Hereditary angioedema and pregnancy complications and outcomes in a population-based cohort

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Background

- Hereditary angioedema (HAE) is a rare, autosomal dominant genetic disorder predominantly caused by C1 esterase inhibitor (C1-INH) deficiency or dysfunction and is characterized by localized acute edema attacks resulting from increased vascular permeability.[1]
- Pregnancy has been reported to potentially worsen HAE symptoms in relation to the physiological increase in estrogens, but the impact of HAE on pregnancy outcomes has not been investigated systematically in larger patient cohorts. Moreover, there is controversy regarding whether HAE confers a higher risk of adverse pregnancy outcomes compared to an age-matched non-HAE population.[2]
- Current international treatment guidelines recommend C1-inhibitor replacement therapy as the only 1st line HAE treatment during pregnancy and delivery.[3]
- Real-world evidence of the association of HAE with pregnancy outcomes, and observed comorbidities during pregnancy, may direct more targeted research into the clinical management for this population.

Objective

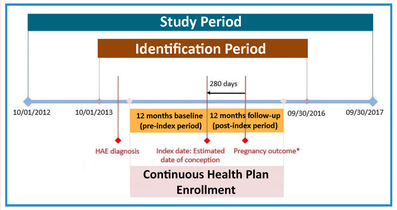
- To compare comorbidities, outcomes, and post-partum complications among pregnant patients with and without HAE using nationally-representative, pooled commercial claims data.

Methods

Data Source & Study Design

- A retrospective study design using pooled data from the IBM Watson Health MarketScan Commercial Claims and the IQVIA PharMetrics Plus databases from 01OCT2012-30SEP2017 was used to identify pregnant patients with and without HAE (Figure 1).
- The MarketScan database offers data on 29 million covered lives, and the PharMetrics Plus claims database reflects ~40 million lives in any given recent year.
- Pooling both databases provided a sample size large enough to create a nationally-representative data sample of Americans with employer-provided health insurance and Medicaid.

Figure 1. Study design



HAE: hereditary angioedema
*Pregnancy outcomes included the outcome of delivery (i.e. live/still birth and spontaneous/induced abortion).

Patient Selection

- *HAE Pregnancy Case Cohort :*
  - had ≥1 claim for a pregnancy outcome including live or still birth during the identification period (International Classification of Diseases–Ninth Revision–Clinical Modification [ICD-9-CM]: V27) and spontaneous/induced abortion (ICD-9-CM: 634, 635, 636, 637; Current Procedural Terminology [CPT]: 59840, 59841, 59850, 59851, 59852, 59855, 59856, 59857; Healthcare Common Procedure Coding System [HCPCS]: S0199, S2260, S2262, S2265, S2266, S2267);
  - had ≥1 claim for HAE diagnosis (ICD-9-CM:277.6; ICD-10-CM: D84.1) or ≥1 prescription claim for an HAE medication (icatibant, ecallantide, or intravenous or subcutaneous C1-INH) at any time prior to or after the pregnancy outcome;
  - had ≥280 days of continuous health plan enrollment prior to the pregnancy outcome; the date of conception was estimated as the date 280 days prior to the pregnancy outcome date and was designated as the index date;
  - were aged 15-49 years on the index date; and
  - had continuous health plan enrollment ≥12 months pre- (baseline) and post-index date (follow-up period).
- *Non-HAE Pregnancy Control Cohort:*
  - met all the inclusion criteria above, except that non-HAE patients had no evidence of HAE diagnosis or HAE medications at any time in the study period.

Baseline Characteristics

- Demographic characteristics including age, US geographic region, and health plan type were assessed as of the index date.
- Clinical characteristics including Quan-Charlson comorbidity index (CCI) scores, individual comorbidities, and pregnancy-related risk factors in the 12-month baseline period were evaluated.

