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Short communication

Management of pregnancy in hereditary angioedema in a resource constrained setting: Our experience at Chandigarh, North India

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disorder distinguished clinically by recurrent episodes of non-pruritic swelling. Although pregnancy has been considered a trigger, it may have variable effect on frequency of attacks of HAE. C1-inhibitor (C1-INH) is the treatment of choice for management of HAE during pregnancy. However, because of non-availability of C1-INH therapy in developing countries, fresh-frozen plasma (FFP) and tranexamic acid remain the drugs of choice in pregnancy for treatment of acute attacks and for prophylaxis respectively. There is paucity of data on outcome of pregnancy with patients with HAE from developing countries such as India where all the first line medications are not available.

A retrospective review was done including four HAE patients who conceived (with a total of 9 pregnancies). Our results suggest that frequency of attacks may increase during pregnancy especially during second trimester and post-delivery (during breastfeeding). However, HAE attacks are rare at the time of delivery.

In resource limited settings, treatment with FFP/tranexamic acid needs to be individualised.

Hereditary angioedema (HAE) is an uncommon genetic disorder characterised clinically by recurrent episodes of swelling (Jindal et al., 2021). Most attacks are spontaneous. However, common triggers include stress and trauma (Banday et al., 2020). Pregnancy may have variable effect on frequency of attacks of HAE (Caballero et al., 2014). C1-inhibitor (C1-INH) is the treatment of choice for management of HAE during pregnancy (Caballero et al., 2012). However, there is paucity of data on this aspect especially from developing countries where C1-INH and other first line medications are not easily available. We report our experience in managing 9 pregnancies amongst 4 women with HAE.

A review of medical records of all patients diagnosed to have HAE in Allergy Immunology Unit, Department of Paediatrics and Medico-surgical Disorder Clinic, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India was done. Diagnosis was made on basis of suggestive clinical history, low C4 and low C1-INH levels. *SERPING1* gene sequencing was carried out in all patients.

Clinical details of 4 patients who had conceived were assessed in detail (Table 1).

Median age at onset of symptoms and median age at diagnosis was 2 years (range: 1–18 years) and 18 years (range: 5–25 years) respectively. Median age at pregnancy was 28 years (range: 22–31 years). Tranexamic acid was used as prophylaxis for prevention of attacks in 5 pregnancies (during 2nd and 3rd trimester in 2 pregnancies, during first trimester only in 2 pregnancies and all 3 trimesters in 1 pregnancy). Stanozolol and fresh-frozen plasma (FFP) were used as prophylaxis at time of delivery (short-term prophylaxis) in one patient. Attenuated androgens were not used as long-term prophylaxis during pregnancy. There were 3 abortions (1 was a planned medical termination of pregnancy in first trimester and 2 were spontaneous abortions in first trimester associated with poor fetal growth). Six pregnancies went till term. Mode of delivery was vaginal in 4; lower segment Caesarean section (LSCS) was performed in 2 pregnancies for obstetric indications.

We found that frequency of attacks increased during pregnancy, especially during second trimester (Table 1). Patient 3 reported an increased frequency of attacks at time of conception during her 3rd and

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Table 1
Clinical details of 4 patients with hereditary angioedema and frequency of episodes of angioedema during pregnancy and post-partum (Figures in bold indicate more than usual frequency of episodes).

