



Managing Severe Acute Asthma Exacerbation in Pregnancy during the COVID-19 Pandemic: A Case Report from a Resource-limited Setting

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Abstract

BACKGROUND: One-third of pregnant women will experience worsening asthma requiring emergency hospitalization. However, no report comprehensively discussed the management of asthma attacks in pregnant women in impoverished settings. We attempt to illuminate what general practitioners can do to stabilize and improve the outcome of severe acute asthma exacerbations in primary care with resource limitations.

CASE REPORT: A nulliparous 29-year-old woman in her 21st week of pregnancy presented severe acute asthma exacerbation in moderate persistent asthma with uncontrolled asthma status along with gestational hypertension, uncompensated metabolic acidosis with a high anion gap, anemia, respiratory infection, and asymptomatic bacteriuria, all of which influenced her exacerbations. This patient was admitted to our resource-limited subdistrict hospital in Indonesia during the COVID-19 pandemic for optimal stabilization. Crystalloid infusions, oxygen supplementation, nebulized beta-agonist with anticholinergic agents, inhaled corticosteroids, intravenous methylprednisolone, broad-spectrum antibiotics, subcutaneous terbutaline, mucolytics, magnesium sulphate, oral antihypertensives, and continuous positive airway pressure were used to treat her life-threatening asthma. After she was stabilized, we referred the patient to a higher-level hospital with more advanced pulmonary management under the supervision of a multidisciplinary team to anticipate the worst scenario of pregnancy termination.

CONCLUSION: Limitations in primary care, including the lack of sophisticated intensive care units and laboratory panels, may complicate challenges in managing severe acute asthma exacerbation during pregnancy. To enhance maternal-fetal outcomes, all multidisciplinary team members should be well-informed about key asthma management strategies during pregnancy using evidence-based guidelines regarding the drug, rationale, and safety profile.

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Introduction

Asthma is a major chronic illness encountered during pregnancy, common between 17 and 24 weeks of gestation [1]. The prevalence of asthma in pregnancy is between 3% and 12% [2], with one-third of pregnant women will experience worsening asthma and 20% requiring further medical intervention [3]. Uncontrolled asthma during pregnancy will deprive oxygen saturation and thus affect fetal development negatively [4].

Some severe exacerbation arises from issues related to worrying about the side effect of asthma medications during pregnancy. Pregnant women tend to reduce or stop their controllers, thus indirectly increasing the use of relievers [5]. Moreover, the COVID-19 pandemic has been a concerning issue for the asthmatic patient because it may impact asthma control status [6], [7] due to prolonged lockdowns,

social restrictions, transportation restraints, limitation of patients in the polyclinic, or personal anxieties of contracting an infection in health-care facilities [8].

Asthma management has been primarily ineffective worldwide, particularly in resource-limited areas [9]. The lack of affordable essential asthma medication, which leads to low prescribing rates during pregnancy, and the lack of access to current information about medication effects on the fetus, are the main barriers reported when treating asthma in pregnancy [9]. Furthermore, pulmonary monitoring equipment, sophisticated intensive care units (ICUs), and multidisciplinary specialized doctor personnel are scarce in primary care settings. All of these hurdles will make managing severe asthma exacerbations in developing countries like Indonesia more complicated.

Today, no report comprehensively discussed the management of asthma attacks in pregnant women during the COVID-19 pandemic in impoverished

settings. Therefore, we attempt to illuminate what general practitioners (GPs) can do to stabilize and improve the outcome of severe acute asthma exacerbations in primary care settings, along with reviewing evidence-based medicine in terms of the rationale of our diagnosis and therapy for enhancing asthma management during pregnancy.

Case Illustration

A 29-year-old female, G2P1A0, in the 21st week of pregnancy, complained of worsening shortness of breath and chest tightness 6 h before admission. There was no paroxysmal nocturnal dyspnea or orthopnea, but there was dyspnea on exertion. She had difficulty walking and felt more comfortable bending forward while sitting. On admission, she could only say a few words or short phrases. The patient had used nebulized salbutamol 3 times at home and 2 × 2 mg of salbutamol orally, but the symptoms did not improve (usually, after 1–2 of nebulization, the symptoms would have improved). She had a history of asthma since the age of five, which relapsed in her first pregnancy 2 years ago, and worsened in this second pregnancy. In the past 4 weeks, asthma attacks were felt almost every day, mostly at night, disrupting her sleep due to shortness of breath (waking due to asthma at night 1–3×/week). Daytime asthma symptoms occurred 3–5 times each week, primarily during strenuous activities, which restrained her activities. The patient nebulized herself with inhaled salbutamol 2 puffs/day almost every day (2×/week, especially at night) and occasionally consumed oral salbutamol.

During this pregnancy, she stopped her asthma controller and never went to the doctor due to personal anxieties about the COVID-19 pandemic in health-care facilities. She had allergies to dust, cold temperatures, and seafood but no comorbidities other than asthma. In the past 3 days, she had bouts of cough with yellow-greenish and thickened phlegm and a runny nose in the morning. No lower abdominal pain, flank pain, or abnormality in urination existed. Our patient is a housewife and a secondhand smoker. About 250 m from her house, there were convections, tempeh, and bread factories.