Outcome Variables

- Pregnancy outcomes including live birth and still birth (singleton and multiple births), spontaneous abortion/miscarriage, induced abortion, premature delivery, caesarean delivery, and induced labor were evaluated in the 12-month follow-up period.
- Complications including gestational hypertension, pre-eclampsia/eclampsia, gestational diabetes, placenta previa, ectopic pregnancy, premature rupture of membranes, hyperemesis gravidarum, and oligohydramnios in the 12-month follow-up period were captured.
- Postpartum complications were assessed, including postpartum hemorrhage, hemorrhage following abortion or ectopic and molar pregnancies, blood transfusion, hospitalized postpartum infection, postpartum infection diagnosed in outpatient setting, venous thromboembolism, and postpartum depression during the 3 months following delivery.

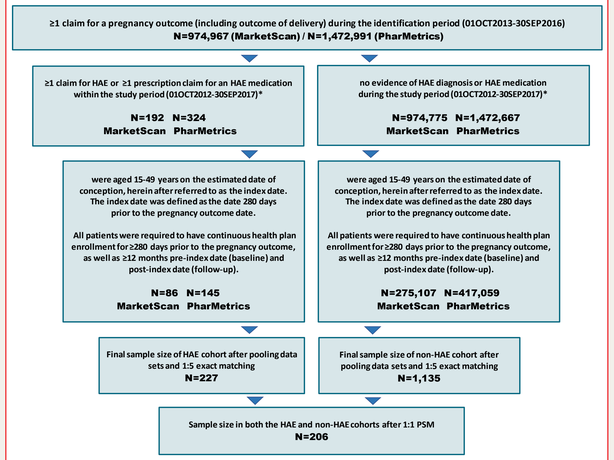
Statistical Analysis

- For each HAE patient (pregnant with HAE), 5 non-HAE patients (pregnant without HAE) of identical age, region, and health plan were included.
- Descriptive statistics including χ2 tests, student t-tests, and standardized differences (STDs) were calculated for each variable.
- 1:1 propensity score matching (PSM) was performed to compare HAE and non-HAE cohorts, using the nearest neighbor method with a caliper of 0.2 times the standard deviation of the logit of the propensity score, and a cutoff of STD <10% was considered well-balanced:
  - Covariates in the logistic regression model used for propensity score calculation included age, US geographic region, health plan type, Quan-CCI scores, and significant individual comorbidities and pregnancy-related risk factors.

Results

- After applying the sample selection criteria, a total of 1,362 pregnant patients were identified (Figure 2), including 227 HAE patients and 1,135 non-HAE patients.

Figure 2. Patient selection criteria



*If there were multiple pregnancies during the study period, only the first pregnancy was considered.
HAE: hereditary angioedema

Baseline Characteristics (Table 1)

- After 1:5 exact matching of HAE patients to non-HAE patients based on demographics, both cohorts had a mean age of 32 years, and patients were most likely to reside in the South US region (43.6%) and receive care through a preferred provider organization (77.1%) health plan.
- As compared with non-HAE patients, those in the HAE cohort had a significantly higher mean Quan-CCI score (0.4 vs 0.2, p<0.0001) and likelihood of ≥1 pregnancy-related risk factor (18.9% vs 10.2%, p=0.0002, STD=24.9) or having ≥1 individual comorbidity (65.6% vs 50.0%, p<0.0001, STD=31.9). The most notable of those co-morbidities included systemic lupus erythematosus (5.7% vs 0.1%, p<0.0001), thrombogenic mutations (5.3% vs 0.7%, p<0.0001), and allergic rhinitis (22.5% vs 9.9%, p<0.0001).
- After PSM, there were a total of 206 patients in each cohort, and the cohorts were well balanced in terms of age, residency, type of health plan, and clinical characteristics (i.e., Quan-CCI score, individual comorbidities, and pregnancy-related factors) observed with STD <10%.

