Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate

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OBJECTIVE: The objective of the study was to investigate the rates and characteristics of hereditary angioedema (HAE) attacks associated with pregnancy, delivery, and the postpartum period and their treatment with C1 esterase inhibitor (INH) concentrate.

STUDY DESIGN: This was an observational study including 22 women with type I HAE, with data collected before, during, and after 35 pregnancies (37 children) based on patient diaries, interviews, and case report forms.

RESULTS: In 83% of pregnancies, attack rates increased during pregnancy; highest mean rates occurred in the second and third trimesters.

CONCLUSION: Increased attack rates during pregnancy in women with HAE are well controlled with C1-INH concentrate, indicating the clear benefit of integrating the availability of C1-INH concentrate into the management plan for these women during pregnancy and delivery.


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We investigated the course of HAE during pregnancy and breast-feeding in women cared for by our HAE clinic for a period of more than 12 years, investigating any consequences for the women and their newborn children. Our aim was to characterize the rate and location of acute HAE attacks associated with pregnancy and, as appropriate, assess the efficacy and safety of treating these attacks with C1-INH concentrate. The C1-INH preparation used was Berinert P (CSL Behring GmbH, Marburg, Germany), which is a virus-inactivated C1-INH concentrate derived from human plasma. It has long been approved for the treatment of acute HAE attacks in several European and South American countries as well as Japan, and approval in the United States was obtained in October 2009. The efficacy and safety of Berinert P and predecessor formulations have been demonstrated in more than 30 years of clinical use.

Materials and Methods
This observational study was conducted at the Johann Wolfgang Goethe University Hospital in Frankfurt am Main, Germany. The Clinical Ethics Committee of the Frankfurt University Hospital had previously confirmed that ethical approval was not required for this noninterventional study. We investigated pregnancies in 22 women with HAE type I from March 1995 through August 2007, collecting data associated with 35 pregnancies, including the postpartum period during and after breast-feeding. All patients had first given their written informed consent.

Depending on the medical need and individual course of HAE, acute attacks were treated with C1-INH concentrate with on-demand therapy or individual replacement therapy (IRT). On-demand therapy involved treatment with C1-INH concentrate on presentation of edema or other typical symptoms of an attack either in the clinic or via self-administration at home after consulting the clinic.

IRT involved self-administration of C1-INH concentrate at home following early signs for the onset of an attack. Patients using IRT generally had high rates of severe attacks (≥1 per week), whereas patients using on-demand therapy generally had lower attack rates (maximum of 3 per month). In both cases, 500 or 1000 U of C1-INH concentrate were administered according to the patients’ clinical histories. Typically, the dose of C1-INH concentrate required no adjustment during long-term treatment, and the doses used before pregnancy were also suitable for treating attacks during pregnancy. In addition, based on the gynecologist’s judgment, C1-INH concentrate (usually 1000 U) was to be given prophylactically to all patients approximately 1 hour before delivery, regardless of whether a vaginal delivery or a cesarean section was planned. No recommendation was made for pain relief during labor but, where given, epidural anesthesia was the method of choice. Danazol was not allowed during pregnancy.

Patient diaries, interviews, and case report forms were used to collect the following:
- Maternal demographic characteristics and background information, including disease status and prior therapy.
- Timing and location of HAE attacks before, during, and after pregnancy, including an assessment of attack rate during pregnancy by trimester.
- Routine evaluations of plasma C1-INH activity and antigen as well as C4 levels before and during pregnancy. Samples for these analyses were taken either once or twice per year at routine visits to the clinic and/or at 1 or more visits at unspecified times during the pregnancy.
- Treatment of HAE attacks with C1-INH concentrate and patient-reported outcome with respect to efficacy.
- Pregnancy outcome, including timing and type of delivery.
- Characteristics of newborn children, including HAE status.
- Safety of C1-INH treatment, assessed according to adverse events, safety laboratory parameters, and plasma viral status.