Physical examination

On arrival, the patient seemed severely ill and weak but was alert and oriented on admission. Her hemodynamics were unstable with blood pressure (BP): 143/89 mmHg; heart rate (HR): 133 beats per minute (bpm) with no abnormalities on electrocardiography; respiratory rate (RR): 34 times per minute (tpm); body temperature: 36.5°C; and oxygen saturation (SaO₂)

90% on room air. Because a blood gas analysis (BGA) was not done at the time of admission, we could not precisely compute the PaO₂/fraction of inspired oxygen (FiO₂) ratio. Therefore, we generated PF ratios using estimated values from the SaO₂/FiO₂ table, yielding a range of 105–192 [10]. Remarkable physical findings included paleness in both conjunctivae, intercostal, and suprasternal retractions, with wheezing and rhonchi on both lung fields.

Laboratory findings

The low value of hemoglobin, erythrocytes, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration in Table 1 indicated microcytic hypochromic anemia. The leukocyte count and erythrocyte sedimentation rate (ESR) were both high, with neutrophilia suggesting bacterial infection. This patient's urinalysis revealed 20 WBCs/HPF, bacteriuria +5, negative leukocyte esterase (LE), and nitrite. According to antigen and polymerase chain reaction (PCR), testing, no evidence of COVID-19 was suspected in this patient. On arrival, the fetal monitoring revealed no indicators of distress, and all four features were within "normal" ranges or "reassuring" criteria with no decelerations [11]. Due to the lack of a peak flow meter (PFM) test to assess peak expiratory flow (PEF) rate in our settings, we did not assess this parameter. Furthermore, our patient did not undergo a chest X-ray throughout her second-trimester pregnancy.

Table 1: Laboratory work results for complete blood count, differential white blood cell count, electrolytes, and tests for COVID-19 on admission

Components	Results	Reference values
Complete blood count		
Hemoglobin	10.3 g/dL	11.5–15.5 g/dL
Erythrocyte	4.46 million/ μ L	4.0–5.2 million/ μ L
Hematocrit	32%	35–45%
MCV	71 fL	79–99 fL
MCH	21 pg	27–31 pg
MCHC	23 g/dL	33–37 g/dL
Leukocyte	14,400/ μ L	4,500–14,500/ μ L
Platelet count	330,000/ μ L	150,000–450,000
ESR	53 mm/h	0–10 mm/h
Differential white blood cell count		
Basophils	0%	0–2%
Eosinophils	0%	0–5%
Neutrophils	89%	50–70%
Lymphocytes	7%	20–40%
Monocytes	3%	0–8%
Electrolyte		
Sodium (Na)	136 mmol/L	136–146 mmol/L
Potassium (K)	3.5 mmol/L	3.5–5.0 mmol/L
Chloride (Cl)	98 mmol/L	98–106 mmol/L
Rapid antigen test		
SARS-CoV2-Ag	Negative	Negative
Polymerase chain reaction		
SARS-CoV2 PCR	Negative	Negative

MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, ESR: Erythrocyte sedimentation rate, SARS-CoV2-Ag: Antigen testing for severe acute respiratory syndrome coronavirus 2, SARS-CoV2 PCR: Polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2.

The BGA results, as given in Table 2, were interpreted as metabolic acidosis considering the value of pH, HCO₃⁻, and base excess [12]. The value of PCO₂ in this patient did not fall proportionally to the calculation of the compensatory acidosis formula (1.25 × [HCO₃⁻]), suggesting uncompensated acidosis [12].

The calculation of the anion gap using the value of electrolytes and bicarbonate $[(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)]$ indicated a high gap, making the diagnosis was uncompensated metabolic acidosis with a high anion gap [12].

Table 2: The results of blood gas analysis 8 h after admission to the intensive care unit

Components	Results	Reference values
PCO ₂	40.5 mmHg	35–45 mmHg
PO ₂	120 mmHg	80–105 mmHg
pH	7.26	7.35–7.45
SaO ₂	98%	92–99%
HCO ₃ ⁻	17.6 mmol/L	22–27 mmol/L
Total CO ₂	19 mmol/L	24–29 mmol/L
BE	-9.5 mmol/L	(-2)–3 mmol/L

PCO₂: The partial pressure of carbon dioxide, PO₂: The partial pressure of oxygen, pH: The potential of hydrogen, SaO₂: Oxygen saturation, HCO₃⁻: Bicarbonate ion, CO₂: Carbon dioxide, BE: Base excess.

Differential diagnosis

Our patient was diagnosed with severe acute exacerbation of moderate persistent asthma with uncontrolled symptom status. The pregnancy was “high-risk” based on the criteria of HR (+3), SBP (+1), RR (+3), temperature (0), SaO₂ (+1), and mental state (0) in the modified early warning scoring systems. This elevated BP was suspected due to an asthma exacerbation, and she was diagnosed with gestational hypertension. Our patient was also suspected of having asymptomatic bacteriuria and respiratory infection before the hospital. The diagnosis of infection was supported by leukocytosis with neutrophilia and increased inflammatory markers of ESR in laboratory results. Her prolonged acute asthma resulted in uncompensated metabolic acidosis with a high anion gap. Another diagnosis was microcytic hypochromic anemia, suspected due to iron deficiency anemia.

Treatment

The patient was administered a maintenance dosage of crystalloid Ringer lactate (500 mL/8 h). We started the oxygen supplementation with a nasal cannula at 3 LPM, increasing to 6 LPM, and switched to NRM at a flow of 10 LPM to maintain her saturation $\geq 96\%$. In the emergency room (ER), we nebulized the patient with 2.5 mL of ipratropium bromide 0.5 mg/salbutamol sulfate 3 mg per mL every 20 min for 1 h with additional one-dose nebulization of 2 mL of budesonide 0.5 mg/mL every 12 h. Nebulization of ipratropium bromide/salbutamol sulfate was continued every 6 h and budesonide every 12 h due to the lacking improvement in her exacerbations. We additionally gave her N-acetylcysteine (NAC) 3 × 200 mg orally for her cough, methylprednisolone 1 × 125 mg on the 1st day, and 1 × 62.5 mg on subsequent days, and ceftriaxone 1 × 2 g intravenously for her concurrent infections.

