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## CLINICAL INFORMATION

### Insulinoma and pregnancy: anesthesia and perioperative management<sup>☆</sup>



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#### KEYWORDS

Neuroendocrine tumor: insulinoma;  
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Hypoglycemia and hyperglycemia;  
Pregnancy

**Abstract** Insulinoma is a functional neuroendocrine tumor derived from beta cells of the pancreatic islets of Langerhans, usually solitary, benign, and curable with surgery (enucleation). It rarely occurs during pregnancy and is clinically manifested by hypoglycemia, particularly in the first trimester of pregnancy. During pregnancy, both conservative therapeutic measures (medication) and surgical treatment are challenging regarding the impossibility of studies on drug teratogenicity as well as the maternal-fetal repercussions during surgery, such as hypoglycemia and changes due to stress.

**Case report:** A 33-year primiparous woman, 86 kg, 1.62 m, BMI 32.7 kg·m<sup>-2</sup>, at 15 weeks' gestation, physical status ASA III, investigated for a reduced level of consciousness. Laboratory tests showed: hypoglycemia (45 mg·dL<sup>-1</sup>) associated with hyperinsulinemia (24 nUI·mL<sup>-1</sup>), glycosylated hemoglobin (4.1%); other laboratory findings and physical examination were normal. Magnetic resonance imaging showed a 1.1 cm nodule in the pancreatic tail with suspected insulinoma. Due to the difficult glycemic control with bolus and continuous infusion of glucose, laparotomy was performed for tumor enucleation under total intravenous anesthesia combined with epidural block. Monitoring, central and peripheral venous access, radial artery catheterization, diuresis, and glucosimetry were recorded every 15 minutes. Intraoperatively, there was severe hypoglycemia while handling the tumor and shortly before its enucleation, which was controlled through continuous infusion of 10% glucose balanced crystalloid solution (100–230 mL·h<sup>-1</sup>). The patient's postoperative evolution was uneventful, with resolution of hypoglycemia and total withdrawal of glucose intravenous infusion.

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**PALAVRAS-CHAVE**

Tumor neuroendócrino: insulinoma;  
Anestesia: venosa total e peridural;  
Hipoglicemia e hiperglicemia;  
Gravidez

**Insulinoma e gestação: anestesia e manejo perioperatório**

**Resumo** O insulinoma é um tumor neuroendócrino funcional de células beta das ilhotas de Langerhans pancreáticas, geralmente solitários, benignos, curáveis com cirurgia (enucleação). Raramente ocorre durante a gravidez e se manifesta clinicamente por hipoglicemia, principalmente no primeiro trimestre da gravidez. Durante a gestação as condutas terapêuticas conservadoras (medicamentosas) e o tratamento cirúrgico constituem desafios tendo em vista a impossibilidade de estudos sobre teratogenicidade de fármacos, assim como as repercussões materno-fetais durante intervenções cirúrgicas, como a hipoglicemia e alterações decorrentes do estresse.

**Relato de caso:** Paciente com 33 anos, 86 Kg, 1,62m, IMC 32,7 kg·m<sup>-2</sup>, primigesta, 15 semanas de idade gestacional, estado físico III da ASA, investigada por rebaixamento do nível de consciência. Aos exames laboratoriais constataram-se: hipoglicemia (45 mg·dL<sup>-1</sup>) associada à hiperinsulinemia (24 nUI·mL<sup>-1</sup>) e hemoglobina glicosilada (4,1%); demais exames laboratoriais e exame físico normais. A ressonância magnética mostrou nódulo de 1,1 cm em cauda de pâncreas com hipótese de insulinoma. Devido ao difícil controle glicêmico com infusão em *bolus* e contínua de glicose, foi feita laparotomia para enucleação do tumor sob anestesia venosa total associada a bloqueio peridural. Monitoração, acesso venoso central e periférico, cateterização de artéria radial, diurese, glicosimetria a cada 15 minutos. No intraoperatório, observou-se hipoglicemia acentuada nos momentos de manipulação e imediatamente antes da enucleação do tumor, controlada com infusão contínua de solução cristalóide balanceada glicosada a 10% (100 a 230 ml/h). A evolução no pós-operatório seguiu sem intercorrências, com resolução dos quadros de hipoglicemia e retirada total da infusão venosa de glicose.