Data were analyzed descriptively and are presented as tabulations and figures, as appropriate. Statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

Results
Maternal characteristics and pregnancy details
A total of 35 pregnancies were analyzed in 22 women: 11 women had a single pregnancy, 9 women had 2 pregnancies, and 2 women had 3 pregnancies. C1-INH concentrate at a dose of 500 or 1000 U was used for treating HAE attacks before 24 of the pregnancies using on-demand therapy and before 2 of the pregnancies using IRT. No C1-INH concentrate was used before the remaining 9 pregnancies. Before 10 pregnancies, prophylactic treatment with danazol at a median dose of 150 mg/day (range, 50–400 mg/day) was documented.

The median age at confirmation of pregnancy was 29.5 years (range, 20–38 years), and the median body mass index before pregnancy was 28.2 kg/m² (range, 16.9–37.9 kg/m²). The median gestation period was 39 weeks (range, 34–42 weeks). The premature delivery at 34 weeks involved twins. No abortions occurred. Deliveries in approximately half the pregnancies were vaginal (17 pregnancies), and 8 pregnancies involved primary or secondary cesarean sections (no details for 2 pregnancies). Breast-feeding was documented for 21 of the 35 births, with a median duration of 4.8 months (range, 1–34 months).

Characteristics of newborn children
A total of 37 children (2 twin births) were delivered (19 female and 18 male). The median birth weight was 3.3 kg (range, 2.0–4.3 kg), and the median crown-heel length was 51 cm (range, 46–57 cm). The weight and length of the newborn children generally fell within the 10th and 90th percentiles for Germany. Eighteen children (8 female and 10 male) were diagnosed with HAE. No malformations were observed. At birth, severe asphyxia occurred in 1 child and dysplasia of 1 hip and dislocation of the first vertebra were diagnosed in a second child. Both cases were unrelated to HAE or its treatment. Further details are available in the following sections.
HAE attacks and treatment with C1-INH concentrate

In 29 of the 35 pregnancies, increases in attack rates occurred, compared with decreases in only 4 pregnancies (no change in 1 pregnancy and no details for 1 pregnancy).

The mean attack rate per 9 month period increased from 9.4 before pregnancy to 44.0 during pregnancy (Figure 1, A). The rate then decreased to 25.4 attacks per 9 months during breast-feeding and 18.6 attacks per 9 months after breast-feeding. During pregnancy, the highest rates occurred during the second and third trimesters (16.2 and 18.0 attacks per 3 months, respectively) (Figure 1, B).

Throughout the study, the highest mean attack rates were observed in the abdominal region (eg, gastrointestinal colic attacks), followed by the extremities and the facial region (Figure 2). The highest attack rates in the abdominal region were observed during pregnancy and breast-feeding (27.4 and 17.0 attacks per 9 months, respectively). Attacks were less frequent in the urogenital region and laryngeal attacks were rare (associated with only 5 pregnancies).

In the overall study population, there were no relevant changes in C1-INH activity or antigen or C4 levels during pregnancy, as compared with before pregnancy (Table 1).

C1-INH concentrate (500 or 1000 U) was used to treat attacks occurring before, during, and/or after 29 of the pregnancies (except during delivery; see the following text). Compared with before pregnancy (see previous text), the use of IRT increased during pregnancy, with on-demand therapy being used during 11 pregnancies and IRT during 18 pregnancies (no treatment was given during 6 pregnancies). The increased use of IRT during pregnancy was driven by the often dramatic increases in rate and severity of attacks during this period.

The use of IRT decreased again after pregnancy, with on-demand therapy being used during the postpartum period after 29 pregnancies (during and after breast-feeding) and IRT being used after 8 pregnancies during breast-feeding and after 7 pregnancies after breast-feeding. For 5 of these 7 pregnancies, the women had continued to use the IRT they had begun during pregnancy because of their deteriorated condition.

In all cases, including potentially life-threatening laryngeal attacks that occurred before or during 5 pregnancies, patients reported that their HAE attacks were successfully treated with C1-INH, leading to regression of the attack. The efficacy of C1-INH treatment was therefore consistent before, during, and after pregnancy. No other
HAE treatment was given during any of the pregnancies. Immediately before delivery, all patients were to receive prophylactic treatment with C1-INH concentrate. None of the patients experienced an attack during delivery.