Despite receiving maximal bronchodilator medication in the ER, the therapeutic response was not achieved, and asthma deteriorated, resulting in refractory exacerbation. She was transferred to the ICU

and given a continuous positive airway pressure (CPAP) of 5 mmHg with a FiO₂ of 50% and airflow of 10–15 LPM. We injected 0.5 mL terbutaline subcutaneously (SC) and 2 g magnesium sulfate (MgSO₄) by slow drip in 100 mL of NaCl 0.9% over 30 min. Methylodopa 3 × 250 mg was also given orally to control her hypertension. Within 8 h of admission, she was getting stable. The use of sternocleidomastoid muscle and intercostal retraction had subsided. The BP (130/76 mmHg), HR (106 bpm), and RR (28 tpm) had diminished with improved SaO₂ of 98%. However, she remained dyspneic, even with CPAP, so we increased the oxygen flow to 15 LPM. This patient was suspected of having lactic acidosis due to excessive salbutamol administration, which worsened her respiratory function. Nonetheless, we could not objectively confirm it since no blood lactic acid monitoring is available in our facility.

Outcome and follow-up

Concerning about this patient’s life-threatening asthma, she was referred to a higher-level healthcare facility after stabilization (10 h post-admission) to aggressively manage her asthma by a complete objective lung examination and serial inflammatory biomarker tests. We required a hospital with complete mechanical ventilation and a sophisticated neonatal ICU (NICU) capable of caring for a 21-week baby if pregnancy termination was indicated (i.e., due to status asthmaticus). This patient also needed a multidisciplinary team of a fetomaternal obstetrician, an anesthesiologist, and a pulmonologist to monitor the fetal and mother’s well-being continually.

Discussion

The incidence of asthma in low-middle-income countries, including Indonesia, is frequently worse due to inadequate control. As we reported, lack of access to healthcare services and affordable medications, unavailability of comprehensive diagnostic modalities, uninsured status, low education level, and cultural beliefs all may contribute to the patient’s poor adherence [13]. These hurdles become even more complicated due to a scarcity of pulmonology centers that provide a multidisciplinary approach to evaluating asthma treatment response in pregnancy [13].

Asthma symptoms and severity levels can worsen at any moment during pregnancy, albeit most prevalent around the 25th week, as in our case [14]. The leading cause of asthma exacerbation during pregnancy is a decreasing trend of dosage and/or frequency in inhaled corticosteroids (ICS) as controllers, which are now combined with long-acting beta-agonists (LABAs) and referred to as LABACs. Otherwise, relievers such as

short-acting beta-agonists (SABAs) and low-dose ICS-formoterol are more routinely utilized during pregnancy [5], [15]. Healthcare providers should be able to educate patients about the need to use controllers based on the severity of their disease and reassure mothers that low-dose ICS is deemed safer for their babies than oral corticosteroids [16].

Another possible precipitating factor for asthma attacks in our patients was infections, which accounted for 20–73% of cases globally [17]. The dispersion of fungal spores, which may also provoke bronchospasm [18], was also possibly presented in this report. Our patient may have been exposed to extensive spores from tempeh and bread factories near her residence within the last year. There were also dust-spreading convection industries in the vicinity of her house. Furthermore, she is a housewife who is always at home, rendering her more vulnerable to the effects of these precipitating agents. Passive smoke exposure and frequent air pollutant exposure in the metropolitan city of Jakarta could also have contributed to her asthma recurrence [19]. Immunoglobulin E's response to allergic substances may be triggered by air pollution, resulting in asthma attacks [20].

The uncontrolled asthma status in this patient was also due to her anxieties that the COVID-19 pandemic might affect her pregnancy and that the hospital could be a source of transmission. This case was documented in Jakarta in 2021, between the second and third waves of the pandemic. The COVID-19 pandemic has been linked to increased personal anxiety, as seen in our patient, and thus contributed to her uncontrolled asthma status [6], [7]. Eldeirawi *et al.* [7] revealed that 48% of asthmatic patients had a high anxiety score during the pandemic, 43% had uncontrolled status, and 57% of people self-reported exacerbations. Compared with participants in the lowest anxiety quartile, the odds of uncontrolled asthma in those with higher anxiety quartiles ranged from 1.64 to 3.83 [7]. The uncontrolled status and worsening severity will make a pregnant woman prone to experience exacerbations. Therefore, telemedicine consultation is recommended in this situation for remotely managing and assessing patients' asthma control test scores regularly [21].

An ideal objective evaluation of a pregnant woman with asthma exacerbation should include a disease severity assessment, a physical examination, PFM measurement, and necessary laboratory tests. Investigations comprise complete blood count, arterial BGA, chest X-ray, or other tests to identify triggering factors [22]. However, not all modalities were available, and we did not have PFM as the most basic asthma diagnostic tool in the ER. In emergencies, hospital treatment of severe acute asthma exacerbations relies on pressurized metered-dose inhalers and/or oxygen-driven disposable nebulizers for SABAs and ipratropium bromide to the lungs, as well as systemic

corticosteroids administration (oral or parenteral). In 1 h of nebulization, relievers and supplemental oxygen were given every 20 min if the hypoxia was evident. We employed budesonide and ipratropium bromide/salbutamol sulfate for our patient's nebulization. The initial dose of budesonide of 2 mg, followed by 1 mg every 12 h, is expected to improve symptoms within 12–24 h [23]. Ipratropium bromide/salbutamol sulfate could be given 3–4 times a day if the three doses in the previous 1st h were inadequate. Since its discovery, ipratropium bromide and salbutamol sulfate have been widely used in asthma treatment during pregnancy. They are safe with no conclusive evidence of detrimental consequences (category B) [24].