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**Introduction**

Insulinoma is a functional neuroendocrine tumor derived from beta cells of the pancreatic islets of Langerhans, usually solitary, benign, curable with surgery (enucleation), and with an incidence of 1–4 per million/year, 20% in female patients.<sup>1–3</sup>

The insulinoma-pregnancy association is very rare, with about 20 cases been reported in the literature. During pregnancy, the conservative therapeutic approaches (drugs) and surgical treatment are challenges due to both difficulty to study drug teratogenicity in large populations and the uncertainty of maternal-fetal repercussions of surgical interventions, such as hypoglycemia and postoperative stress.<sup>4,5</sup> The aim of this report is to present the case report of a pregnant patient with insulinoma undergoing tumor enucleation under general anesthesia and epidural block.

**Case report**

Pregnant patient, 33 years old, 86 kg, height 1.62 m, BMI 32.7 kg·m<sup>-2</sup>, primipara, 15 weeks of gestational age, physical status ASA III, admitted in the emergency care for reduced level of consciousness investigation. Laboratory tests revealed hypoglycemia (45 mg·dL<sup>-1</sup>), associated with hyperinsulinemia (24 nUI·mL<sup>-1</sup>) and glycosylated hemoglobin (4.1%); other laboratory tests and physical examination were normal. Magnetic resonance imaging showed a 1.1 cm nodule in pancreatic tail, with a diagnostic hypothesis of insulinoma. For normoglycemia maintenance, dietary measures

and continuous infusion of glucose were provided, but without success, requiring additional administration of repeated bolus of glucose. Due to the difficult glycemic control, despite continuous infusion of glucose, and the limited experience with the use of octreotide, beta-blockers, and diazoxide in pregnant women, the consensus among the responsible experts was for surgical treatment by laparotomy. At preanesthetic evaluation, the patient was in good general condition, ruddy, hydrated, upper extremity blood pressure (90×60 mmHg), heart rate (70 bpm). The patient was on continuous infusion of glucose and, one hour before induction of anesthesia, ranitidine (50 mg) and metoclopramide (10 mg) were given.

In the operating room, monitoring was performed with cardioscope (DII), invasive blood pressure (radial artery), pulse oximetry, capnography. Central venous access and venipuncture in upper limb with a 14G cannula, bladder catheter, glucosimetry every 15 minutes (min), and maintenance on continuous infusion of 10% glucose, adjusted according to glycemia. Faced with normal coagulation, with the patient in the sitting position, epidural anesthesia was performed with median puncture in L3-L4 with an 18G Tuohy needle. After the epidural space identification with the loss of resistance technique (syringe with air), bupivacaine 0.25% with epinephrine 1:200,000 (25 mg) associated with morphine (2 mg) were injected. After the blockade, the patient was positioned in the supine position and total intravenous anesthesia was initiated. Induction of anesthesia was obtained with sufentanil (50 µg) followed by propofol (150 mg) and atracurium (0.5 mg·kg<sup>-1</sup>). Subsequently, the patient was ventilated via face mask with 100% oxygen

and maneuvers for laryngoscopy and tracheal intubation were performed. Remifentanyl (0.15–0.25  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and propofol (1.830 mg total) were used for maintenance in continuous infusion via target-controlled infusion pump ( $\text{O}_2$  and air mixture). The surgery lasted three hours and 30 min, after which the neuromuscular blockade reversal and extubation were performed. The patient was taken conscious and oriented to the ICU, with spontaneous ventilation under face mask oxygen, stable and without vasoactive drugs.

