Case report: Gestational diabetes mellitus in a seven year-old German Shorthair Pointer bitch

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Summary

A seven year-old pregnant female German Shorthair Pointer presented to the Florida Veterinary Referral Center on June 28, 2010 for reduced appetite, polydipsia and lethargy. The bitch was 53 days pregnant (based on date of mating) at presentation. Serum biochemistry, blood glucose measurement and urinalysis were performed. The results indicated hyperglycemia and glycosuria. An abdominal radiograph confirmed the presence of seven fetuses. The bitch was diagnosed with the rare condition gestational diabetes mellitus (GDM) and managed medically with neutral protamine Hagedom (NPH) (Novolin™, Novo Nordisk, Bagsværd, Denmark) insulin at increasing doses towards the end of gestation. An elective cesarean section and ovariohysterectomy were performed on day 63 after breeding. Seven live puppies were delivered. Three died within 15 days of birth and four puppies were alive at 24 weeks postpartum. The dog remained insulin dependent.

Keywords: Gestational diabetes mellitus, insulin, insulin resistance, neonatal mortality, pregnancy

Background

Gestational diabetes mellitus is an extremely rare condition in bitches with only 15 reported cases in the veterinary literature.[1,2] The 15 reported cases come from two studies. The first was a study published in 2006 as a case report of two dogs. In these two cases, seven puppies were born and all died within five days. The other study was a retrospective study involving 230 clinics across Sweden. It described 13 cases of GDM. In this study bitches were separated into two treatment groups: termination of pregnancy (achieved through chemical abortion, ovariohysterectomy and cesarean section) or insulin therapy until the end of gestation (intermediate acting forms of human and porcine insulin). The results showed that termination of pregnancy at the time of diagnosis was associated with the bitch having a lower risk of developing permanent diabetes mellitus (DM).[1]

Bitches with GDM display the classical quartet of clinical signs of DM: weight loss, polyphagia, polydipsia and polyurea. Typically GDM occurs 50 days after mating in the last trimester of gestation and in the third or greater parity.[1]

Gestational diabetes mellitus occurs as a result of insulin resistance mediated by progesterone and growth hormone (GH).[3,4] These two hormones combine to have a synergistic antagonistic effect causing peripheral insulin resistance and producing hyperglycemia. In GDM, a post-receptor deficit results in an interruption of the normal intracellular signal transduction pathway preventing the normal action of insulin binding to its receptor.[5]

The beta cells of the islets of Langerhans are subjected to glucotoxicity (blood glucose greater than 14 mmol/L, [252mg/dl])[2,3] whereby irreversible damage occurs. Subsequently the bitch has an increased susceptibility to sustaining permanent DM after parturition. These affects are related to the severity and duration of hyperglycemia.[1] Termination of pregnancy and ovariohysterectomy are advised once a diagnosis is confirmed to reduce the risk of the bitch developing permanent DM. Additionally, the offspring may develop juvenile diabetes and other complications since the risk of fetal macrosomia increases as the length of GDM increases.[5]

Although pregnancy termination at the time of diagnosis is the therapy most likely to prevent permanent DM in the bitch, each individual case is unique and there are multiple variables that need to be taken into account. These include the desire of the breeder and the potential monetary value of the litter. This case report and literature review describes the management of a bitch with GDM and supports the approach of pregnancy termination at time of diagnosis for treatment. Furthermore, this case illustrates the lack of data pertaining to GDM and highlights the need for further research into the insulin management requirements of bitches with GDM in order to reduce the associated morbidity and mortality.

Case presentation

A seven year-old intact female German Shorthair Pointer presented to the Florida Veterinary Referral Center for reduced appetite, polyuria and lethargy on June 28, 2010. No abnormalities apart from tacky mucous membranes were noted on physical examination. The bitch was heavily pregnant with seven fetuses confirmed by abdominal radiographs. Hematology, serum chemistry and urinalysis showed mild anemia (hematocrit 33.2%), neutrophilia (13.6x10^9/L), eosinophilia (2.96x10^9/L), hyperglycemia (26.5 mmol/L, [477 mg/dl]), high normal blood urea nitrogen (BUN; 27 mmol/L) and 2+ glycosuria. There were no ketones in the urine. The serum progesterone concentration was 7.5 ng/ml and abdominal ultrasonography showed fetal heart rates ranging from 220 to 240 bpm.

