Case Report

Hemoperitoneum secondary to bilateral ovarian enlargement due to undiagnosed male cotwin pregnancy in a mare

Natalie Orner,[a] Michael Whitacre,[b] Megan Burke,[b] Amber Nebel-Karp,[c] Jose Len,[d] Sara Lyle[b‡]
[a]Southern Oaks Animal Hospital, Hope Mills, NC, USA
[b]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
[c]Animal Hospital of East Davie, Advance, NC, USA
[d]Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA, USA
[‡]Current affiliation: Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA, USA

Abstract

A 17-year, Quarter Horse mare, was presented for colic symptoms that began the day prior to presentation; patient had no breeding history. Severe bilateral ovarian enlargement precluded transrectal palpation of the gastrointestinal tract and much of the uterus. Transrectal ultrasonography revealed severely enlarged ovaries with multiple, large, ovarian follicles, and structures with an echotexture consistent with hemorrhagic anovulatory follicles, corpora hemorrhagica, and hematoma formation. Transcutaneous abdominal ultrasonography revealed a large volume of peritoneal fluid. Abdominocentesis was performed that identified fluid consistent with frank blood (packed cell volume of 40% consistent with intraabdominal hemorrhage). Initial differential diagnoses included bilateral granulosa-theca cell tumors, other ovarian neoplasia, or ruptured ovarian corpora hemorrhagicum/hematoma resulting in hemoperitoneum. Repeat abdominal ultrasonography revealed a viable pregnancy (~ 70 days). Additional diagnostics obtained 5 days after admission had severely elevated serum testosterone (517.8 pg/ml), elevated inhibin B (160.7 pg/ml), and normal antiMüllerian hormone (0.12 ng/ml) concentrations. After misoprostal and dinoprost tromethamine treatment, manual termination was performed that resulted in the removal of 2 male cotwins. Ovarian size markedly reduced soon after pregnancy termination and serum hormonal concentrations decreased 1 week later to concentrations approaching the reference range for a mare in the first trimester of pregnancy.

Keywords: Mares, twin pregnancy, peritoneal fluid, pregnancy termination

Background

Cases of hemoperitoneum secondary to ovarian pathology are rare but have been reported.[1,2] If an ovarian cause of hemoperitoneum is suspected, the primary rule out is granulosa-theca cell tumor (GCT); other ovarian neoplasia and ruptured corpus hemorrhagicum have also been reported.[1-4] Other causes of hemoperitoneum secondary to gastrointestinal conditions or vascular anomalies such as rupture of hepatobiliary vasculature, neoplasms, traumatic injury to the pelvis, coagulopathy, and foaling or pregnancy complications.[3,4] Because of nonspecific clinical symptoms including colic and lethargy, multimodal approach was necessary for diagnosis and treatment.

Case presentation

A 17-year, 461 kg, Quarter Horse mare, was presented for evaluation of mild colic symptoms that began a day before and were not responsive to 200 mg of flunixin meglumine treatment. According to the owner, the mare had no breeding history within the past year and was used for competitive barrel racing. The mare was examined by the primary veterinarian on the farm who diagnosed a potential large colon impaction and recommended referral. On initial examination by the emergency service, the mare was observed to be bright and alert with mild tachycardia (60 beats per minute [bpm]); had normal respiratory rate and temperature. The mare's mucous membranes were pink and tacky with capillary refill time

CONTACT Sara Lyle **saraklyle3@gmail.com**

Citation: Clinical Theriogenology 2024, 16, 10705, http://dx.doi.org/10.58292/CT.v16.10705

