy.

A more difficult question relates to whether there is any justification for the continued availability of this potentially toxic form of erythromycin. The superior absorption of erythromycin estolate from the gastrointestinal tract may be more apparent than real. Most of the erythromycin in the serum is in the form of the estolate (S. T. Brown, V. C. Stevens, and K. K. Holmes, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 15th, Washington, D.C., Abstr. no. 353, 1975), which may be less active biologically than erythromycin base (15). In addition, there is no convincing evidence that erythromycin estolate offers any clinical advantage. Recent studies, for example, have shown erythromycin estolate to be no more or less effective than other forms of erythromycin in the treatment of gonococcal urethritis in men (Brown et al., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 15th, Washington, D.C., Abstr. No. 353, 1975) and upper respiratory tract infections due to group A streptococci (7).

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