The intraoperative events observed were changes in blood glucose levels during manipulation and immediately prior to tumor enucleation (minimum of 79  $\text{mg}\cdot\text{dL}^{-1}$ ), ranging from 79 to 140  $\text{mg}\cdot\text{dL}^{-1}$ , maintained through dynamic control of continuous infusion of 10% glucose balanced crystalloid solution and rate changes of 100–230  $\text{mL}\cdot\text{h}^{-1}$ ; hypokalemia (2.9  $\text{mEq}\cdot\text{L}^{-1}$  minimum), requiring intravenous replacement of potassium (25  $\text{mEq}$ ).

The postoperative course was uneventful, with resolution of the episodes of hypoglycemia and total withdrawal of glucose intravenous infusion. Fetal vitality was periodically monitored by ultrasound and remained unchanged until the 32nd week of gestation. The fetus was eutrophic and without other anomalies during evaluation.

## Discussion

Pancreatic neuroendocrine tumors are relatively rare, affecting predominantly female (1.4 women for every man), average age of 47 years. Insulinoma is a pancreatic insulin-secreting beta cell tumor that leads to severe hypoglycemia associated with high concentrations of an endogenous insulin secretion by-product (C-peptide).<sup>2,6,7</sup>

It is a rare case and, although the association of insulinoma, pregnancy, and postpartum is rarely observed, it is described in the literature, presenting with clinical signs similar to those found in healthy adults, especially weight gain associated with increased food intake.<sup>1,8,9</sup> Some cases of insulinoma diagnosed and described in the literature were found and considered differential diagnoses in pregnant women with postpartum psychosis due to the presence of neuroglycopenic symptoms, which is manifested as glucose levels below 45  $\text{mg}\cdot\text{dL}^{-1}$ , and can divert the diagnostic reasoning due to its complex presentation.<sup>9</sup> The Whipple's triad is pathognomonic of insulinoma and includes hypoglycemia, with plasma glucose levels below 50  $\text{mg}\cdot\text{dL}^{-1}$ , relief of symptoms after glucose injection, and neuroglycopenic symptoms with varied presentations. Its manifestation can range from mild confusion to focal symptoms, seizures, and coma. Taking into account such neurological condition, a diagnostic hypothesis of pregnancy hypertensive disorders that progress to eclampsia is not uncommon.<sup>1</sup>

Unlike that observed in healthy subjects, in whom insulin production is dependent on blood glucose levels, in cases of insulinoma, the increased levels of insulin are not related to blood glucose levels and the presence of hypoglycemia can aid in the diagnosis of insulinoma. In diabetic pregnant woman, episodes of hypoglycemia due to insulin treatment are often observed, which is rarely found in those non-diabetic.<sup>1,2</sup>

Although many imaging tests can be used for tumor location, due to the small size and location of insulinoma, the

success rate is low.<sup>1</sup> In a review article, Besemer and Müssig<sup>6</sup> reported that in 27 described cases, the tumor location in 12 cases was only possible during laparotomy. Half of the cases showed signs in the first trimester of pregnancy and, in one third of cases, the clinical manifestations were evident only in the postpartum period. The difficulties of diagnosing the presence of insulinoma in early pregnancy may also be attributed to the presence of signs and symptoms similar to those seen in normal pregnancies. Regarding the low glucose levels observed in this period of pregnancy, it is justified by an increase in both insulin production and sensitivity, possibly related to hormonal changes during pregnancy, such as increased estrogen levels.<sup>1,3,8</sup>

Considering the maintenance of the mother-fetus binomial and facing the possibility of a safe clinical treatment, there is evidence to avoid surgery. For such management, the use of diet supervised by specialist, as well as the use of drugs such as diazoxide, beta blockers, calcium channel blockers, and octreotide are considered.<sup>1,2</sup>

