Thyroid Storm and Diabetic Ketoacidosis in Pregnancy: An algorithmic approach

Om Lakhania[1], Surender Kumar[2]

[1]Senior Endocrinologist, Zydus Hospital-Ahmedabad, [2]Senior Endocrinologist, HOD Department of Endocrinology, Sir Ganga Ram Hospital, New Delhi

Thyroid Storm in Pregnancy

1. Introduction

Thyroid storm is an acute complication of thyrotoxicosis. It manifests as severe life-threatening symptoms of thyrotoxicosis. Thyroid storm carries high mortality of 10-30%.[1]

Hyperthyroidism complicates 0.2% of pregnancy and thyroid storm is known to occur in less than 1% of patients with hyperthyroidism.[2] Hence Thyroid storm in pregnancy is a very rare entity with the knowledge restricted to mainly case reports and case series.

2. Precipitating factors for thyroid storm

Thyroid storm is often precipitated in pregnant women with uncontrolled hyperthyroidism during parturition. Sudden discontinuation of anti-thyroid medications during pregnancy can also potentially precipitate a thyroid storm. The likelihood of a pregnant woman developing thyroid storm is 10 times more than for a non-pregnant individual.[3]

The pathophysiology behind the precipitation of a thyroid storm as compared to routine hyperthyroidism is unclear. A sudden increase of thyroid hormone can be one factor that leads to thyroid storm. Apart from this increased tissue response to thyroid hormone and increased catecholamine action are other factors that may precipitate an acute thyroid event like a thyroid storm.[1]

3. Clinical features of thyroid storm

Patients with thyroid storm often present with typical symptoms of hyperthyroidism but in an exaggerated form.[1]

New onset of Atrial fibrillation or cardiac tachyarrhythmia are some common presentations. The patient can also have heart failure. Hyperpyrexia is often present. Gastrointestinal symptoms like nausea and vomiting may be exaggerated especially in pregnancy. The patient may also have jaundice and other signs of liver failure. Neurological symptoms ranging from anxiety to comatose state may be associated with the other clinical symptoms.[1]

On clinical examination, one must look for the presence of goiter and the presence of thyroid-associated orbitopathy (also called Graves' ophthalmopathy). [1]

4. Diagnosis of Thyroid storm

In a patient with Thyroid storm, the lab evaluation may show thyrotoxicosis with elevated T3 and T4 and normal TSH. The degree of thyroid hormone elevation does not correlate with the severity of symptoms. Hyperglycemia and hypercalcemia may be often associated with thyroid storm.[4]

A high tire of the TSH Receptor antibody (TRAb) is useful for establishing the diagnosis of Graves' disease as an etiology for the thyroid storm. However, in an emergency situation, the treatment should not be delayed because of non-availability or delay in the results TRAb.[4]

An ECG with a rhythm strip must be done in all patients and cardiac monitoring in ICU is advisable for all patients with thyroid storm. A liver function test is mandatory to rule out liver involvement which is not uncommon in thyroid storm.[3]

The diagnosis of Thyroid storm is established based on a scoring system called the Burch and Wartofsky score (**Figure 1**). A score of more than 45 is the sine-qua-non of thyroid storm. A score of less than 25 makes thyroid storm unlikely. A score of 25-45 is suggestive of an impending thyroid storm.[4]

5. Management of Thyroid Storm

A patient of thyroid storm is typically managed in the ICU. The basics of any critical illness disease management like securing the airway, breathing and circulation should be followed.[2] The initial assessment and triage of the patient with potential thyroid storm is summarized in **Figure 2**

Criteria	*Points*	*Criteria*	*Points*
Thermoregulatory dysfunction		Gastrointestinal–hepatic dysfunction	
Temperature (°F)[b]		Manifestation	
99.0–99.9	5	Absent	0
100.0–100.9	10	Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
101.0–101.9	15	Severe (jaundice)	20
102.0–102.9	20		
103.0–103.9	25		
≥104.0	30		
Cardiovascular		Central nervous system disturbance	
Tachycardia (beats per minute)		Manifestation	
100–109	5	Absent	0
110–119	10	Mild (agitation)	10
120–129	15	Moderate (delirium, psychosis, extreme lethargy)	20
130–139	20	Severe (seizure, coma)	30
≥140	25		
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure		Precipitant history	
Absent	0	Status	
Mild	5	Positive	0
Moderate	10	Negative	10
Severe	20		
Scores totaled			
>45	Thyroid storm		
	Impending storm		
<25	Storm unlikely		