This was the third litter and the bitch had no history of these clinical signs during any previous gestation. A diagnosis of GDM was made and managed medically with twice daily subcutaneous injections of NPH insulin commencing at 17 units. The intentions were to manage the pregnancy and control the clinical signs prior to an elective cesarean section closer to the due date. The dog was discharged with instructions to measure blood glucose three times daily; once before each insulin injection and once in the middle of the day.

The dog was fed three times daily using the same food. Blood glucose levels were measured at 09:00, 14:00 and 21:00 each day. The insulin dose was increased as the length of gestation increased, with insulin requirements increasing from 17 units BID to 30 units BID within five days. Despite the increased dose, glycemic control was not achieved, and the bitch experienced increased levels of hyperglycemia.

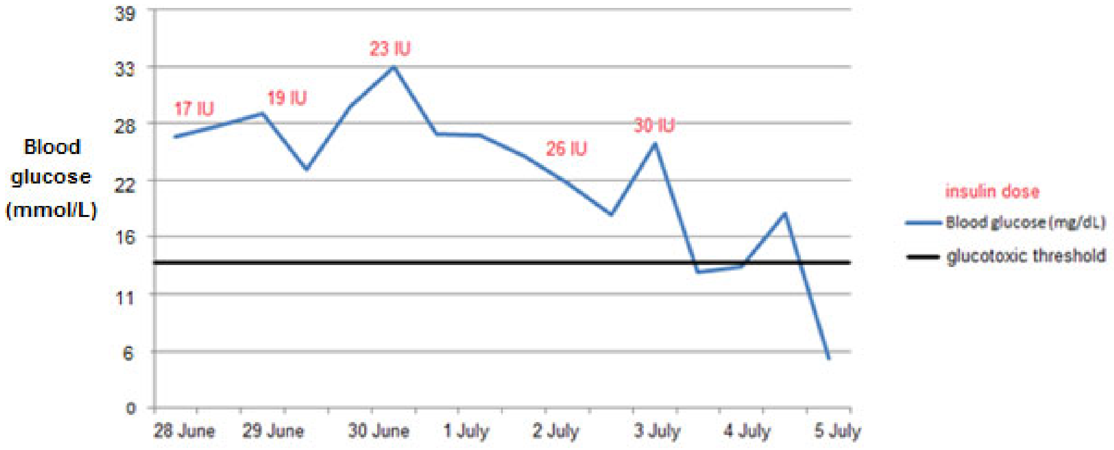

Figure. Blood glucose levels and insulin doses pre-partum

The owner reported that seven days after presentation, the bitch began to display nesting behavior and the rectal temperature dropped from 37.7°C to 36.9°C. Fetal ultrasound examination revealed heart rates of 160 to 180 bpm, a placental width of 0.8 cm, clear amniotic fluid and no evidence of fetal intestinal peristalsis. The plan was to examine the bitch with ultrasound the following day to determine if a cesarean section was required.

The following day fetal ultrasound examination revealed heart rates as low as 130 bpm. An elective cesarean section and ovariohysterectomy were performed. The uterus contained seven fetuses, all of which were delivered alive. The dog's blood glucose postoperatively was 35 mmol/L (630 mg/dl) and the dog was given a dose of short acting insulin. The following day the bitch was discharged with instructions to monitor blood glucose every two to three hours. The night after surgery the blood glucose was 13.1 mmol/L (235 mg/dl) and no insulin was given. The following day the blood glucose was 33.3 mmol/L (>600 mg/dl) and one of the puppies was not feeding well, did not gain weight and subsequently died that day.

In the days following surgery the dog was maintained on 15 units of insulin BID and achieving glycemic control remained difficult with sporadic episodes of hyperglycemia. On day four postpartum another puppy was vocalizing and refused to suckle. The neonate died at four days of age. Two weeks after surgery the owner reported that two of the seven puppies had died and the following day, the third pup died. The four remaining pups were doing well, suckling and gaining weight.