between 1-2 seconds. Gastrointestinal borborygmi were normal in all 4 abdominal quadrants and colic symptoms were absent on presentation. Transrectal palpation revealed 2 severely enlarged ovaries that limited palpation of the remainder of the gastrointestinal tract. Transrectal ultrasonography confirmed enlarged ovaries (> 10 cm) with multiple large structures with an echotexture consistent with corpora hemorrhagica, hematomas, or hemorrhagic anovulatory follicles (Figure 1). Images of the uterine body also confirmed a large volume of hypoechoic fluid. Due to ovarian and uterine size, the entire reproductive tract was not palpable transrectally. Transabdominal ultrasonography revearled a large volume of swirling free peritoneal fluid; abdominocentesis was performed. Fluid obtained via abdominocentesis was consistent with frank blood (6.3 mmol/l lactate, 40% packed cell volume [PCV], 4.5 g/dl total protein). Comparison of peripheral PCV (33%) and total protein (4.6 g/dl) confirmed acute hemorrhage into the peritoneal cavity. Elevation of abdominal and peripheral lactate was presumably a result of combination of dehydration and acute blood loss into the peritoneal cavity leading to decreased tissue perfusion. Hemoperitoneum can also be responsible for intense local inflammation that may lead to hyperlactatemia.[5] Although physical examination parameters did not suggest that the patient experienced hemorrhagic shock due to blood loss, the decision to stabilize the patient using whole blood was made by the attending emergency clinician out of concern for the potential for further losses and resultant destabilization of the patient. Initial stabilization was performed prior to a theriogenology consult and included an unmatched 8.5 liters whole blood transfusion and constant rate infusion of aminocaproic acid, followed by maintenance treatment of isotonic crystalloids to ensure adequate hydration. The patient's heart rate returned to 46 bpm immediately after transfusion and serial PCVs confirmed that there was no continued blood loss. Follow up focused abdominal ultrasonographic revealed resorption of free peritoneal fluid. Repeat transrectal ultrasonography was performed, and ovarian findings and uterine echotexture were similar to that at presentation. Hypoechoic fluid in the uterine lumen was similar in appearance to allantoic fluid, and amniotic membrane was suspected. Extensive transabdominal ultrasonography revealed a viable fetus (~ 70 days).[6] Fetal heart rate was within normal limits, and blood flow to the umbilicus was confirmed using color doppler. Serum was submitted (UC Davis Clinical Endocrinology Laboratory) for GCT panel and results were: normal antiMüllerian hormone (AMH) [0.12 ng/ml]), moderately elevated inhibin B (160.7 pg/ml), and markedly elevated testosterone (517.8 pg/ml) concentrations.

Differential diagnoses

Initial differentials included ovarian enlargement secondary to eCG production in pregnancy, ruptured ovarian hematomas, GCT, or some combination thereof. Based on confirmation of pregnancy and endocrinological findings of markedly elevated testosterone and moderately elevated inhibin concentrations, a provisional diagnosis (bilateral GCT development during pregnancy) was made. Since pregnancy was not planned, coupled with suspicion of a GCT and risk for continued hemoperitoneum formation, decision was made to terminate the pregnancy. To confirm our diagnosis, we decided to repeat endocrinological testing after pregnancy termination.

Treatment

The owners elected to terminate pregnancy and agreed to pursue potential ovariectomy once mare was stabilized.

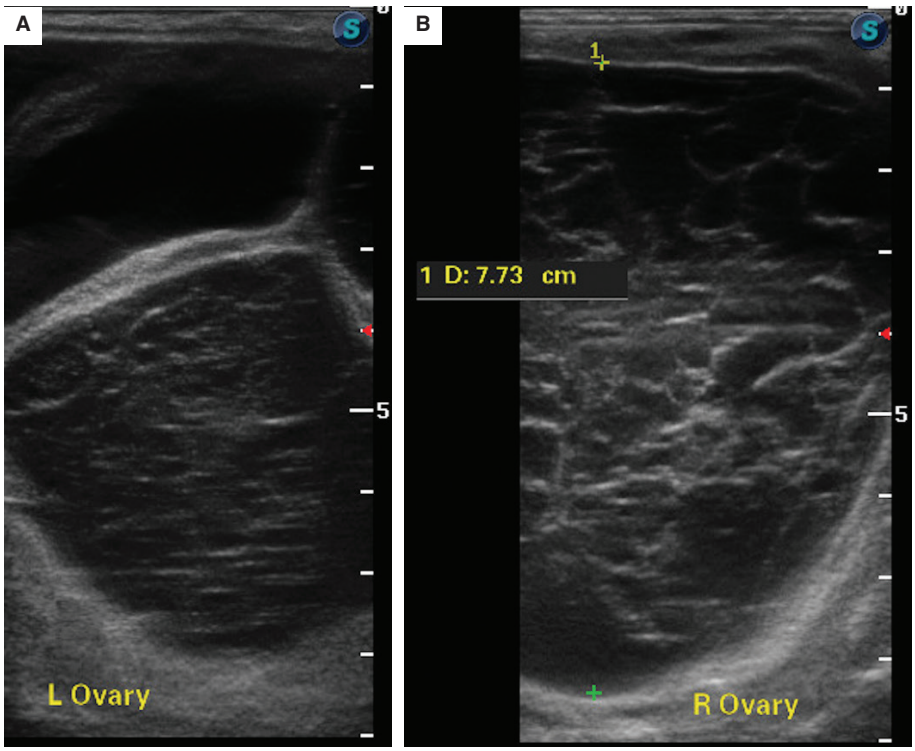

Figure 1. Transrectal ultrasonographic images of ovaries on initial presentation. (A) Left ovary (note multiple large follicular like structures and fibrin strands). (B) Right ovary (note a 7.7 cm structure [echotexture resembling corpus hemorrhagicum, hematoma, or hemorrhagic anovulatory follicle] and fibrin strands)