Fig 1: The Burch and Wartofsky score for the diagnosis of Thyroid storm. [4]

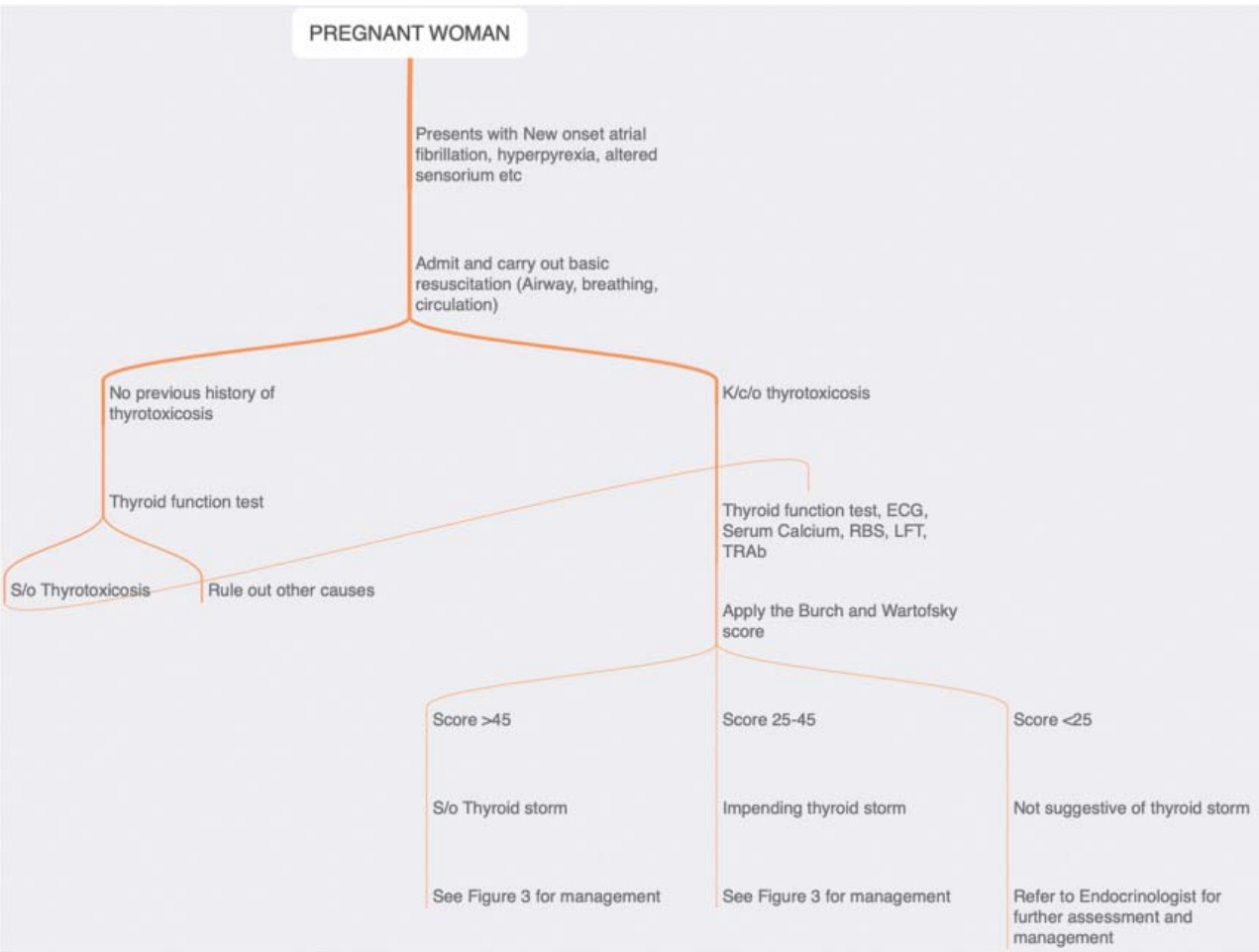

Fig 2: Initial assessment and triage of a pregnant woman suspected to have thyroid storm. (k/c/o is known case of; s/o suggestive of; ECG- Electrocardiogram; RBS- Random blood sugar; TRAb- TSH receptor antibody; LFT- liver function test)

Beta-blockers are started in these patients as early as possible. Beta-blockers block the over-activation of the sympathetic system that occurs in thyrotoxicosis. Propranolol is used as the beta-blocker of choice. An intravenous bolus of Esmolol followed by infusion is another alternative.[4]