Managing asthma attacks during pregnancy was more challenging during COVID-19. Reflecting on our experience, the practice of nebulization for exacerbation asthma during COVID-19 was diminished and only provided in particular cases in isolation rooms. In addition to nebulization, our patient got intravenous steroids to modulate her immune system during severe asthma exacerbations that were difficult to control. We gave the patient methylprednisolone at a dosage of 60–80 mg/day until PEF reached 70% of the predicted value or until the patient's best PEF was achieved [25]. Alternatively, intravenous hydrocortisone 4 × 100 mg can be utilized [25]. Because these systemic corticosteroids do not cross the placenta and do not induce lung maturation, it is appropriate for this use [26]. These medicines are also reasonably safe for pregnant women; however, the risks and benefits should be weighed [27].

As an additional treatment, our patient received terbutaline sulfate 0.25–0.5 mg/dose SC up to 4 times daily (0.01 mg/kg/dose, max 1–2 mg/day) [28]. This administration was because the patient's symptoms were not relieved with the aforementioned drugs. Subcutaneous terbutaline 0.5 mg (0.5 mL) produces clinical improvement in adults with severe acute asthma equivalent to epinephrine with no adverse drug effects [29] and has a safety category of B [25]. One study noted that injected terbutaline has similar benefits but slightly higher tachycardia rates than epinephrine [30]. Aside from bronchodilation, this medicine also has a tocolytic effect which is beneficial in our context [31]. Terbutaline may also be an option when aerosol-generating procedures are less practiced during the COVID-19 pandemic [30].

Two grams of MgSO₄ in 100 mL of NS were given to our patient within 30 min as an adjunct therapy for asthma exacerbations, tocolytic, and preeclampsia prevention [32]. The MgSO₄ dose we employed was 40 (25–75) mg/kg, with a maximum of 2 g, given as a slow bolus in 20 min [33]. Some suggest that response to intravenous MgSO₄ depends on achieving a serum magnesium concentration of 4–6 mg/dL (1.6–2.4 mmol/L). These values are similar to those used to achieve tocolysis. Lower magnesium concentrations

are also found in asthmatic patients than in controls, which correlates with bronchial hyperresponsivity in asthmatics [32]. In treating asthma, $MgSO_4$ may produce bronchodilation in a dose-dependent manner by blocking the voltage-dependent calcium channels across smooth muscle membranes to inhibit calcium influx, causing vascular, and bronchial smooth muscle relaxation. Furthermore, magnesium potentially enhances the effects of β_2 -agonists [32]. Another study suggested that $MgSO_4$ helps reduce histamine release by inhibiting mast cell degranulation, thus improving asthma exacerbations [33]. Although $MgSO_4$ appears safe and beneficial for a severe asthma attack, it is currently categorized as D by the FDA and should not be used for more than 5–7 days [34], [35].

When asthma becomes life-threatening, the patient should be transferred to ICU to get advanced treatment from anesthesiologists, including intubation and ventilation support [18]. In the ICU, we employed CPAP because it is the most effective treatment for poorly-controlled asthma with the acute respiratory syndrome. It may reduce airway inflammation and other asthmatic symptoms, including nocturnal asthma attacks [36]. However, no study has precisely assessed the effects of CPAP therapy on asthmatic pregnant women's airway responsiveness. Research by Lafond *et al.* [36] found that CPAP successfully improved patients' quality of life. It is more effective in obese patients, which was relevant to our subject because of her increased body weight [36]. Adding CPAP to conventional acute asthma treatment may result in faster PEF rate improvement with fewer SABAs required, a lower relapse rate, and a shorter hospital stay [37]. After using low-to-medium levels of CPAP, the use of accessory inspiratory muscles in our patient diminished, resulting in decreased respiratory fatigue. By overcoming the detrimental effects of auto-positive end-expiratory pressure, CPAP reduces the magnitude of inspiratory effort and improves tidal volume [38]. In patients with various respiratory disorders, CPAP has been utilized as an alternative to intubation, avoiding the complications of this invasive procedure [39]. Furthermore, aerosolized bronchodilators delivered through CPAP will improve FEV1 and PEF rates, implying that CPAP could disperse the bronchodilators to more peripheral airways [38].

Asthma exacerbations are often associated with respiratory and genitourinary infections. The coexistence of asthma and anemia, which increases the risk of lung infection [40] and UTI [41], could be the root of our patient's problems. A study discovered that the overall risk of asthma in UTIs was almost twice that of the average population (HR: 1.74; 95%CI: 1.65–1.80) [42]. For these reasons and purposes, we administered a 7–14 days treatment course of ceftriaxone 1 × 2 g (category B) as an effective empiric parenteral antibiotic [43], [44], [45]. Early antibiotic treatment (within 12 h) during the first 2 days of hospitalization

and optimal oxygenation can improve maternal-fetal outcomes and reduce mortality in the exacerbated asthmatic patient [46]. However, this should be given in aggressive de-escalation, and further microbiological examination consisting of standard sputum culture and a viral screening panel should be done to confirm the etiology, regardless of presenting symptoms [47].