**Safety evaluation**

No adverse events were associated with C1-INH treatment before, during, or after pregnancy. Nine women had adverse events associated with danazol treatment, 8 before pregnancy, and 1 after pregnancy. The most frequent events were depression (8 events), virilization (6 events), and weight increase (5 events).

No stillbirths or spontaneous abortions were reported. Serious adverse events not associated with C1-INH treatment were reported in 2 children: severe asphyxia and neurogenic coordination disturbances in 1 child and dysplasia of the left hip (type IIa) together with dislocation of the first vertebra (C1) arising from a breech birth in a second child. The first case was the result of oxygen deprivation because of a placental abruption. In both cases, the children have since developed well.

There were no relevant changes in any of the laboratory safety parameters during pregnancy, as compared with before pregnancy. No confirmed conversions of viral titers for hepatitis A, B, C, or G or human immunodeficiency virus occurred in any of the mothers or newborn children.

**Exploratory assessment of factors affecting attack rates during pregnancy**

No relationship was apparent between the lack of, or early discontinuation of, danazol treatment before pregnancy and attack rates during pregnancy. There was also no relationship between attack rates during pregnancy and whether the fetus had HAE. The mean attack rate was 42.8 attacks per 9 months (range 0–114) in women bearing a child with HAE compared with 45.2 attacks per 9 months (range, 0–135) in women bearing a child without HAE (Figure 3).

**TABLE**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Before pregnancy</th>
<th>During pregnancy</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>C1-INH activity, %</td>
<td>17</td>
<td>18.5 ± 7.64</td>
<td>20</td>
</tr>
<tr>
<td>Newborns with HAE, %</td>
<td>9</td>
<td>18.4 ± 9.49</td>
<td>11</td>
</tr>
<tr>
<td>Newborns without HAE, %</td>
<td>8</td>
<td>18.6 ± 5.53</td>
<td>9</td>
</tr>
<tr>
<td>C1-INH antigen, mg/dL</td>
<td>16</td>
<td>5.2 ± 1.27</td>
<td>18</td>
</tr>
<tr>
<td>C4, mg/dL</td>
<td>12</td>
<td>5.7 ± 4.32</td>
<td>16</td>
</tr>
</tbody>
</table>

Reference ranges: C1-INH activity = 64–146%; C1-INH antigen = 15.4–35.1 mg/dL; C4 = 10–40 mg/dL.

C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; n, number of patients.

However, a trend was observed toward a lower level of C1-INH activity during pregnancy in women bearing a child with HAE. The mean C1-INH activity was 18.6% (range, 1–59%) in women bearing a child with HAE compared with 29.3% (range, 12–64%) in women bearing a child without HAE (Table and Figure 3).

**COMMENT**

In our study of 35 pregnancies, there was a marked increase in attack rate during pregnancy. The mean rate of 9.4 attacks per 9 months before becoming pregnant increased to 44.0 attacks per 9 months during pregnancy, representing increased rates in 29 of the 35 pregnancies. Although the rate then decreased to 25.4 attacks per 9 months during breast-feeding and 18.6 attacks per 9 months after breast-feeding, it had not yet returned to the baseline rate during the observation period of this study.

To date, the few published case reports and studies that exist, generally involving low numbers of patients, provide a variable picture on the course of HAE during pregnancy. As expected, because pregnancy and childbirth include stress and trauma situations that are known to trigger HAE attacks, various authors have reported increased attack rates during pregnancy and the postpartum period. However, either no increases, or decreases, in attack rate or no attacks at all can also occur during pregnancy.

One factor potentially influencing the attack rate, but which was not measured in our study, is hormonal fluctuation during and after pregnancy because increased estrogen levels and changes in hormonal balances can have a negative impact on the course of HAE, and there is a degree of variability among women with HAE in sex hormone sensitivity.

A further factor that potentially influenced our findings is an unavoidable selection bias that could have arisen because of our clinic being the largest center of expertise for HAE in Germany, with a consequently high proportion of patients with severe disease being referred to us during pregnancy.