Propranolol is typically given in the dose of 20 mg every 4-6 hourly either orally or as a crushed suspension via the Ryle's tube (RT). Propranolol also blocks the T4 to T3 conversion.[4] It must be remembered that propranolol is a pregnancy category C drug. It can lead to fetal bradycardia, hypoglycemia, and respiratory depression. Hence fetal monitoring is vital.[5]

Amongst the anti-thyroid drugs, Propylthiouracil (PTU) is proffered over carbimazole or methimazole in thyroid storm. The onset of the action of PTU is faster than carbimazole/ methimazole and additionally, it is not known to produce any significant teratogenicity. PTU can also be used in the first trimester of pregnancy. PTU is typically given in a higher dose of 200 mg every 4 hourly. PTU can be delivered by RT if the patient cannot take the same orally. PTU can lead to idiosyncratic hepatotoxicity.[1,2,4]

Lugol's iodine or Saturated solution of Pottasium iodide (SSKI) may be used one hour after the administration of PTU. Glucocorticoids like hydrocortisone as given along with the other medications. Glucocorticoids also block T4 to T3 conversion and help correct an undiagnosed adrenal insufficiency which may be unmasked in the period of severe physiological stress. Hydrocortisone in the dose of 100 mg IV every 8 hourly or dexamethasone, 1 to 2 mg every six hours can be used.[4]

Other agents that can be used in case of non-availability of contraindications to any of the above agents include Lithium or Cholestyramine.[6] In patients with pre-existing hepatotoxicity, the use of PTU may be deemed inappropriate. Hence in such cases, these other agents may prove to be effective. Plasmapheresis has also be used in thyroid storm in severe cases.[7]

There is little or no data on the management of the obstetric aspect of thyroid storm. The question of continuing the pregnancy should be decided based on individual cases. It must be kept in mind that thyroid storm is a potentially life-threatening condition of the mother.[2]

Diabetic Ketoacidosis in Pregnancy

1. Introduction

Diabetic ketoacidosis (DKA) in pregnancy complicates about 1-2% of pregnancies and leads to fetal loss in 10-30% of cases. [8] DKA can occur in both type 1 diabetes, Latent-autoimmune diabetes of adulthood (LADA) as well as in selected cases of type 2 diabetes. DKA can be the first presentation of type 1 diabetes.[9]

The standard diagnostic criteria for DKA is described in table 1.

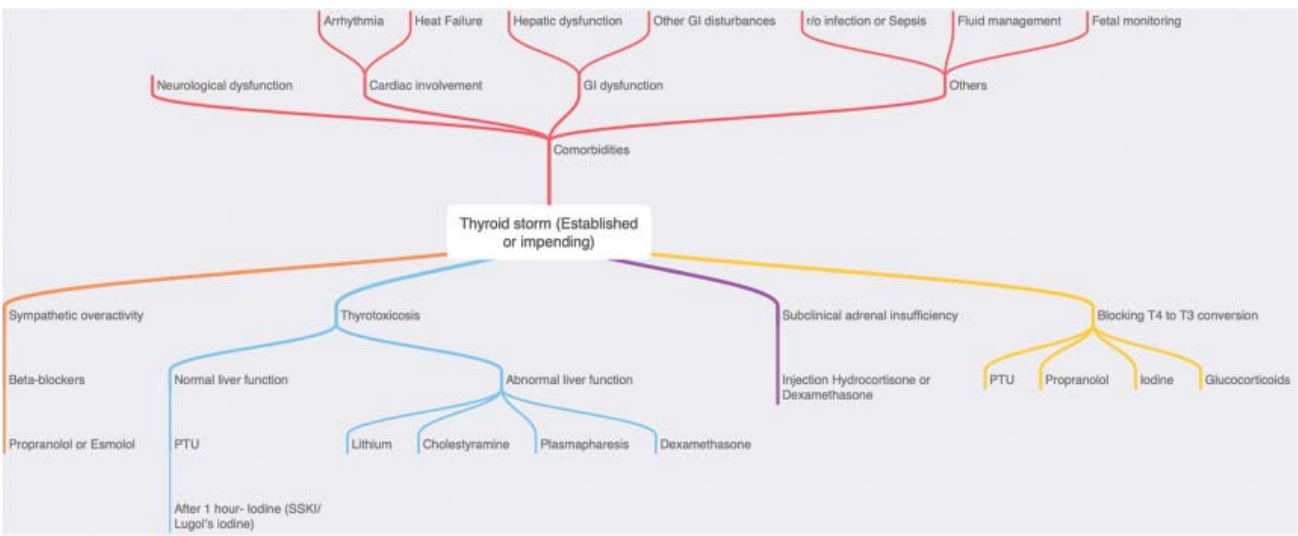

Fig 3: Overview of the management of thyroid storm in pregnancy (PTU- Propylthiouracil; GI- Gastrointestinal; SSKI - Saturated solution of pottasium iodide)