Patient	Age at onset of symptoms (years)	Age at diagnosis of HAE (years)	Clinical manifestations	Laboratory investigations including *SERPING1* gene sequencing	Family history of HAE	Details of treatment		Age at pregnancy (years)	No of attacks in 1st trimester (per month)	No of attacks in 2nd trimester (per month)	No of attacks in 3rd trimester (per month)	Mode of delivery	No of attacks post-delivery/during breastfeeding (per month)
1[#]	18	24	Swelling of face, hands and feet	C4- <3mg/dL (N = 10–40) C1-INH: 38 (N = 195–345) *SERPING1* gene [Exon 8c.1429 T > G, p. Phe477Val]	Yes	–	TA	22* 24 28*[a]	0 0 1	**4** **4** –	1 1 –	Vaginal Vaginal	1 1 –
2[##]	2	25	Swelling of forehead, hands and feet and larynx	C4- <8mg/dL (N = 10–40) C1 INH-38 mg/L (N = 195–345) *SERPING1* gene [Exon7 c.1100 T > G, p.Leu367Arg]	No	FFP	S, TA	27	0	**2**	2(Laryngeal oedema)	Vaginal	**2**
3[###]	1	12	Swelling of face, hands, feet and larynx and abdominal pain	C4 < 10.7 mg/dL (N = 20–50) C1 INH- 65 mg/L (N = 195–345) *SERPING1* gene [intron 2c.51 + 1G > A, splicing defect]	Yes	FFP	S, D, TA	28[b] 29[b] 30* 31*	1 1 ** **	– – 1 (1 episode of pain abdomen) 0	– – 0 0	 LSCS LSCS	– – **4** **4**
4[####]	2	5	Swelling of face, hands, feet and larynx and abdominal pain	C4 < 10.7 mg/dL (N = 20–50) C1 INH- 95 mg/L (N = 195–345) *SERPING1* gene [intron 2c.51 + 1G > A, splicing defect]	Yes	FFP	S, D, TA	27	**2**	**4**	**3**	Vaginal	**3**

[a] Planned medical termination of pregnancy.
[b] Spontaneous abortion.
[#]Her diagnosis was established at time of second pregnancy.
[##]Prior to pregnancy, she was on long term prophylaxis with stanozolol and tranexamic acid and had minimal symptoms. These drugs were discontinued as soon as she conceived. First 5 months of her pregnancy were uneventful. Later she had episodes of peripheral oedema. During 3rd trimester, she had two episodes of laryngeal oedema requiring hospitalisation and use of fresh-frozen plasma. No complications were noted at time of delivery. At present she is 2 months post-partum and continues to have 2 episodes of angioedema every month.
[###]She had 2 spontaneous abortions during first trimester. She was taking tranexamic acid as long-term prophylaxis during both pregnancies. Soon after that, her TA was discontinued. She had an increased frequency of attacks at time of conception in 3rd and 4th pregnancies. She was given stanozolol and FFP as short-term prophylaxis at time of LSCS during 3rd pregnancy. She experienced more frequent attacks of angioedema during breast feeding (for 1st 6 months).
[####]She is younger sister of patient 3. She had more frequent symptoms as compared to her sister prior to pregnancy and was taking intermittent stanozolol and tranexamic acid. She had more frequent attacks of angioedema during all trimesters of pregnancy while her delivery period was uneventful. She experienced more frequent attacks post-partum during breast-feeding and continues to have 2–3 episodes of angioedema per month despite taking stanozolol and tranexamic acid prophylaxis (1-year post-partum now).
* Not on any medication (TA was used during all other pregnancies).
** Increased attacks noted at the time of conception (3/week).
SERPING1 gene variants in case 1 and 2 are novel and are predicted to be pathogenic based on *in silico* prediction tools while *SERPING1* gene variant in case 3 and 4 is previously reported in patients with HAE.

4th pregnancies. The most common attack site was peripheral. One patient had an abdominal attack in addition to peripheral oedema while one patient had 2 episodes of laryngeal oedema during the 3rd trimester requiring emergency hospitalisation and FFP. In 2 patients, in whom more than 1 pregnancies were followed, it was observed that patient 1 had similar pattern of attacks during 2nd trimester in both pregnancies while patient 3 had no increase in frequency of attacks except an increased frequency reported during the time of conception.

None of the patients had pre-term labour, an angioedema attack or any other complications during delivery. One patient received short term prophylaxis with FFP and stanozolol for one delivery. In the post-partum period, frequency of attacks increased in 3/4 patients (4/6 pregnancies). These were managed with tranexamic acid. Patient 3 chose not to take prophylaxis despite having an increased frequency of attacks post-partum. Patient 1 did not experience an increased frequency of episodes in the post-partum period.

There have been several reports on association between HAE attacks and pregnancy. Pregnancy may decrease or aggravate frequency of attacks or, at times, may have no effect on HAE attacks (Caballero et al., 2012). There is paucity of data on this aspect from developing countries such as India where first line treatments are not available.

