Therapy for Patients with Hereditary Angioedema during Pregnancy

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Hereditary angioedema (HAE) is a rare, inherited disease caused by a deficiency (HAE-1) or lack of functional (HAE-2) C1 inhibitor protein. The symptoms present with mucocutaneous swelling of various organ systems, such as the respiratory and gastrointestinal systems, which can manifest as stridor and abdominal pain, respectively. HAE can present with increased frequency and severity of attacks during the pregnancy and lactation period. This is thought to be due to hormonal changes, which may trigger HAE attacks. The management of this condition in pregnant and lactating patients can be challenging for providers due to disease rarity and the lack of data regarding the management of this specific population.

pregnancy lactation gestation prophylaxis hereditary angioedema

1. Long-Term Prophylaxis

Long-term prophylaxis (LTP) serves to reduce the frequency and severity of hereditary angioedema (HAE) attacks. However, LTP does not guarantee the complete prevention of attacks, and, for this reason, rescue treatment should also be available to patients. Given the hormonal changes that occur during pregnancy, pregnant women are more likely to experience frequent and severe HAE attacks. Thus, LTP should be discussed with all female patients anticipating pregnancy to subsequently improve the quality of life during pregnancy and throughout the lactation period. In addition, LTP should highly be considered in cases of frequent and/or severe attacks or when attacks are triggered by mood changes or stressors [1]. Overall, shared decision-making is recommended to establish the need for LTP. Patients with LTP should be educated on how to self-administer the medication. They should also be monitored for efficacy and side effects associated with the treatment [2]. In addition, it should be noted that despite being on LTP, all patients must have at least two doses of rescue therapy available for breakthrough attacks.

Although no clinical studies exist regarding the safety and efficacy of LTP during pregnancy and lactation, there have been multiple expert consensus panels that have published recommendations regarding management during pregnancy and lactation. The USA Hereditary Angioedema Medical Advisory Board and World Allergy Organization (WAO) both published consensus guidelines recommending LTP in patients according to their individual needs and tolerance to various medications [3][4]. They recommend SC or IV use of pdC1-INH as first-line therapy for pregnant and lactating patients, as they have the least reported side effects as well as a 40-year history of safe usage in Europe during pregnancy and lactation. The data regarding the use of rhC1-INH during pregnancy and lactation are limited; however, the guidelines include its use as appropriate and safe [5]. In contrast, the use of androgens,

such as danazol, is contraindicated in pregnancy and lactation. Androgens can cross the placenta and affect the fetus during pregnancy and can be secreted in the milk of a breastfeeding HAE patient. Maternal androgen use can ultimately cause virilization in the neonate. Anti-fibrinolytics, such as tranexamic acid, can be used, but their efficiency and risk are not clear. For this reason, the current guidelines suggest avoidance during pregnancy [3][4]. Tranexamic acid, however, can safely be used during lactation and has an indication during pregnancy for hemorrhage. The efficacy of tranexamic acid for HAE has not been demonstrated by clinical trials, but it appears to be safe to use if alternatives do not exist and if it is effective at reducing attacks [6]. Due to a lack of safety data during pregnancy for berotralstat and lanadelumab, recommendations regarding their use have not been made at this time. In addition, due to gastrointestinal adverse events with berotralstat and the ability of lanadelumab to cross the placenta, both should generally be avoided in these populations [3][4][7][8].

The International/Canadian guidelines also stress the importance of LTP in pregnant and/or lactating females with HAE. They recommend pdC1-INH as a first-line treatment in these patients, with a recommended dosage of 1000 IU of IV pdC1-INH every 3–4 days or 60 IU/kg body weight of SC C1-INH twice a week. They also recommend against using androgens due to the risk of virilization in the fetus [9].

The German-speaking consensus recommends LTP in pregnant females with recurrent attacks during the third trimester or a history of genital edema due to mechanical trauma during labor, such as a vacuum-assisted vaginal delivery [10].

