Comorbidities of Gestational Diabetes Mellitus and Urinary Tract Infection: A Case Report

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1. Introduction

Diabetes mellitus (DM) in pregnancy is divided into two groups, which are previously known as DM when the patient is pregnant, and DM, which was discovered during pregnancy (gestational diabetes mellitus). Gestational diabetes mellitus (GDM) is defined as a condition of glucose intolerance that occurs during pregnancy or is discovered during pregnancy.1-3 Urinary tract infection (UTI) is the most common bacterial infection in pregnant women. The prevalence of asymptomatic bacteriuria is 2-10%, and cystitis is about 1-4% in pregnancy.

Women who are at high risk of experiencing a UTI in pregnancy usually have co-morbidities such as diabetes, polycystic kidney disease, congenital abnormalities, sickle cell disease, and a history of recurrent UTIs. E. coli and gram-negative bacteria (Klebsiella, Acinetobacter baumannii, Proteus mirabilis) are the cause of 70-80% of UTI cases during pregnancy, while gram-positive organisms (Enterococcus faecalis and group B Streptococcus) are found in 10% of UTI cases in pregnant women.4,5

The prevalence of UTI during pregnancy in women without diabetes ranges from 3% to 10.1%, while in pregnant women with diabetes, it reaches 27.6%. During pregnancy, there are physiological and anatomical changes occurring in the urinary tract that may increase the incidence of asymptomatic
bacteriuria and the development of acute cystitis/pyelonephritis. Diabetes will exacerbate the incidence of infection in pregnant women, predisposing things such as glycosuria, bacterial adhesion to the uroepithelium, and immune system dysfunction.\textsuperscript{6,7}

The management of UTI in DMG is generally the same as the management of UTI in pregnant patients without diabetes, with the administration of antibiotics based on the sensitivity of the organism from urine culture. The most commonly used antibiotics are amoxicillin, ampicillin, cephalosporins, nitrofurantoin, and trimethoprim-sulfamethoxazole. Untreated UTI can progress to emphysematous cystitis/pyelonephritis, kidney abscess, and urosepsis. UTI in pregnancy is also associated with preeclampsia and neonatal defects at birth.\textsuperscript{8} In addition to UTI management, it is important to ensure that blood sugar levels are well controlled because DM can affect pregnancy outcomes such as the incidence of preeclampsia, preterm delivery, caesarean delivery, low birth weight, or macrosomia babies.\textsuperscript{7} This study aimed to present a case of gestational diabetes mellitus and urinary tract infection.

2. Case Presentation

A 38-year-old woman came with complaints of fever for 1 week before entering the hospital. The patient had not menstruated since 4 months ago and had been going to the midwife but had not been declared pregnant yet. Nausea and vomiting were found 3 months ago, yellowish, frequency 4-5 times a day, volume 1/4 cup. Decreased appetite and tiredness for 3 months before being admitted to the hospital. The patient only eats \( \frac{1}{4} - \frac{1}{3} \) of a regular meal. There was a history of increased urination at night since 2 months ago, frequency >5 times, in normal volume and colour. Since the last week, urination has been accompanied by pain in the lower central region. The frequency is more frequent with a small volume. History of increased hunger and thirst, coughing, blurred vision, numbness, and tingling at the tips of the fingers and toes was denied.

Based on physical examination, the patient was aware and cominsensitivis, blood pressure 130/70 mmHg, pulse 102 times per minute, regular breathing 26 times/minute, and temperature 37.8°C. The patient had a body weight of 51 kg, height of 154 cm, and body mass index of 21.5 cm/kg\textsuperscript{2} (normoweight). No abnormalities were found on other physical examinations. Laboratory examination showed hemoglobin 12.7 g/dL, leukocytes 13,860/mm\textsuperscript{3}, hematocrit 35%, blood sedimentation rate 10 mm/hour, the differential count found basophils 0%, eosinophils 0%, rod neutrophils 2%, segment neutrophils 83%, lymphocytes 11% and monocytes 4%, blood glucose 566 mg/dL, urea 124 mg/dL, creatinine 2.8 mg/dL, sodium 114 mmol/L, potassium 2.3 mmol/L, chloride 82 mmol/L.