Twenty-five days after surgery, the bitch represented with hematuria. Urinalysis was performed and the results showed increased microalbuminuria (16.4 mg/dl), urine specific gravity of 1.022, 2+ protein, 3+ blood and rod-shaped bacteria were seen on sediment examination. There was no glycosuria. Bacterial cultured yielded a moderate growth of *E. coli* that was sensitive to amoxicillin/clavulanic acid. The bitch was treated with 250 mg amoxicillin trihydrate/clavulanate potassium (Clavamox®, Pfizer, New York, NY) BID for 14 days. One week later a urine culture was repeated and no bacterial growth was detected. Control of the dog's diabetes improved after the urinary tract infection resolved. The bitch was maintained on a dose of 12 units of NPH insulin BID with four remaining healthy pups at the time of writing. This dose of insulin, being the lowest the bitch received, supports the presence of type II insulin-dependent DM.

Insulin resistance mediated DM should be suspected in a bitch with supranormal blood insulin concentrations in the presence of normal or increased blood glucose concentrations. Demonstrating the absence of islet-related autoantibodies along with supranormal insulin levels would be further evidence to support an insulin resistance mediated DM. This, along with serial measurement of serum progesterone and growth hormone concentrations would have been necessary to unequivocally support the diagnosis of GDM. Despite the lack of irrefutable evidence to demonstrate pregnancy as the cause of gylcemic control, the previous history of the bitch in combination with the coincidence of clinical signs with gestation and improvement in glycemic control postpartum supports the diagnosis of GDM.

The current recommendation is for bitches with diestrus diabetes to be spayed prior to their next cycle due to high risk of sustaining permanent DM if they go through another estrous cycle.[3] A similar recommendation is made for cases of GDM. The longer pregnant bitches are subjected to insulin resistance, the more likely they are to develop permanent DM. Although there is no biochemical evidence to support the presence of type II diabetes in these cases, anecdotal evidence is strongly suggestive.

Discussion

Pregnancy is a diabetogenic condition. The fetus requires growth factors in-utero to mediate its growth and development. The hormones of pregnancy coalesce to cause peripheral insulin resistance which facilitates fetal growth and development in-utero. The two most notable hormones of pregnancy contributing to peripheral insulin resistance and GDM are progesterone and GH. In the bitch, progesterone is produced exclusively by the corpora lutea during pregnancy.[6] In the absence of progesterone, GH production by the pituitary gland is pulsatile. However, under the influence of progesterone, higher concentrations of GH are constantly secreted by the hyperplastic ductular epithelium of the mammary gland.[7] The combination of the progesterone and increased levels of GH have a strong synergistic effect resulting in significant peripheral insulin resistance. This combination provides the fetuses with glucose to support growth.

Evidence relating to the severity of insulin resistance under the influence of progesterone developed during the 1980's. Pioneering work by Eigenmann demonstrated the relationship between progesterone and diabetes and that mean insulin requirements were 4.9 IU/kg in dogs with diestrus diabetes compared with much lower levels in diabetic dogs that were not in diestrus.[8] This finding paved the way for the investigation into pregnancy-related insulin resistance and GDM.

The increase in insulin resistance and concurrent reduction in insulin sensitivity is vital to the development of GDM. In humans, insulin action during the third trimester of pregnancy is reduced by 45 to 70% compared with that in non-pregnant women.[9] Similarly, in pregnant bitches a 43% reduction in peripheral insulin sensitivity has been demonstrated.[9] The bitch has often been used as a subject to investigate carbohydrate metabolism and is described as "an excellent biological model for the understanding of carbohydrate metabolism in late pregnancy".[1] The major tissues responsible for the insulin resistance in bitches are skeletal muscle and adipose tissue. The liver retains some insulin sensitivity during pregnancy.[9]

The pathophysiology of insulin resistance during diestrus diabetes is identical to GDM,[4] yet the insulin resistance during pregnancy is much greater compared to that during diestrus diabetes.[3] Even though the insulin resistance during pregnancy is much greater, the incidence of GDM is negligible compared to diestrus DM. In the non-pregnant diestrus bitch, despite lower insulin resistance, the absence of the fetal drain of maternal glucose predisposes to development of diabetes more frequently and earlier than in pregnant dogs.[2] Bitches with diestrus DM develop the condition three to five weeks after estrus, which is much earlier than the average of seven weeks of gestation in bitches with GDM. The fetus plays an important role in draining maternal blood glucose and negating development of GDM.