Our patient also received a mucolytic as supportive medication to help her difficulty in expelling the phlegm. We chose NAC 3 × 200 mg because it has FDA category B, compared to others mucolytics [48]. Chronic irritation of the airways causes mucus hypersecretion and may impair its mucociliary clearance in asthma, leading to mucus plug, entrapment of inflammatory agents, and persistent inflammation [49]. This mechanism will increase the risk of bacterial invasion; thus, the vicious cycle continues, ending in further asthma exacerbation. NAC is indicated in such conditions and is superior to ambroxol (another classical mucolytic) in long-term efficacy, ciliary motility, cellularity of secretions, and acceptability [50]. In addition, NAC also has a pleiotropic effect in lowering SBP and proteinuria levels due to its potent antioxidant effect [51]. This impact is favored for pregnant women, as pregnancy has been linked to an oxidative stress state [52].

The patient has also been given methyldopa 3 × 250 mg, an α_2 -adrenoceptor agonistic agent, to treat her high BP, likely caused by asthma exacerbation. Asthma and elevated BP are two events that increase each other's exacerbation. These two comorbidities may emerge because of the similarity of their molecular genetic basis, predisposing the patient to acquire both diseases in one circumstance [53]. The recommended dose of methyldopa in pregnancy is 500 mg–2 g daily [54]. This drug has no teratogenic effects (category B), which is better than other more commonly used antihypertensive drugs, for example, calcium channel blockers and β -blockers with category C [55]. Methyldopa was chosen over nifedipine to avoid excessive tocolysis and antihypertensive effects in our treated patient who had previously received $MgSO_4$ and salbutamol [56]. Methyldopa has a mild to moderate antihypertensive effect with a short half-life, and this feature suited our patient with no pre-existing hypertension [57].

One worthwhile lesson, in this case, was the presence of unusual metabolic acidosis rather than the more typical respiratory acidosis in severe asthma attacks. This metabolic acidosis might be explained by a mechanism of SABAs generating lactic acidosis in acute asthma, as our patient experienced after self-medicating with excessive salbutamol [58]. β_2 -adrenoceptor agonists increase intracellular cAMP levels allowing activation of glycolysis and lipolysis with increased production of free fatty acids, diverting pyruvate metabolism from the Krebs cycle and towards lactate formation [58], [59]. Accumulatively, the overproduction of lactate by the increased effort of respiratory muscles, metabolic abnormalities induced by hepatic hypoperfusion, and excessive salbutamol

medication can all contribute to elevated blood lactic acid levels in severe acute asthma [59], [60]. Sevoflurane and ketamine can treat salbutamol-induced acidosis in acute asthma with refractory bronchospasm by reducing airway resistance and lowering the need for β 2-agonists, lowering lactate generation in asthma [61], [62]. Correcting metabolic acidosis with sodium bicarbonate may also improve breathing by boosting the action of bronchodilator catecholamines [63].

The worst-case scenario for severe and life-threatening asthma is that it may force a pregnancy to be terminated. A study reported that maternal asthma improves within 24 h after termination in a first-trimester pregnant woman [64]. Therefore, after the patient was stabilized, our patient was referred to a higher-level hospital equipped with on-site fetomaternal obstetricians, pulmonologists, neonatologists, and anesthesiologists. This referral issue may restrict this case report due to the lack of complete endpoint outcome data. Nevertheless, our primary goal was to highlight the critical role of primary care physicians with limited resources in performing evidence-based management to stabilize severe acute asthma exacerbations in pregnancy.

Conclusion

Significant barriers to treating severe acute asthma in pregnancy among communities with limited resources arise from patients and health-care providers. Poor knowledge about asthma during pregnancy and pandemic anxieties in accessing health-care facilities forced patients to change their prescribed asthma medication and self-treatment at home, resulting in poorly controlled asthma and adverse drug effects. Health-care facility factors that may hamper managing severe acute asthma exacerbation during pregnancy include rare pulmonologists, limited laboratory panels, no available lung function tests, lack of a sophisticated ICU and NICU capacity, and inadequate understanding of safe medications for asthma during pregnancy among GP. To date, multidisciplinary team members should be well-informed about key asthma management strategies during pregnancy, using evidence-based guidelines focusing on efficacious and safe drugs to improve maternal-fetal outcomes. It is also crucial to ensure that the mother is oxygenated adequately and secure maternal and fetal well-being.

Authors' Contributions

- Conceptualization: Muhammad Habiburrahman

- Data curation: Muhammad Habiburrahman
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Consent

The patient has given her consent and permission for publication with the concealment of her identity details. The CARE guidelines were followed for this case report writing.