Table 1: Diagnostic criteria for Diabetic ketoacidosis in pregnancy

1. Hyperglycemia- glucose value >250 mg/dl
2. Ketonemia
   a. Serum beta-hydroxybutrate or point-of-care value >3 mmol/l
   b. High serum acetone
   c. Presence or ketonuria- more than 2+ in urine ketone-sticks
3. Acidosis
   a. pH <7.3
   b. Bicarbonate <15 meq/
4. Anion-gap >12 meq/

2. Pathophysiology of Diabetic ketoacidosis

DKA is a result of an imbalance between insulin production and counter-regulatory hormones like glucagon. Low insulin and high glucagon in background of diabetes mellitus leads to DKA.[10] Ketone bodies are reserve fuel for the human body. In the absence availability of intracellular glucose as a fuel, beta-oxidation of fatty acid occurs which kicks off the ketogenesis pathway. This pathway is suppressed by insulin and enhanced by glucagon, growth hormone, and epinephrine. In the situation of an imbalance between insulin and these counter-regulatory hormones, these pathway's come into play and lead to ketogenesis.[10]

Ketone body formation in excess leads to high anion gap metabolic acidosis. DKA is also a state of total body potassium deficit. Most importantly, high glucose levels in the blood lead to high glucose filtration in the urine which leads to dehydration.[10]

3. Precipitating factors for DKA in pregnancy

The most common cause of precipitation of DKA in pregnancy is the discontinuation of insulin in patients with type 1 diabetes or ketosis-prone type 2 diabetes. Miscommunication and misinformation are often the causes of such a situation.[8]

In some cases, the non-availability of insulin, incorrect insulin delivery, and loss of efficacy of insulin due to poor storage and transport can lead to precipitation of DKA. For those patients with type 1 diabetes on an insulin pump, the disconnection of the pump can lead to DKA.[10]

Apart from this infection is the second most common cause of DKA in pregnancy. Urinary tract infection (UTI) is often a culprit and a urine routine examination must be performed in all such patients. In some cases, hyperemesis graivdarum, new-onset, or poor controlled thyrotoxicosis in pregnancy and antenatal glucocorticoid injection in patients with poorly controlled diabetes can precipitate DKA.[11]

4. Clinical features and diagnosis of DKA in pregnancy

Symptoms of DKA in pregnancy can often mimic other symptoms of pregnancy. The patient may present with incessant vomiting, abdominal pain, and signs of dehydration. It is essential to have a high index of suspicion for recognizing DKA, especially in patients having pre-existing diabetes.[8]

Measurement of serum beta-hydroxybutyrate (BOHB) is sin-quo-non for the diagnosis of DKA.[12] In absence of the same, serum acetone levels of urinary ketone levels may act as a substitute.[13] Currently, we have a point of care devices available in India which help in the assessment of beta-hydroxybutyrate in a matter of seconds.[14]

A blood gas analysis should follow the initial testing for ketone bodies. It is not necessary to perform an arterial blood gas analysis, a venous blood gas analysis may also suffice. Patients typically have metabolic acidosis with a high anion gap.[10]

The patient may have low serum potassium and also hyponatremia. The presence of hyponatremia may be spurious and the sodium levels need to be corrected for glucose levels. [10]

Renal function needs to be assessed and many patients may have pre-renal acute kidney injury because of associated dehydration. A urine function test, not only reveals the presence of glycosuria and ketonuria but also the presence or absence of pus cells in urine suggestive of UTI needs to be assessed. As described earlier, UTI is an important precipitating factor for DKA in pregnancy.[11]

5. Management of DKA in pregnancy

Management of DKA in pregnancy has three main principles: Correction of dehydration, management of potassium, and insulin infusion. [13] Table 2 summarizes the management of DKA in pregnant women.