In the case reported, due to the necessity of glucose bolus preoperatively, in addition to continuous infusion, it was discussed the use of octreotide, a somatostatin analog, and pindolol, a beta blocker, both with security level B for use during pregnancy.<sup>6,7</sup> However, due to the disease rarity and, consequently, to the small and unimpressive number of cases in which these drugs were used in pregnant women, the consensus among the experts in charge was for surgical treatment by laparotomy. In case of malignant tumors, with metastasis and aggressive chemotherapy indication, the interruption of pregnancy is discussed after mother's consent. A conservative approach to pregnancy maintenance has been reported and the use of octreotide showed efficacy in controlling episodes of hypoglycemia until the end of pregnancy.<sup>4,7</sup>

Although hypoglycemia during pregnancy can affect the fetal vitality, both increased placental lactogen hormone and insulin resistance attenuate the intensity of clinical signs and symptoms seen in cases of insulinoma; there are reports in the literature of cases treated only with diet adjustment until the end of pregnancy. In these patients there was significant weight gain and worsening of symptoms shortly after birth, which led to a definitive treatment with surgical excision.<sup>3,7,10</sup>

Regarding anesthetic management in these patients, the main goal is prevention of hypoglycemia and controlling the hyperglycemic rebound after resection; therefore, a frequent blood glucose monitoring is crucial during the procedure.<sup>1,6,7</sup> Knowledge of the physiological changes in pregnancy and its anesthetic implications is also of great importance. The presence of respiratory disorders contributes to the increased risk of hypoxia and hyperventilation associated with anxiety and stress, with consequent hypocapnia, left shift of the oxyhemoglobin dissociation curve, and reduced oxygen availability to the fetus, conditions that are minimized by proper ventilation. Thus, it is important to prevent the preoperative and intraoperative anxiety and stress, while maintaining respiratory rate to avoid  $\text{PETCO}_2$  values below 30 mmHg. Additionally, gastrointestinal disorders increase the risk of gastric content aspiration, and preventative measures such as intravenous metoclopramide (10 mg) and ranitidine (50 mg) should be considered.<sup>11</sup>

Regarding cardiovascular events, the inferior vena cava compression by the gravid uterus during supine position should be avoided, as the reduction in venous return and arterial hypotension with decreased uterine blood flow may be followed by loss of fetal well-being; moving the uterus to the left is imperative.<sup>11</sup> Although there is no consensus on the choice of anesthetic agents, it is recommended to opt for drugs that reduce the metabolic rate and cerebral oxygen consumption, such as the hypnotics thiopental or propofol. Thiopental should be used with caution in patients taken diazoxide, due to the increased risk of hypotension. This evident and pronounced effect on blood pressure can be attributed to the high affinity and competition of these drugs and its binding to plasma proteins.<sup>12</sup> Propofol has been widely used in anesthesia during pregnancy because it prevents nausea and vomiting and promotes early awakening,<sup>11</sup> besides not having effects on insulin release and glucose regulation—effects that justify its use in anesthetic management of patients with insulinoma.<sup>13–15</sup> Although volatile agents may reduce the insulin release, a non-clinically proven property, but desirable, its use seems to be interesting in cases of insulinoma.<sup>1,6,7,16</sup> As described by other authors,<sup>17</sup> the anesthetic technique used in this case—intravenous anesthesia with propofol associated with epidural block—is a useful technique for insulinoma removal.

## Conclusion

Total intravenous anesthesia and epidural block association proved to be safe and appropriate in the surgical management of insulinoma in pregnant patient. Appropriate drugs in terms of teratogenicity to the fetus were used. It is worth noting the importance of anesthesia programming, particularly the anesthetic implications correlated to the physiological changes of pregnancy and the endocrine-metabolic effects of this secreting tumor. Perioperative and postoperative monitoring and control to prevent major changes in blood glucose levels is recommended and of great importance.

## Conflicts of interest

The authors declare no conflicts of interest.

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