References

1. Popa M, Peltecu G, Gica N, Ciobanu AM, Botezatu R, Gica C, *et al.* Asthma in pregnancy. Review of current literature and recommendations. *Maedica (Bucur)*. 2021;16(1):80-7. <https://doi.org/10.26574/maedica.2020.16.1.80>

- PMid:34221160
2. Couillard S, Connolly C, Borg C, Pavord I. Asthma in pregnancy: An update. *Obstet Med.* 2021;14(3):135-44. <https://doi.org/10.1177/1753495X20965072>
PMid:34646341
 3. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol.* 2003;112(2):283-8. <https://doi.org/10.1067/mai.2003.1516>
PMid:12897733
 4. Liu X, Agerbo E, Schlünssen V, Wright RJ, Li J, Munk-Olsen T. Maternal asthma severity and control during pregnancy and risk of offspring asthma. *J Allergy Clin Immunol.* 2018;141(3):886-92.e3. <https://doi.org/10.1016/j.jaci.2017.05.016>
PMid:28712803
 5. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: Incidence and association with adverse pregnancy outcomes. *Thorax.* 2006;61(2):169-76. <https://doi.org/10.1136/thx.2005.049718>
PMid:16443708
 6. Priandari N, Wiyono WH, Yunus F, Antariksa B, Isbaniah F, Susanto AD, et al. O17-1: Asthma status during COVID-19 pandemic. *Respirology.* 2021;26(Suppl 3):45. https://doi.org/10.1111/resp.14149_98
 7. Eldeirawi KM, Nyenhuis SM, Huntington-Moskos L, Polivka BJ. Coronavirus disease 2019-related anxiety is associated with uncontrolled asthma in adults. *Ann Allergy Asthma Immunol.* 2022;129(1):109-11. <https://doi.org/10.1016/j.anai.2022.04.011>
PMid:35470038
 8. Ekström S, Mogensen I, Georgelis A, Westman M, Almqvist C, Melén E, et al. General stress among young adults with asthma during the COVID-19 pandemic. *J Allergy Clin Immunol Pract.* 2022;10(1):108-15. <https://doi.org/10.1016/j.jaip.2021.10.069>
PMid:34785389
 9. Chiang CY, Ait-Khaled N, Bissell K, Enarson DA. Management of asthma in resource-limited settings: Role of low-cost corticosteroid/ β -agonist combination inhaler. *Int J Tuberc Lung Dis.* 2015;19(2):129-36. <https://doi.org/10.5588/ijtld.14.0363>
PMid:25574908
 10. Gadrey SM, Lau CE, Clay R, Rhodes GT, Lake DE, Moore CC, et al. Imputation of partial pressures of arterial oxygen using oximetry and its impact on sepsis diagnosis. *Physiol Meas.* 2019;40(11):115008. <https://doi.org/10.1088/1361-6579/ab5154>
PMid:31652430
 11. Ayres-de-Campos D, Spong CY, Chandraran E, FIGO Intrapartum Fetal Monitoring Expert Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. *Int J Gynaecol Obstet.* 2015;131(1):13-24. <https://doi.org/10.1016/j.ijgo.2015.06.020>
PMid:26433401
 12. Sabatine MS. Pocket Medicine: The Massachusetts General Hospital Handbook of Internal Medicine. 7th ed. North American: Wolters Kluwer; 2019.
 13. Dubaybo BA. The care of asthma patients in communities with limited resources. *Res Rep Trop Med.* 2021;12:33-8. <https://doi.org/10.2147/RRTM.S247716>
PMid:33727880
 14. Clifton VL, Busuttill MD. A case study of stillbirth in a pregnancy complicated by asthma. *Obstet Gynecol Cases Rev.* 2015;2:1-3. <https://doi.org/10.23937/2377-9004/1410027>
 15. GINA Committees. Global Strategy for Asthma Management and Prevention. Fontana, USA: Global Initiative for Asthma (GINA); 2022. p. 1-225.
 16. Lim AS, Stewart K, Abramson MJ, George J. Management of asthma in pregnant women by general practitioners: A cross sectional survey. *BMC Fam Pract.* 2011;12:121. <https://doi.org/10.1186/1471-2296-12-121>
PMid:22047491
 17. Baarnes CB, Hansen AV, Ulrik CS. Enrolment in an asthma management program during pregnancy and adherence with inhaled corticosteroids: The 'management of asthma during pregnancy' program. *Respiration.* 2016;92(1):9-15. <https://doi.org/10.1159/000447244>
PMid:27348313
 18. Sellers WF. Inhaled and intravenous treatment in acute severe and life-threatening asthma. *Br J Anaesth.* 2013;110(2):183-90. <https://doi.org/10.1093/bja/aes444>
PMid:23234642
 19. Duki MI, Sudarmadi S, Suzuki S, Kawada T, Tri-Tugaswati A. Effect of air pollution on respiratory health in Indonesia and its economic cost. *Arch Environ Health.* 2003;58(3):135-43. <https://doi.org/10.3200/AEOH.58.3.135-143>
PMid:14535572
 20. Baldacci S, Maio S, Cerrai S, Sarno G, Baiz N, Simoni M, et al. Allergy and asthma: Effects of the exposure to particulate matter and biological allergens. *Respir Med.* 2015;109(9):1089-104. <https://doi.org/10.1016/j.rmed.2015.05.017>
PMid:26073963
 21. Lin CH, Cerrone DA. Shifts in asthma evaluation and management during COVID-19. *Curr Treat Options Allergy.* 2022;9(2):42-51. <https://doi.org/10.1007/s40521-022-00304-7>
PMid:35582628
 22. Namazy JA, Schatz M. Asthma and pregnancy. *J Allergy Clin Immunol.* 2011;128(6):1384-5.e2. <https://doi.org/10.1016/j.jaci.2011.10.034>
PMid:22133321
 23. Boehringer Ingelheim. Pulmicort Respules 0.5mg. Datapharm; 2017. Available from: <https://www.medicines.org.uk/emc/product/880/smpc#gref> [Last accessed on 2022 Jan 09].
 24. Boehringer Ingelheim. Combivent UDV. Datapharm; 2020. Available from: <https://www.medicines.org.uk/emc/product/1423/smpc#pregnancy> [Last accessed on 2022 Jan 09].
 25. Gaga M, Oikonomidou E, Zervas E, Papageorgiou-Georgatou N. Asthma and pregnancy: Interactions and management. *Breathe.* 2007;3(3):267-76. <https://doi.org/10.1183/18106838.0303.266>
 26. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2017;3(3):CD004454. <https://doi.org/10.1002/14651858.CD004454.pub3>
PMid:28321847
 27. Gregersen TL, Ulrik CS. Safety of bronchodilators and corticosteroids for asthma during pregnancy: What we know and what we need to do better. *J Asthma Allergy.* 2013;6:117-25. <https://doi.org/10.2147/JAA.S52592>
PMid:24259987
 28. Simons FE, Gillies JD. Dose response of subcutaneous terbutaline and epinephrine in children with acute asthma. *Am J Dis Child.* 1981;135(3):214-7. <https://doi.org/10.1001/archpedi.1981.02130270006004>
PMid:7211775
 29. Kane BG. Alternative Treatments for Acute Asthma during COVID. American College of Emergency Physicians: ACEP COVID-19 Field Guide. 2021. Available from: <https://www.acep.org/corona/covid-19-field-guide/treatment/alternative-treatments> [Last accessed on 2022 Jan 09].
 30. Shaker MS, Oppenheimer J, Grayson M, Stukus D, Hartog N, Hsieh EW, et al. Reply to Subcutaneous terbutaline as an alternative to aerosolized albuterol. *J Allergy Clin Immunol Pract.*