Pregnancy Outcomes and Complications After PSM

Pregnancy Outcomes for the HAE Cohort (Figure 3)

- Significantly lower likelihood of having a singleton live birth (73.3% vs 83.0%, p=0.0171, STD=23.6).
- Although not statistically significant, the following outcomes were clinically relevant based on STD>10%.
  The HAE cohort had a:
  - higher proportion of patients who had a spontaneous abortion (17.5% vs 12.1%, p=0.1270, STD=15.0) or induced abortion (5.8% vs 3.4%, p=0.2402, STD=11.6); and
  - lower proportion of patients with induced labor (11.7% vs 16.0%, p=0.1991, STD=12.6).

Complications During Pregnancy (Figure 4)

- As compared with the non-HAE cohort, the HAE cohort had a significantly higher proportion of patients with premature rupture of membranes (9.7% vs 3.9%, p=0.0188, STD=23.2).
- Although not statistically significant, the following outcomes were clinically relevant based on STD>10%.
  The HAE cohort had a:
  - higher proportion of patients who had oligohydramnios (11.2% vs 5.8%, p=0.0519, STD=19.2), hyperemesis gravidarum (5.3% vs 2.9%, p=0.2155, STD=12.2), and ectopic pregnancy (1.9% vs 0.5%, p=0.1771, STD=13.3); and
  - lower proportion of patients with gestational diabetes (10.2% vs 15.0%, p=0.1379, STD=14.6).

Complications During 3 Months Postpartum

The HAE cohort had a higher proportion of patients with postpartum:

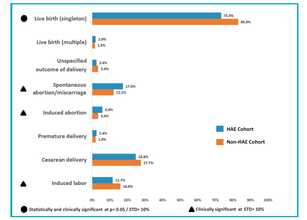
- infection (1.0% vs 0.0, p=0.1563, STD=14.0),
- hemorrhage (6.3% vs 3.9%, p=0.2627, STD=11.0), and
- depression (8.3% vs 5.3%, p=0.2402, STD=11.6).

Table 1. Baseline demographic and clinical characteristics among pregnant HAE vs non-HAE patients

	Before propensity score matching				
	HAE cohort (N=227)		Non-HAE cohort (N=1,135)		P-value
	N/ Mean	%/ SD	N/ Mean	%/ SD	
Baseline characteristics					
Age (in years)	31.7	5.6	31.7	5.6	1
Median age (in years)	32		32		
15-19 years	5	2.2%	25	2.2%	1
20-24 years	20	8.8%	100	8.8%	1
25-29 years	51	22.5%	255	22.5%	1
30-34 years	83	36.6%	415	36.6%	1
35-39 years	52	22.9%	260	22.9%	1
40-44 years	15	6.6%	75	6.6%	1
45-49 years	1	0.4%	5	0.4%	1
US geographic region					
Northeast	46	20.3%	230	20.3%	1
North central	46	20.3%	230	20.3%	1
South	99	43.6%	495	43.6%	1
West	32	14.1%	160	14.1%	1
Unknown	4	1.8%	20	1.8%	1
Health plan type					
HMO	24	10.6%	120	10.6%	1
POS	13	5.7%	65	5.7%	1
Preferred provider organization	175	77.1%	875	77.1%	1
Consumer driven health plan	9	4.0%	45	4.0%	1
Others	6	2.6%	30	2.6%	1
Quan-Charlson comorbidity index score	0.4	0.7	0.2	0.5	<0.0001
Individual comorbidities					
Patients with ≥1 individual comorbidity*	149	65.6%	568	50.0%	<0.0001
Breast cancer	3	1.3%	2	0.2%	0.0092
Valvular heart disease	7	3.1%	12	1.1%	0.0175
History of bariatric surgery	9	4.0%	13	1.2%	0.0021
Ischemic heart disease	10	4.4%	15	1.3%	0.0016
Chronic liver disease including fatty liver	6	2.6%	7	0.6%	0.0042
Solid organ transplantation history	3	1.3%	0	0.0%	0.0001
Systemic lupus erythematosus	13	5.7%	1	0.1%	<0.0001
Thrombogenic mutations	12	5.3%	8	0.7%	<0.0001
Allergic rhinitis	51	22.5%	112	9.9%	<0.0001
Asthma	25	11.0%	58	5.1%	0.0007
Mental disorders, except psychoses	55	24.2%	196	17.3%	0.0135
Headache, including migraine	40	17.6%	136	12.0%	0.0208
Osteoarthritis	43	18.9%	120	10.6%	0.0004
Pregnancy-related risk factors					
Patients with ≥1 pregnancy-related risk factor*	43	18.9%	116	10.2%	0.0002
Kidney disorder	2	0.9%	1	0.1%	0.0200
Heart disease	1	0.4%	0	0.0%	0.0253
H/o Isoimmune disease	3	1.3%	2	0.2%	0.0092
H/o Gestational diabetes	4	1.8%	3	0.3%	0.0040
H/o Intrauterine growth restriction	6	2.6%	9	0.8%	0.0148
H/o Chromosome abnormality	2	0.9%	1	0.1%	0.0200