Although GDM is rare, diestrus diabetes is common and is responsible for the higher incidence of DM in females than in males. In populations where juvenile females are not spayed, the incidence of diabetes in females is twice that of males while in populations where juvenile females are spayed, the incidence in females approaches that in males.[5]

In an uncomplicated case of GDM where minimal glucotoxicity occurs and pregnancy is terminated at the time of diagnosis, there is an abrupt cessation of progesterone secretion and progesterone-mediated GH concentrations, restoring glucose metabolism to normal.[10] Bitches return to normoglycemia within seven[1] to 21[5] days postpartum. Carbohydrate intolerance resolves once GH concentrations return to normal, whether through ovariohysterectomy, spontaneous regression of corpora lutea or withdrawal of progesterone.[12] In this case, hyperglycemia exceeded the glucotoxic levels and consequently there was irreversible beta cell damage resulting in permanent DM. Women with GDM are seven times more likely to develop permanent type II DM postpartum compared to those who have a non-diabetic pregnancy.[11] The same phenomenon occurs in the bitch and her offspring are at a greater risk of developing DM later in life.[4]

Termination of pregnancy is reported to be the best option to reduce the likelihood of the bitch developing permanent DM.[1] In that study bitches in which pregnancy was terminated did not go on to develop DM. Eighty percent of the bitches treated with insulin developed permanent DM.[1] One bitch that did not develop DM was the only one to receive an insulin dose > 2 IU/kg. Despite insulin therapy (mean 1.3 IU/kg) during pregnancy, the mean blood glucose concentration was 28 mmol/L (504 mg/dl). In the case reported here, an insulin dose of >60 IU would have been required to achieve similar glucose concentrations. The highest dose of insulin given was 30 IU (approximately 1 IU/kg).

In that study the bitches that were treated with insulin were on average older than those in which pregnancy was terminated. Aging might be expected to make development of permanent DM more likely since amongst humans, aging is associated with decreased insulin secretory capacity.[12] Drawing a conclusion between treatment and outcome is thus difficult because of the confounding effect of age in addition to the low power of the study.

Gestational diabetes mellitus in the bitch is associated with a high neonatal morbidity and mortality rate. Three of this bitch's seven pups died before 15 days of age and at six months after delivery there are four surviving puppies. Estimates of neonatal mortality following natural birth are 10 to 15% and 20% following cesarean section.[13] In cases of GDM, a neonatal mortality rate of 27% is reported.[1] In the case reported here the neonatal mortality rate was 43%.

As in humans with GDM, if canine neonates do survive, they are at increased risk of developing DM. In a previous study, three of 60 pups born to bitches with GDM developed DM.[1] The incidence of five percent found in that study is higher than the incidence of diabetes in the general population (0.3-1.3%).[14] In another study, the incidence of stillborn pups, fetal macrosomia and associated complications was higher in pups born to bitches with experimentally induced DM.[15] Eighty percent of bitches with

GDM that go to term experience dystocia from fetal macrosomia[3] which contributes to the reduced survival rate of neonates.

Bitches are also subject to higher morbidity when pregnancy is complicated by GDM. Bacterial urinary tract infections are common in dogs with DM. A decrease in immunity and increased glucose in the urine allow growth of bacteria and development of urinary tract infections. The effect of diabetes on the risk of infection is well-documented in humans. Diabetic dogs suffer a similar increased susceptibility to infection. Proposed mechanisms in humans include decreased blood supply due to microangiopathy and atherosclerosis leading to decreased phagocytes and antibodies, impaired humoral and cell mediated immunity and abnormal chemotaxis.[16] In this report the bitch developed a postpartum urinary tract infection which complicated control of diabetes. After the effect of pregnancy on insulin resistance had subsided, the presence of a urinary tract infection contributed to ongoing insulin resistance making it difficult to find a consistent insulin dose to control the diabetes. Following recovery from the infection, the bitch was maintained on a low dose of insulin (12 IU) suggesting that insulin resistance declined and was related to progesterone and GH concentrations and the infection.

Learning points

- Consider GDM as a differential for any pregnant bitch with hyperglycaemia. Despite pregnancy, bitches should maintain normoglycemia.
- Pregnancy termination at the time of diagnosis of GDM is associated with the most favorable outcome and reduces the bitch's chance of developing permanent DM.
- The neonatal mortality and morbidity rates are higher in pups born to bitches with GDM.
- Medical management of the bitch with insulin requires doses to be >2 IU/kg.
- Much more information is required regarding the dose and frequency of insulin required to manage bitches with GDM.

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