On follow-up laboratory tests, fasting blood sugar was 202 mg/dL, oral glucose tolerance test was 75 grams, 253 mg/dL, and HbA1c was 10.4%. Peripheral blood smear showed leukocytosis with neutrophilia (shift to the right). Urinalysis examination revealed leukocyturia, proteinuria, glucosuria, and a positive plano test. The stool examination was found to be within normal limits. The electrocardiography revealed sinus tachycardia. The patient was diagnosed with gestational diabetes mellitus, urinary tract infection, acute kidney injury stage II due to pre-renal due to dehydration, hypokalemia due to GI loss, and G4P3A0H3 preterm gravid 15-16 weeks.

Patients were given a 1900 kcal diabetes diet (1150 kcal carbohydrates, 300 kcal protein, 450 kcal fat), intravenous insulin drip, intravenous injection of ceftriaxone 1 gram/12 hours, paracetamol 500 mg/8 hours orally, domperidone 10 mg/8 hours orally. The patient was also given a 25 mEq KCl drip via intravenous. The patient was then consulted for subdivision of fetomaternal in the obstetrics and gynecology department, with an impression of normal gravid at 15-16 weeks gestational age. After undergoing treatment for 6 days, the patient was allowed to be discharged while continuing control to the internal medicine outpatient clinic.
3. Discussion

The diagnosis of gestational diabetes in this patient was based on history, physical examination, and laboratory examination. From historical taking, it was found that the patient had not menstruated since 4 months ago, had nausea and vomiting since 3 months ago, decreased appetite since 3 months ago, and increased urination at night since 2 months ago. From the physical examination, we found the abdomen was visible, enlarged according to gestational age, and laboratory parameters showed a positive pregnancy test with levels of blood glucose exceeding normal limits.

The prevalence of GDM is still not certainly known because the diagnostic criteria used for screening differ in each country. According to the ADA (American Diabetes Association), in 2018, there was an increased prevalence of diabetes in pregnancy in the US. Type 1 DM and type 2 DM in pregnancy have a greater risk to the mother and fetus than DMG alone. Risks that can arise from uncontrolled DM conditions in pregnancy include spontaneous abortion, congenital abnormalities in the fetus, preeclampsia, fetal death, macrosomia, neonatal hypoglycaemia, and neonatal hyperbilirubinemia. Diabetes in pregnancy can also increase the risk of obesity and type 2 DM in children later in life.

Gestational diabetes usually develops because of a pre-existing increase in insulin. An imbalance between insulin resistance and secretion can lead to hyperglycemia during pregnancy. Target of blood glucose according to ADA recommendations; fasting blood glucose less than 95 mg/dL (5.3 mmol/L), blood glucose 1-hour post prandial less than 140 mg/dL (7.8 mmol/L), blood glucose 2 hours postprandial less than 120 mg/dL (6.7 mmol/L). In DMG, A1c is recommended to be monitored every month with a target of 6-6.5% (42-48 mmol/mol), and 6% (42 mmol/mol) was optimal during pregnancy. This target must be achieved without the occurrence of hypoglycemia, which can increase the risk of low birth weight.

A previous study reported 3-20% of pregnant women suffer from gestational diabetes, with risk factors as the following; aged ≥ 35-year-old, race (African, Arabic, Asian, Hispanic, Indigenous race), history of using corticosteroid drugs, obesity (body mass index ≥30kg/m²), history of prediabetes and gestational diabetes in previous pregnancies, delivering babies weighing more than 4 kgs, family history (parents, brothers, or sisters) of type 2 DM, and polycystic ovarian syndrome or acanthosis nigricans (dark skin).