Our results suggest that frequency of attacks increases during pregnancy especially during second trimester and after birth during breast feeding (Table 1 and Fig. 1). We reviewed published literature on this aspect and included only those studies wherein more than 5 pregnancies were evaluated (Table 2). The review shows that there is increased frequency of attacks during pregnancy as was also seen in present cohort (Martinez-Saguer et al., 2010; Baker et al., 2013; González-Quevedo et al., 2016; Machado et al., 2017; Hakl et al., 2018; Fox et al., 2017; Bouillet et al., 2008). However, studies by Frank et al and Chinniah et al have shown reduced attacks during last two trimesters of pregnancy, and increased frequency and severity of attacks post-partum (Chinniah and Katelaris, 2009; Frank et al., 1976). Our data, on the other hand, suggest a clear increase in attacks in second trimester and post-partum. One patient had more attacks at time of conception.

A few studies have also shown that severity of attacks in pregnancy is essentially similar to pre-pregnancy states, except that they are more predisposed towards abdominal attacks possibly due to mechanical pressure by increasing uterine size and foetal movement (Caballero et al., 2012; González-Quevedo et al., 2016; Hakl et al., 2018; Fox et al., 2017; Czaller et al., 2010). However, in our cohort, peripheral attacks were more common followed by abdominal and laryngeal attacks.

Although trauma is often recognised as a trigger for HAE, in most case series it has been reported that angioedema attacks are relatively rare at time of delivery despite obvious perineal trauma. Exact mechanism for this effect is not known. In the present series also, we observed no angioedema episodes during delivery even though short-term prophylaxis was used in only 1 patient.

A Brazilian survey of 13 pregnancies has also reported that peripheral attacks were more common in pregnancy and most attacks occurred in second trimester with no attacks at time of delivery. None of the patients in this series received C1-INH therapy (Machado et al., 2017).

It has been postulated that presence of high levels of serum oestrogen in first trimester may lead to increase in frequency and severity of attacks while the progesterone surge during second trimester may lead to reduced frequency of attacks. In the third trimester, increases in concentrations of oestrogen and placental prolactin along with mechanical stress due to increased uterine size and foetal movements may lead to more frequent attacks (Caballero et al., 2012). However, reasons for increased frequency of angioedema episodes observed during second trimester in the present series and in the one reported from Brazil is not clear.

The rate of spontaneous abortions in the present series was 22.2% (2/9 pregnancies) which is slightly higher than the rate of spontaneous abortion reported in patients with HAE (Bouillet et al., 2008) but less than the rate of spontaneous abortions seen in India (approximately 33%) (Patki and Chauhan, 2016).

A strength of our study is that this is one of the largest single centre cohorts on management of pregnancy in patients with HAE from developing countries. Limitations include retrospective analysis of data using patient records and recall methods wherein patients were asked to recall the number of episodes of angioedema during various trimesters of pregnancy.

Pregnancy may have variable effects on frequency of attacks in patients with HAE. Most patients experience increased frequency of attacks, especially during second trimester and post-partum during breast feeding. Treatment, including long term and short-term prophylaxis, has to be individualised.

1. Author's statement

AKJ: Conception of idea, writing of initial draft, patient management, editing of manuscript at all stages of its production and final approval, review of literature.

PB: Writing of initial draft, patient management, editing of manuscript at all stages of its production, review of literature.

SC/AK/RT: Editing of manuscript, laboratory investigations, review of literature.

PS/SC: Editing of manuscript, patient management, review of literature.

HL: Editing and critical revision of manuscript.