- 2020;8(7):2450-2. <https://doi.org/10.1016/j.jaip.2020.04.016>
PMid:32340824
31. Boehringer Ingelheim. Bricanyl Injection, 0.5 mg/ml, Solution for Injection or Infusion. Datapharm; 2021. Available from: <https://www.medicines.org.uk/emc/product/867/smpc#gref> [Last cited on 2022 Jan 09].
 32. Kelly HW. Magnesium sulfate for severe acute asthma in children. *J Pediatr Pharmacol Ther.* 2003;8(1):40-5. <https://doi.org/10.5863/1551-6776-8.1.40>
PMid:23300395
 33. Kokotajlo S, Degnan L, Meyers R, Siu A, Robinson C. Use of intravenous magnesium sulfate for the treatment of an acute asthma exacerbation in pediatric patients. *J Pediatr Pharmacol Ther.* 2014;19(2):91-7. <https://doi.org/10.5863/1551-6776-19.2.91>
PMid:25024668
 34. Food and Drug Administration. FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-Term Labor Due to Bone Changes in Exposed Babies. Silver Spring: Food and Drug Administration; 2013. p. 5-8.
 35. Rahman Z, Helali AM. Facts about magnesium sulfate: Time to revise the safety concern in obstetric use. *J Enam Med Coll.* 2014;4(3):177-83. <https://doi.org/10.3329/jemc.v4i3.20957>
 36. Lafond C, Sériès F, Lemièrre C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. *Eur Respir J.* 2007;29(2):307-11. <https://doi.org/10.1183/09031936.00059706>
PMid:17050561
 37. Sutherasan Y, Kiatboonsri S, Theerawit P, Kiatboonsri C, Trakulsrichai S. Impact of continuous positive airway pressure on the treatment of acute exacerbation of asthma: A randomised controlled trial. *Crit Care.* 2013;17 Suppl 2:P149. <https://doi.org/10.1186/cc12087>
 38. Soroksky A, Klinowski E, Ilgyev E, Mizrachi A, Miller A, Ben Yehuda TM, *et al.* Noninvasive positive pressure ventilation in acute asthmatic attack. *Eur Respir Rev.* 2010;19(115):39-45. <https://doi.org/10.1183/09059180.00006109>
PMid:20956164
 39. Nowak R, Corbridge T, Brenner B. Noninvasive ventilation. *Proc Am Thorac Soc.* 2009;6(4):367-70. <https://doi.org/10.1513/pats.P09ST3>
PMid:19675346
 40. Goodnight WH, Soper DE. Pneumonia in pregnancy. *Crit Care Med.* 2005;33(10 Suppl):S390-7. <https://doi.org/10.1097/01.ccm.0000182483.24836.66>
PMid:16215363
 41. Brabin L, Brabin BJ, Gies S. Influence of iron status on risk of maternal or neonatal infection and on neonatal mortality with an emphasis on developing countries. *Nutr Rev.* 2013;71(8):528-40. <https://doi.org/10.1111/nure.12049>
PMid:23865798
 42. Hsu YL, Lin CL, Wei CC. Association between vesicoureteral reflux, urinary tract infection and antibiotics exposure in infancy and risk of childhood asthma. *PLoS One.* 2021;16(9):e0257531. <https://doi.org/10.1371/journal.pone.0257531>
PMid:34547047
 43. Crofts J, Obs S, St G. Women and Children's Health Maternity Guideline. NHS; 2021. Available from: https://www.oaa-anae.ac.uk/assets/_managed/cms/files/clinicalguidelines/sepsis guideline 2019.pdf [Last accessed on 2022 Jan 04].
 44. Mittal P, Wing DA. Urinary tract infections in pregnancy. *Clin Perinatol.* 2005;32(3):749-64. <https://doi.org/10.1016/j.clp.2005.05.006>
PMid:16085031
 45. Laibl V, Sheffield J. The management of respiratory infections during pregnancy. *Immunol Allergy Clin North Am.* 2006;26(1):155-72, viii. <https://doi.org/10.1016/j.iac.2005.11.003>
PMid:16443149
 46. Stefan MS, Shieh MS, Spitzer KA, Pekow PS, Krishnan JA, Au DH, *et al.* Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids. *JAMA Intern Med.* 2019;179(3):333-9. <https://doi.org/10.1001/jamainternmed.2018.5394>
PMid:30688986
 47. Sandrock CE, Norris A. Infection in severe asthma exacerbations and critical asthma syndrome. *Clin Rev Allergy Immunol.* 2015;48(1):104-13. <https://doi.org/10.1007/s12016-014-8435-x>
PMid:24984968
 48. Beloosesky R, Ginsberg Y, Khatib N, Maravi N, Ross MG, Itskovitz-Eldor J, *et al.* Prophylactic maternal N-acetylcysteine in rats prevents maternal inflammation-induced offspring cerebral injury shown on magnetic resonance imaging. *Am J Obstet Gynecol.* 2013;208(3):213.e1-213.e6. <https://doi.org/10.1016/j.ajog.2013.01.023>
PMid:23433325
 49. Gupta R, Wadhwa R. Mucolytic medications. In: StatPearls. Treasure Island FL, StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559163> [Last accessed on 2021 Jan 10].
 50. Macchi A, Terranova P, Castelnuovo P. Recurrent acute rhinosinusitis: A single blind clinical study of N-acetylcysteine vs ambroxol associated to corticosteroid therapy. *Int J Immunopathol Pharmacol.* 2012;25(1):207-17. <https://doi.org/10.1177/039463201202500123>
PMid:22507333
 51. Shimaa MM, Hossam EG, El-Mansoury AM. Effect of N-acetyl cysteine supplementation on blood lead levels in pregnant women suffering from pre-Eclampsia. *Obstet Gynaecol Cases Rev.* 2018;5(3):1-8. <https://doi.org/10.23937/2377-9004/1410126>
 52. Amin AF, Shaaban OM, Bediawy MA. N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. *Reprod Biomed Online.* 2008;17(5):722-6. [https://doi.org/10.1016/s1472-6483\(10\)60322-7](https://doi.org/10.1016/s1472-6483(10)60322-7)
PMid:18983759
 53. Zolotareva O, Saik OV, Königs C, Bragina EY, Goncharova IA, Freidin MB, *et al.* Comorbidity of asthma and hypertension may be mediated by shared genetic dysregulation and drug side effects. *Sci Rep.* 2019;9(1):16302. <https://doi.org/10.1038/s41598-019-52762-w>
PMid:31705029
 54. Gupta M, Al Khalili Y. Methyl dopa. In: StatPearls. Treasure Island FL: StatPearls Publishing; 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK551671> [Last accessed on 2022 Jan 09].
 55. Kattah AG, Garovic VD. The management of hypertension in pregnancy. *Adv Chronic Kidney Dis.* 2013;20(3):229-39. <https://doi.org/10.1053/j.ackd.2013.01.014>
PMid:23928387
 56. Haas DM, Benjamin T, Sawyer R, Quinney SK. Short-term tocolytics for preterm delivery-current perspectives. *Int J Womens Health.* 2014;6:343-9. <https://doi.org/10.2147/IJWH.S44048>
PMid:24707187
 57. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, Kayser A, *et al.* Pregnancy outcome after first trimester use of methyl dopa: A prospective cohort study. *Hypertension.* 2017;70(1):201-8. <https://doi.org/10.1161/HYPERTENSIONAHA.117.09110>
PMid:28533329
 58. Najout H, Moutawakil M, Elkoundi A, Doghmi N, Bekkali H.