Nutritional medicine and combination with insulin therapy as needed is the basis of GDM management. The goal of dietary modification for DMG is to achieve the target level of glycaemic control, provide adequate weight gain, contribute to the well-being of the mother and fetus, and prevent ketosis. The guidelines recommend a moderate exercise program of 30 minutes 3-4 times per week for women with GDM who have no medical or obstetric contraindications for physical activity. Examples of moderate-intensity exercise include brisk walking, cycling, or 10 minutes of sitting arm exercises after meals.

Drug therapy should be considered when nutritional therapy and moderate-intensity physical activity fail to reach the target of glucose within 1-2 weeks. One of the approaches is to initiate pharmacological therapy if most of the glucose levels in the 1-week period are increased. ACOG recommends starting drug therapy if FBG concentrations are >95 mg/dL, or 1PPBG/2PPBG are ≥140 mg/dL and ≥120 mg/dL, respectively. Another option is to start drug therapy if two or more FBG or PPBG values are >100 mg/dL or >126 mg/dL in a 2-week period. In general, there is no threshold for the initiation of drug therapy for DMG. Clinicians should consider the severity and frequency of hyperglycemia, fetal growth, and factors of the patients when deciding to initiate pharmacotherapy.

The ADA and ACOG guidelines recommend insulin as a first-line treatment for GDM that cannot be controlled with nutritional therapy. National Institute for Health and Care Excellence (NICE) guidelines
suggest initial treatment with insulin, either with or without metformin, for any patient with a fasting glucose of 7 mmol/L (126 mg/dL) or greater at diagnosis. NICE also recommends considering insulin (with or without metformin) for women with complications of DMG, such as macrosomia, and a GDP of 6.0-6.9 mmol/L (108-125 mg/dL).10-12

While the ACOG recommends metformin as first-line therapy for GDM management, the NICE guidelines also support metformin as initial therapy in women with GDM and fasting glucose less than 7 mmol/L (126 mg/dL) at diagnosis. Conversely, the Endocrine Society recommends metformin as an alternative in women who refuse or have contraindications to insulin or glyburide. This recommendation is based on metformin’s higher failure rate and unknown long-term safety profile in the ancestry of females treated with metformin. The ADA recommends insulin as a first-line agent and proposes metformin as an acceptable alternative if glucose control is adequate. The ADA reports a slightly higher risk of prematurity and unknown long-term effects from the use of metformin in DMG (Table 1).10,12

Table 1. Recommendation of glucose index target in patients with GDM.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Fasting blood glucose (mg/dL)</th>
<th>Blood glucose 1 hour postprandial (mg/dL)</th>
<th>Blood glucose 1 hour postprandial (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG</td>
<td>≤95</td>
<td>&lt;140</td>
<td>&lt;120</td>
</tr>
<tr>
<td>ADA</td>
<td>≤95</td>
<td>≤140</td>
<td>≤120</td>
</tr>
<tr>
<td>Endocrine society</td>
<td>≤95</td>
<td>≤140</td>
<td>≤120</td>
</tr>
<tr>
<td>NICE</td>
<td>≤95</td>
<td>≤140</td>
<td>≤115</td>
</tr>
</tbody>
</table>

A study reported that children born to metformin-treated mothers did not differ in height, weight, total fat, or percent body fat compared with children whose mothers were treated and given insulin therapy. However, the heredity of those exposed to metformin had higher amounts of subcutaneous fat, as noted from the circumference of the upper arm and biceps and the subscapular skin folds. The implications of this change in fat distribution are unclear. Women with GDM who are being treated with metformin should be informed that metformin can cross the placenta, and the long-term effects of fetal exposure to this agent are still unknown. The ADA continues to support insulin as a first-line agent for the management of GDM, suggesting that glyburide (glibenclamide) may be inferior to insulin and metformin because of the increased risk of neonatal macrosomia and hypoglycaemia, as well as the risk of maternal hypoglycaemia and strategies for managing hypoglycaemia with these agents.