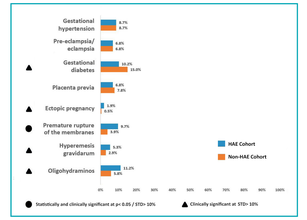
HAE: hereditary angioedema; HMO: health maintenance organization; H/o: history of; POS: point of service; SD: standard deviation.
*The table presents the individual comorbidities and pregnancy-related risk factors that were significant at p<0.05. Pregnancy-related risk factors were assessed in the 12-months prior to the index date, which is the estimated conception date.

Figure 3. Pregnancy outcomes among HAE vs non-HAE cohorts after PSM



HAE: hereditary angioedema;
PSM: propensity score matching;
STD: standardized difference.

Figure 4. Pregnancy complications among HAE vs non-HAE cohorts after PSM



HAE: hereditary angioedema;
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Limitations

- Due to the nature of administrative claims-based studies, findings are subject to potential miscoding or diagnoses entered for administrative processing rather than clinical completeness.
- Certain information that could influence study outcomes, such as clinical and disease-specific parameters, are not readily available in claims data; hence, residual confounding is possible.
- ICD codes used for HAE are not specific enough to distinguish HAE-C1INH from HAE-NI-C1INH, and thus we cannot assess the proportion of each population, or differences in comorbidities, risk factors, or pregnancy outcomes, in this HAE cohort study.
- As the study design is based on the estimated conception date, the results should be interpreted with caution due to the lack of availability of this information in the claims data, especially in patients who had premature delivery or abortion.
- Patients with diagnosis or prescription codes for other forms of angioedema and allergic reactions were not censored.
- The generalizability of the study findings may be limited to patients with continuous commercial insurance coverage.
- Limiting the baseline period to 12 months for adequate sample size may underestimate pregnancy-related risk factors in both HAE and non-HAE cohorts.

Conclusion

- Several comorbidities known to be associated with adverse pregnancy outcomes have been found to be more prevalent in HAE pregnant women (immunodeficiencies, thrombogenic disorders and autoimmune diseases).
- Adverse pregnancy outcomes among HAE patients included a statistically significantly lower likelihood of having a live birth and a higher risk of premature rupture of membranes.
- HAE patients also had clinically relevant higher rates of other adverse pregnancy outcomes such as oligohydramnios, hyperemesis gravidarum, and ectopic pregnancy.
- We conclude pregnant HAE patients are at a higher risk for adverse pregnancy outcomes due to HAE and/ or due to co-morbidities associated with this condition or its therapies. These findings support international treatment recommendations[3] for an interdisciplinary approach to managing HAE pregnant patients by Maternal Fetal medicine and HAE experts.
- These unique findings provide insight into the clinical implications of HAE; further investigations are required to explore the underlying reasons and impact of the C1-INH deficiency status in the pathophysiology of maintaining a healthy pregnancy.

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Author Disclosures

AS Patel: Employment – CSL Behring; **MC Treadwell:** N/A; **S Borra:** Employment – STATinMED Research, a paid consultant to CSL Behring; **T Machnig:** Employment – Former employee of CSL Behring; **A Bica:** Employment: CSL Behring; **FI Hsu** – N/A
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