- Salbutamol-induced severe lactic acidosis in acute asthma. *SAGE Open Med Case Rep.* 2020;8:2050313X20969027. <https://doi.org/10.1177/2050313X20969027>
PMid:35154769
59. Liedtke AG, Lava SA, Milani GP, Agostoni C, Gilardi V, Bianchetti MG, *et al.* Selective β_2 -adrenoceptor agonists and relevant hyperlactatemia: Systematic review and meta-analysis. *J Clin Med.* 2019;9(1):71. <https://doi.org/10.3390/jcm9010071>
PMid:1892109
60. Phoophiboon V, Singhagowinta P, Boonkaya S, Sriprasart T. Salbutamol-induced lactic acidosis in status asthmaticus survivor. *BMC Pulm Med.* 2021;21(1):23. <https://doi.org/10.1186/s12890-021-01404-x>
PMid:33435939
61. Ruzskai Z, Bokrétás GP, Bartha PT. Sevoflurane therapy for life-threatening acute severe asthma: A case report. *Can J Anaesth.* 2014;61(10):943-50. <https://doi.org/10.1007/s12630-014-0213-y>
PMid:25069782
62. Esmailian M, Esfahani MK, Heydari F. The effect of low-dose ketamine in treating acute asthma attack; A randomized clinical trial. *Emerg (Tehran).* 2018;6(1):e21.
PMid:30009223
63. Vasileiadis I, Alevrakis E, Ampelioti S, Vagionas D, Rovina N, Koutsoukou A. Acid-base disturbances in patients with asthma: A literature review and comments on their pathophysiology. *J Clin Med.* 2019;8(4):10.3390/jcm8040563. <https://doi.org/10.3390/jcm8040563>
PMid:31027265
64. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: Mechanisms and treatment implications. *Eur Respir J.* 2005;25(4):731-50. <https://doi.org/10.1183/09031936.05.00085704>
PMid:15802351