Lastly, the Hereditary Angioedema International Working Group (HAWK), which is a group consisting of HAE physician experts around the world, released consensus guidelines recommending LTP in patients who experience more than 24 days of symptoms each year or more than 12 moderate/severe attacks each year. The decision to initiate LTP should involve a discussion regarding the risks and benefits. Although specific management for pregnant and lactating patients was not discussed, they reaffirmed that androgens should not be used [11].

2. Short-Term Prophylaxis

Numerous guidelines note pdC1-INH as being the safest form of treatment for rescue therapy, LTP, and STP during pregnancy and lactation, as noted above, due to minimal side effects on the mother and child [12]. Its long history of use in Europe without reports of adverse outcomes further supports this recommendation. Different guidelines, however, report various dosages for STP. The USA Hereditary Angioedema Medical Advisory Board 2020 recommends 20 IU/kg, while the WAO HAE Consensus Guideline recommends 1000 IU [3]. Given the data extrapolated from STP use, dosing is performed according to the weight, and, thus, 20 IU/kg is more reliable and recommended over a set dose of 1000 IU [13].

The importance of STP cannot be overemphasized [13]. Proper planning is key to success. At the time of delivery, at least two doses of pdC1-INH should be available: one dose for a procedure, if needed, and one dose for rescue therapy, if necessary, for an attack. During preparation for a procedure, surgery, or dental work, STP with pdC1-INH should be administered intravenously over 10 or so minutes shortly before the procedure. Researchers

recommend use of 20 IU/kg, and with the average person weighing 80 kg in the USA, this would result in a 1500 IU infusion. Since each vial has 500 IU, rounding to the nearest 500 prevents waste of this expensive medication. Even with STP, there is a minimal risk of having an attack of HAE, and the second dose can be administered as needed for an attack.

Vaginal delivery with local anesthesia may result in vulvar angioedema over the next three days, but the guidelines suggest that as long as vulvar manipulation, vaginal and uterine procedures, and trauma are not excessive, STP with pdC1-INH is not essential [13][14][15]. For this reason, vaginal delivery is the preferred choice for delivery [14]. If emergency cesarean delivery is indicated, pdC1-INH should be administered to prevent HAE attack secondary to the procedure. If cesarean delivery has already been planned to be the choice of delivery, STP with C1-INH at 20 IU/kg is recommended 30–60 min prior to the procedure [13][14]. In addition, STP should also be given prior to any upper airway manipulation to avoid irritation that may cause upper airway swelling. For this reason, local anesthesia is preferred over general anesthesia to avoid intubation [15]. These recommendations are summarized in **Table 1**.

Table 1. Best practices for managing pregnant HAE patients.

Pre-Operative Period:	Peri-Operative Period:	Post-Operative Period:
Ensure availability of at least 2 doses of appropriate rescue medication *	Use local anesthetic and/or nerve blocking to avoid need for intubation	Ensure availability of appropriate rescue medication throughout recovery and discharge periods
Assess for history of prior HAE attacks during surgical procedures	Perform vaginal delivery when possible to avoid surgical trauma	Prior to discharge, provide patient with education on rescue medication self-administration, if needed
Pretreat patient with appropriate STP medication *	Maintain ability to protect airway at all times during procedure	

3. Recommendations

See **Table 2** for recommended medications and dosing *.

As recommended by various international HAE consensus guidelines, therapy should be available during pregnancy and throughout the lactation period to reduce morbidity and possible mortality. PdC1-INH remains the drug of choice for rescue therapy for HAE attacks, STP, and LTP [5]. This recommendation is maintained despite cases of thrombotic events associated with pdC1-INH. Importantly, the thrombotic events are believed to be due to the presence of IV indwelling port catheters rather than the medication itself [16]. As an alternative for pdC1-INH, rhC1-INH is also recommended during pregnancy and lactation for on-demand therapy. Fresh frozen plasma is another alternative, although there may be variable amounts of C1-INH in each unit and higher rates of adverse effects [17]. Tranexamic acid should not be used for on-demand therapy given the risk of thrombotic/embolic events in addition to a lack of studies regarding its use in pregnant and/or lactating HAE patients [6]. Multiple case reports suggest icatibant as a safe choice for rescue therapy during pregnancy without any reportable adverse effects or abnormalities, but researchers believe the data are far too shallow to make this recommendation [18][19][20][21][22].