The first step for the management of DKA is fluid resuscitation. Fluid management precedes insulin delivery and should be aggressive. The initial fluid of choice is isotonic normal saline (0.9% NS). Once the glucose levels fall below 250 mg/dl, the use of Dextrose continuing fluids is encouraged so as to prevent hypoglycemia.[8]

The second step is to assess serum potassium. Since potassium is predominantly an intracellular ion, the serum potassium levels do not adequately represent the total body potassium stores. Patients with DKA is invariability potassium deficient irrespective of the serum potassium levels. It is also important to note that the use of insulin infusion leads to a further reduction of serum potassium levels due to the intracellular shift of potassium. Hence it is important to first assess and correct potassium deficient before initiating insulin infusion.[10]

The third step in the management of DKA is insulin infusion. In most patients, we give an initial bolus of insulin followed by a steady insulin infusion. The infusion is continued till the DKA is resolved and the patient is able to take orally. The use of sliding scale subcutaneous insulin is discouraged. If the patient had been taking long-acting insulin previously, the same may be given in parallel to the insulin infusion.[10]

Bicarbonate infusion generally has little or no role in DKA management. Correction of ketogenesis leads to correction or the metabolic acidosis without requiring bicarbonate. In some cases, bicarbonate infusion may be detrimental.[15]

Obstetric management includes fetal monitoring. The decision to continue the pregnancy should depend on the clinical circumstances and no general guidance can be suggested for the same. As described earlier, DKA can lead to fetal loss in 10-30% of the cases.[8]

The precipitating factor needs to be identified and corrected, especially if it involves any infection. DKA itself leads to leucocytosis and hence an underlying infection may often be missed out in the presence of diabetic ketoacidosis.[8]

Table 2: Summary of Management of Diabetic ketoacidosis in pregnancy

Fluids

- Initial correction with NaCl 1-1.5 litre/hr during first hour
- Then Calculate corrected sodium (Hyperglycemia causes hyponatremia)
  - Measured sodium + 0.024 * (Serum glucose - 100)
  - If Hypernatremia / normal - 0.45% normal saline- 500 ml/hr
  - If hyponatremia- 0.9% normal saline- 500 ml/hr
  - Continue till glucose reaches <250mg/dl - then start 5% dextrose

Insulin

- 10 units IV bolus- check potassium levels first before starting insulin drip
- With INFUSION PUMP
  - Insulin drip – 50 units in 50 ml of normal saline
  - Start is 3-5 ml/hr and titrate based on glucose values
  - The insulin should fall by 50 mg/dl per hour
  - If no fall than double the rate to 10ml/hr – recheck the fall after 1 hr – keep doubling the rate till glucose in target range
  - Continue till glucose <250 mg/dl

Glucose <250 mg/dl

- Start 5% dextrose @ 200 ml/hr
- Continue insulin drip ½ of above rate
- Keep glucose between 150-200 mg/dl

Potassium

- If K <3.3 meq/l
  - Do not give insulin.
  - 2 ampules of 11.2% KCl in 500ml of NS @200ml/hr
- If K - 3.3- 5 meq/l
  - Can start insulin
  - 1 ampule of 11.2% KCl in 500ml of NS@ 200ml/hr
- If K >5.0 – can give insulin without starting potassium
- For maintenance 20-30 meq of K in 1 litre of fluid is generally adequate

Monitoring therapy

- Glucose monitoring every hourly using Point-of-care device
- Every 2 -4 hrs measure the following
  - Serum electrolytes

6. Resolution of DKA

The anion gap is a useful parameter to assess for resolution of DKA. The measurement of ketone bodies (Serum BOHB, Serum acetone, and/or urine ketone bodies) may be misleading. Normalization of the anion gap is a sign of a good

prognosis and suggests a possible resolution of DKA. The criteria for the resolution of DKA are described in table 3.[10]

Table 3: Resolution of DKA

1. Blood glucose <200 mg/dl
2. Serum bicarbonate- >18 meq/l
3. pH > 7.3
4. Anion gap <10 meq/l
Patient is able to take orally without emesis

It is important to note that apart from the high anion-gap metabolic acidosis, the patients with DKA may also have a hidden normal anion-gap metabolic acidosis due to aggressive fluid infusion of sodium chloride. Hence patients may continue to demonstrate metabolic acidosis even after normalization of the anion gap.[8]