During pregnancy, the mean attack rate per trimester increased from 9.6 in the first trimester to 16.2 in the second trimester and 18.0 in the third trimester. Although a similar trend has been reported previously, decreased attack rates in the second and third trimesters have also been reported. In view of these contradictory results, the course of HAE during pregnancy is difficult to predict in terms of attack rate and will probably be inherently variable between studies.

The strengths of our study include the relatively high number of pregnancies observed and the fact that details were recorded over a long time period from before pregnancy, through the postpartum period, and after finishing breast-feeding.

The most frequent location of the attacks in our study before, during, and after pregnancy was the abdomen. Together with the face, the abdomen is 1 of the most frequent locations for acute attacks in nonpregnant patients (men and women) with HAE.

Most of the increases in attack rates during pregnancy resulted from abdominal attacks, which may have been influenced by the displacement of abdominal organs resulting from growth of the uterus during pregnancy. During this period we also observed notable increases in attack rates in the extremities and the facial region. Attack rates were lower in the urogenital region, and laryngeal attacks were rare.

Although fetal HAE status had no apparent effect on the attack rate during pregnancy, our data did reveal that mean C1-INH activity levels were lower in women bearing fetuses with HAE than women bearing fetuses without HAE. A possible explanation could be that fetuses with HAE may, because of their own deficiency, tend to draw on maternal C1-INH, thereby reducing activity levels more than in women bearing fe-
tuses without HAE. There was no apparent relationship between C1-INH activity levels and attack rate, as observed previously. In addition to providing information on the course of HAE attacks associated with pregnancy, our study has also shown the benefit of treating these attacks with C1-INH concentrate. In the 29 pregnancies during which C1-INH concentrate was administered, all the women reported that the treatment was successful and led to regression of the attack. IRT with C1-INH concentrate is acknowledged to be effective in the treatment of severe attacks, and the increased use of IRT in our study proved to be an effective response to the increased rate and severity of attacks experienced during pregnancy.

Overall, our findings concurred with the consistent efficacy and safety of C1-INH concentrate reported elsewhere. The experience in our clinic that the efficacy of C1-INH therapy is maintained during long-term use, with no consistent need for dose adjustments, regardless of the pregnancy status, indicates that neutralizing antibody formation is not a concern.

All the pregnancies observed in our study progressed normally (ie, as also expected in patients without HAE), with no abortions or drug-related abnormalities. The weight and height of the newborn children generally fell within the anticipated ranges recorded in Germany, and the rate of primary cesarean sections (23%) also concurred with the current rate in Germany (25%).

Thus, although the increased risk of experiencing an attack seen in most patients undoubtedly represented a deterioration in health, treatment with C1-INH concentrate was in all cases safe and effective during and after pregnancy, with no detrimental effects to the women or their children. Furthermore, none of the patients experienced an attack during the traumatic experience of delivery, an event that can often, but not always, stimulate an attack.

Because almost all patients received prophylactic treatment with C1-INH concentrate before delivery, it is not known whether any attacks would have occurred during delivery. Nevertheless, given the high attack rates experienced during pregnancy in our study population, the lack of attacks during delivery appears to reflect a beneficial prophylactic effect of C1-INH treatment at this time.

In conclusion, our study has shown that pregnancy can exacerbate HAE, resulting in an increased risk of having an acute attack and also during the postpartum period. However, we have also shown that these attacks can be safely and effectively treated with C1-INH concentrate, thereby removing any potential anxiety that women with HAE may have with respect to the course of their disease during pregnancy.

Because all the pregnancies progressed normally, with no drug-related adverse effects, our study indicates a clear benefit of including C1-INH therapy in a management plan for pregnant women with HAE. Such a plan should be coordinated between a patient’s gynecologist, midwife, and HAE specialist.

The plan should ensure that, where licensed, an adequate supply of C1-INH concentrate is available either in the clinic or at home, depending on whether on-demand therapy or IRT is indicated, for treating an anticipated increase in the rate of acute attacks during pregnancy.

Provision should also be made for prophylactic C1-INH treatment before delivery. The reasons for increased attack rates during our study, as compared with some other studies in which no such trend was seen, remain unclear. Further investigation is warranted to elucidate the factors that can influence attack rates during pregnancy.

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