For STP, pdC1-INH remains the therapy of choice during pregnancy and lactation. The recommended dosage is 20 IU/kg at least 1 h prior to medical surgeries or dental procedures [3]. The alternatives include rhC1-INH and fresh frozen plasma [18][19][20][21].

The first-line therapy for LTP during pregnancy and lactation is C1-INH, including SC and IV options [3]. SC is preferred due to less invasiveness compared to IV and is dosed at 60 IU/kg twice weekly. The efficacy of this dosage is reported to result in an 85% reduction rate of attacks [19]. The IV route is standardly dosed at 1000 IU twice weekly, but post-approval higher doses of up to 2500 IU can be given twice a week if necessary. The phase 3 data of this dosage every 3–4 days has demonstrated a 50% reduction in attacks [4]. Both SC and IV C1-INH carry similar adverse effect profiles, which have been discussed earlier, with local injection site reactions being the most common [4][19]. Although tranexamic acid should not be used for on-demand therapy, it is frequently used in low- and median-income countries for LTP and appears to be effective and safe. For example, tranexamic acid is considered the first line in countries such as China and India [23][24]. However, it is not considered a first-line agent for LTP in more developed nations, such as the United States, for reasons stated earlier [6]. The cost of C1-INH may make many hesitant to initiate LTP, but researchers believe the risk and cost favor its use during pregnancy and lactation. During pregnancy, abdominal attacks may be misinterpreted as labor contractions or gastrointestinal problems, which can subsequently lead to inappropriate clinical decision-making, surgery, and unnecessary radiologic procedures. Also, since the growing fetus can potentially trigger an attack via mechanical trauma, it is important to suppress attacks. Pregnancy can also increase stress levels, which may lead to increased HAE attacks during this period. Shared decision-making should be encouraged when making the decision to initiate LTP [3][25]. A summary of medications for pregnant and/or lactating HAE patients is shown below in **Table 2**, while **Table 3** summarizes ways of reducing the risk of HAE attacks during pregnancy.

Table 2. Recommended medications for pregnant and lactating females with HAE.

Drug Name (Route of Administration)	Rescue Therapy	Short-Term Prophylaxis	Long-Term Prophylaxis	Dosage
pdC1-INH (IV)	1st line	1st line	1st line	Rescue: 20 IU/kg STP: 20 IU/kg 1–12 h before stressor LTP: 1000 IU every 3–4 days (may be increased up to 2500 IU)
pdC1-INH (SC)	-	-	1st line	60 IU/kg twice weekly
Fresh frozen plasma (IV)	2nd line	2nd line	-	2 to 4 units
Recombinant C1-INH (IV)	2nd line	2nd line	-	50 IU/kg up to 4200 IU
Tranexamic acid (oral)	3rd line	3rd line	-	20–40 mg/kg

Drug Name (Route of Administration)	Rescue Therapy	Short-Term Prophylaxis	Long-Term Prophylaxis	Dosage
Berotralstat (oral)	Recently approved for LTP. Insufficient data for use in pregnancy and lactation			150 mg daily
Icatibant (SC)	Approved for rescue therapy. Insufficient data for use in pregnancy and lactation			30 mg
Lanadelumab (SC)	Approved for LTP. Insufficient data for use in pregnancy and lactation			300 mg every 2–4 weeks
Androgens (oral)	Contraindicated during pregnancy and lactation			
Consider long-term prophylaxis for most pregnant women who have active HAE symptoms				
Pretreat with 20 IU/kg intravenous pdC1-INH 1 h before procedures, dental work, or surgery. Recombinant C1-INH and fresh frozen plasma may be alternate therapies if pdC1-INH is not available				
Have 2 doses of rescue therapy available of C1-INH or recombinant C1-INH at all times				
During delivery, use vaginal delivery when possible				
Always have capability to protect the airway during procedures and for 72 h after procedures				
Consider long-term prophylaxis for most pregnant women who have active HAE symptoms				

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