SS: Patient management, critical revision of manuscript, review of

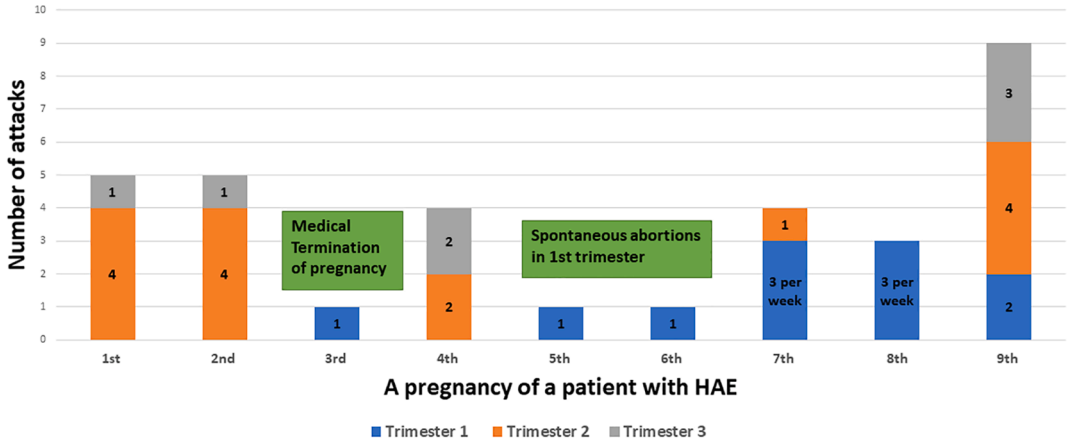

Fig. 1. Bar chart showing frequency of attacks in various trimesters of pregnancy and during breastfeeding in the present series. An attack is defined as an episode of subcutaneous and/or submucosal edema related to HAE.

Table 2
Review of studies on management of pregnancy in hereditary angioedema.

Author, Year, Country	No. of pregnancies	Type of HAE	Salient findings
Frank et al., 1976; Single centre; USA	25	NA	Attack rates were fewer in last two trimesters of pregnancy; no attacks at time of delivery
Bouillet et al., 2008; Multicentric; Europe	227	Type I/ II	Attacks rate were more in 38% of pregnancies while attacks rates were fewer in 30% pregnancies; no change in frequency of attacks in 32% pregnancies; Only 6% experienced increased attacks during delivery
Chinniah and Katelaris, 2009; Multicentric; Australia	16	NA	Attack rates were fewer in last two trimesters of pregnancy; during post-partum, there was increased frequency and severity of attacks
Martinez-Saguer et al., 2010; Single centre; Germany	35	Type I	Attack rates increased during pregnancy - highest during 2nd and 3rd trimester; C1-INH therapy had good efficacy and safety
Baker et al., 2013; Multicentric; USA	16	NA	Attacks reduced in patients receiving C1-INH therapy
González-Quevedo et al, 2016; Multicentric; Spain	125	Type I Type II	More frequent attacks in 59% of patients but no increase in severity during pregnancy; similar semiology in multiple pregnancies; no discernible pattern in frequency of attacks in the three trimesters of pregnancy
Fox et al., 2017; Multicentric; USA, Germany and Switzerland	11	Type I Type II	All patients received C1-INH therapy (more frequent doses required during pregnancy); no attacks at time of delivery; C1-INH therapy was found to be safe
Machado et al., 2017; Single centre; Brazil	22	Type I	Emotional stress was most common trigger followed by trauma; peripheral attacks were more common in pregnancy; most attacks occurred in second trimester; no discernible pattern in severity of attacks in the three trimesters of pregnancy; no attacks at time of delivery; none received C1-INH
Hakl et al., 2018; Single centre; Czech Republic	6	Type I Type II	Most common site of attack was abdominal (67%); attacks most common during 2nd trimester; no attacks at time of delivery; C1-INH and icatibant had equal efficacy in treatment of attacks
Present study, 2021; Single centre; India	9	Type I	Tranexamic acid used in 6 pregnancies; stanozolol and FFP given at time of delivery in 1 patient; none received C1-INH; all patients experienced increased frequency of attacks during pregnancy (most in 2nd trimester); one reported an increased frequency of attacks at time conception; no angioedema attacks were observed at time of delivery; 3 patients also reported an increase in frequency of attacks in post-partum during breastfeeding

Abbreviations: HAE: hereditary angioedema, NA- Not available, FFP: Fresh frozen plasma.

literature, final approval.

2. Ethics approval

The manuscript was approved by Department Review Board. As it pertains only to retrospective collation of data of patients from clinic records, approval of the extant Institute Ethics Committee was not considered necessary. This is as per existing practice in the institute.

3. Consent to participate

An informed consent was obtained from all patients for participation in this study.

4. Consent for publication

An informed consent was obtained from all patients for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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