Once the patient has a good oral intake and does not have emesis, the insulin infusion may be gradually discontinued while overlapping with subcutaneous insulin. The switch-over though, seemingly innocuous is often the critical part of the process and endocrinologists should be involved in handling the switch of the insulin regimen. If not done right, it can both lead to the recurrence of DKA on one hand and severe hypoglycemia on the other.[13]

Table 4: shows the process of switching from insulin infusion to subcutaneous insulin

Table 4: Switching from Insulin resolution to subcutenous insulin once DKA is resolved

1. Calculate the insulin requirement in the last 6 hours and multiply that by 4 which gives the insulin requirement over the last 24 hours
2. 80% of the total insulin requirement as described above is split into 50% basal and 50% of bolus insulin.
3. The basal insulin is given 3-4 hours before discontinuing the insulin infusion. Insulin detemir and insulin NPH are generally the basal insulin that are safe to use in pregnancy.
4. The bolus dose is divided into three equal doses given before the three major meals. Regular human insulin, insulin lispro and insulin aspart are the various short acting insulin which are safe to use in pregnancy.

7. Preventing recurrence of DKA

The patients with type 1 diabetes and/or ketosis-prone type 2 diabetes should be kept on a close follow-up of an endocrinologist. The use of multi-dose insulin (MDI) an/or continuous subcutaneous insulin infusion (CSII, also called insulin pump) is the standard of care in these patients.[10]

Older generation insulin-like insulin NPH and regular human insulin are cost-effective and are available as essential medications in most government supplies and government drug repositories.[16] Hence all patients with type 1 must be placed on standard MDI therapy with regular glycemic monitor using SMBG (self-monitoring of blood glucose). These patients must have regular access to the medical staff person who has expertise in insulin dose adjustment. Self-adjustment of insulin dose may be taught to selected patients based on their status of education and knowledge.

References

1. Satoh, T. *et al.* 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society. *Endocrine journal* EJ16–0336 (2016).
2. Prabawa, A. & Negara, K. S. Diagnosis and Comprehensive Management of Thyroid Storm in Pregnancy: A Case Report. *Biomedical and Pharmacology Journal* **11,** 1329–1334 (2018).
3. Ma, Y., Li, H., Liu, J., Lin, X. & Liu, H. Impending thyroid storm in a pregnant woman with undiagnosed hyperthyroidism: A case report and literature review. *Medicine* **97,** (2018).
4. Ross, D. S. *et al.* 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* **26,** 1343–1421 (2016).
5. Chow, T., Galvin, J. & McGovern, B. Antiarrhythmic drug therapy in pregnancy and lactation. *The American journal of cardiology* **82,** 58I–62I (1998).
6. Oakley, P. W., Oakley, P., Dawson, A. H. & Whyte, I. M. Lithium: thyroid effects and altered renal handling. *Journal of Toxicology: Clinical Toxicology* **38,** 333–337 (2000).
7. Ashkar, F. S., Katims, R. B., Smoak, W. M. & Gilson, A. J. Thyroid storm treatment with blood exchange and plasmapheresis. *Jama* **214,** 1275–1279 (1970).
8. Mohan, M., Baagar, K. A. M. & Lindow, S. Management of diabetic ketoacidosis in pregnancy. *The Obstetrician & Gynaecologist* **19,** 55–62 (2017).
9. Balasubramanyam, A., Nalini, R., Hampe, C. S. & Maldonado, M. Syndromes of ketosis-prone diabetes mellitus. *Endocrine reviews* **29,** 292–302 (2008).
10. Kitabchi, A. E., Umpierrez, G. E., Murphy, M. B. & Kreisberg, R. A. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes care* **29,** 2739–2748 (2006).
11. Umpierrez, G. E. & Kitabchi, A. E. Diabetic ketoacidosis. *Treatments in endocrinology* **2,** 95–108 (2003).

12. Sheikh-Ali, M. *et al.* Can serum β-hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes care* **31,** 643–647 (2008).
13. Savage, M. *et al.* Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabetic medicine: a journal of the British Diabetic Association* **28,** 508 (2011).
14. Arora, S., Henderson, S. O., Long, T. & Menchine, M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: β-hydroxybutyrate versus the urine dipstick. *Diabetes care* **34,** 852–854 (2011).
15. Wolfsdorf, J., Glaser, N. & Sperling, M. A. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. *Diabetes care* **29,** 1150–1159 (2006).
16. Sharma, A. & Kaplan, W. A. Challenges constraining access to insulin in the private-sector market of Delhi, India. *BMJ global health* **1,** (2016).