DMG patients are encouraged to undergo 75-gram OGTT testing 6-12 weeks postpartum for re-evaluation. Obese women are at high risk of developing hyperglycaemic disorders in their next pregnancies, so nutritional guidelines and appropriate dietary therapy should be considered. If a person is diagnosed with gestational diabetes during pregnancy, it is important to breastfeed immediately after birth for at least 4 months to prevent hypoglycaemia in the newborn, childhood obesity, and diabetes for the patient and their child.16,17

This patient was diagnosed with acute kidney injury (AKI) based on complaints of vomiting 3 months ago, with a frequency of 4-5 times per day. A decrease in the urine volume was also found, which was less than usual, around 450 ml. Laboratory parameters showed an increase in urea and creatinine, urea 124 mg/dl, and creatinine 2.8 mg/dl with a glomerular filtration rate (GFR) of 21.93. After being given increased risk of neonatal macrosomia and hypoglycaemia, as well as the risk of maternal hypoglycaemia and strategies for managing hypoglycaemia with these agents.
rehydration fluids for 3 days with NaCl 0.9% finished in 6 hours/kolf and evaluated with a positive balance, there was an improvement in urea and creatinine value with urea 13 mg/dl and creatinine 0.4 mg/dl. The patient also underwent an ultrasound examination of the kidneys with an impression within normal limits.

The causes of AKI can be classified into three major groups: pre-renal or hemodynamic (kidney hypoperfusion), renal (structural damage to the kidney), and post-renal (urine outflow obstruction). Inadequate fluid intake, excessive vomiting, diarrhea, and fever can cause dehydration. Dehydration may reduce renal perfusion, and hypoperfusion can be caused by hypovolemia or decreased effective circulating volume resulting in AKI. In pre-renal AKI, the integrity of the kidney tissue is still preserved so that the prognosis can be better if the causative factors can be corrected. Renal ultrasound is necessary to look for causes of AKI, i.e., obstruction from a kidney stone. Findings of decreased kidney size or echogenicity suggest chronic kidney disease (CKD). Renal ultrasound can help identify ischemic AKI and reduced renal blood flow. Usually, the resistive index is high (greater than 0.75). Crystalloids and colloids are common solutions used for patients with pre-renal AKI. Crystalloid fluids are more commonly used than colloids for resuscitation.\(^\text{13,14}\)

The risk factors for UTI in patients with DMG are variable, such as inadequate glycaemic control, duration of DM, diabetic microangiopathy, impaired leukocyte function, history of recurrent vaginitis, and anatomical and functional abnormalities in the urinary tract.\(^\text{15}\) In this patient, we found RBG 566 mg/dl, which indicates that the patient does not have adequate glycaemic control. Conditions of hyperglycaemia affect the immune system through various mechanisms. In the complement system will be found decreased levels of C4, complement binding with antibodies, and impaired binding to the surface of the pathogen. The process of pathogen recognition can also be disrupted because hyperglycaemia can reduce chemokine production and reduce toll-like receptor (TLR) expression in response to lipopolysaccharides against bacteria and inhibit neutrophil migration.\(^\text{16,18}\) The duration of DM and history of recurrent vaginitis in this patient is unknown.

UTI management, in general, did not differ in patients with DMG and without DMG. The most commonly used antibiotics are amoxicillin, ampicillin, cephalosporins, nitrofurantoin, and trimethoprim-sulfamethoxazole. Fluoroquinolones are not recommended as first-line treatment in pregnancy because their teratogenicity is unclear.\(^\text{8}\) Ampicillin has been shown to be very effective against group B streptococci and Enterococcus species. Fosfomycin is starting to be recommended as the first choice in UTIs caused by E. Coli. A previous study stated that nitrofurantoin was less effective in eradicating E. coli but still very effective against Enterococcus species.\(^\text{19}\) Due to the high resistance to clindamycin, patients who are allergic to Penicillin are recommended vancomycin as an alternative therapy. In this patient, we administered ceftriaxone and provided clinical improvement on the third day.

4. Conclusion

There are many risk factors that can contribute to the development of UTI in pregnant women, with one of those being inadequate glycaemic control. The treatment of UTI in pregnant women with GDM is generally the same as in those without GDM.

5. References