Citation: Clinical Theriogenology 2024, 16, 10705, http://dx.doi.org/10.58292/CT.v16.10705

Intramuscular prostaglandin $F_{2\alpha}$ (dinoprost tromethamine 5 mg, Lutalyse®) was given twice, 24 hours apart. In the afternoon, the second $PGF_{2\alpha}$ treatment was given and 200 µg of prostaglandin E_1 (misoprostol) was applied topically to the cervix. Manual dilation was successfully performed; termination of the pregnancy was completed by manual removal of the fetus and any unattached extra fetal membranes. After cervical dilation and further intrauterine examination, it became apparent that there was another fetus. After removal it was confirmed that both fetuses had male external genitalia (phenotypical male); however, karyotypes (for XY chromosomes) were not test. The next day morning, uterine lavage (sterile lactated Ringer's solution) was performed to remove debris and confirm complete expulsion of fetal membranes. There was no evidence (via transrectal ultrasonography) of retained fetal membranes.

Outcome

Transrectal ultrasonography was repeated the day after pregnancy termination; there was a reduction in ovarian sizes. The left ovary measured 7.19 cm in diameter, whereas the right measured 4.12 cm in diameter. Repeat endocrinological testing was performed 1 week after discharge; AMH (0.31 ng/ml) and inhibin B (64.8 pg/ml) concentrations were normal, and testosterone concentrations remained mildly elevated (73.4 pg/ml). Immediate reduction in ovarian sizes ovaries and echotexture after termination (consistent with early pregnancy) combined with a precipitous decrease in maternal testosterone concentrations confounded the diagnosis (GCT during pregnancy). Transrectal ultrasonography performed (no images were archived) by the referring veterinarian was reportedly normal. Reevaluation (10 weeks after initial discharge) confirmed normal ovarian echotexture and size (5-7 cm in diameter). The left ovary had a single follicular structure (~ 55 mm) with smaller follicles and the right ovary had a structure (~ 55 mm) with an echotexture that resembled a corpus hemorrhagicum or hemorrhagic anovulatory follicle (Figure 2). Concentrations of eCG were 100 IU/ml consistent with the continued presence of endometrial cups and supported ultrasonographic findings.

Discussion

An unusual case of a mare (not expected to be pregnant) having substantial ovarian enlargement and hematoma rupture, most likely secondary to equine chorionic gonadotropin (eCG) production is described. Hemoperitoneum resulting from ovarian enlargement and hematoma during pregnancy has been reported.[1] Other differentials were eliminated after the response to pregnancy termination, also subsequent endocrine testing was not definitively compatible with a GCT; although hemoperitoneum from a GCT during pregnancy has been reported in other instances.[7,8] In our patient, other causes of hemoperitoneum were ruled out using available imaging modalities. Coagulopathy was also ruled out using thromboelastography and initial evaluation via transrectal ultrasonography was consistent with substantial ovarian stimulation, ovarian hematomas, or corpora hemorrhagica.

We speculated that ovarian stimulation by high concentrations of eCG led to extensive growth and follicular luteinization, formation of multiple ovarian hematomas, rupture of ovarian hematoma(s), and ultimately accumulation of hemorrhagic peritoneal fluid. The authors are unaware of a reported case of hemoperitoneum during pregnancy sharing similar pathogenesis.

In the normal equine ovary, antral follicles are composed of 3 layers (theca externa, theca interna, and granulosa cell layer). Theca externa's rich blood supply is responsible for the evacuation of serosanguinous fluid during ovulation. During pregnancy, eCG is produced after invasion of trophoblast cells into the endometrium beginning ~ on day 35 of pregnancy, reaching a maximum ~ on days 65-70 of pregnancy. The resulting structures are referred to as endometrial cups and are responsible for production of eCG that has both follicle stimulating hormone and luteinizing hormone activity in the mare. Mares continue to have follicular waves during early pregnancy due to eCG secretion, resulting in ovarian enlargement because of growth of ovarian follicles; formation of secondary and

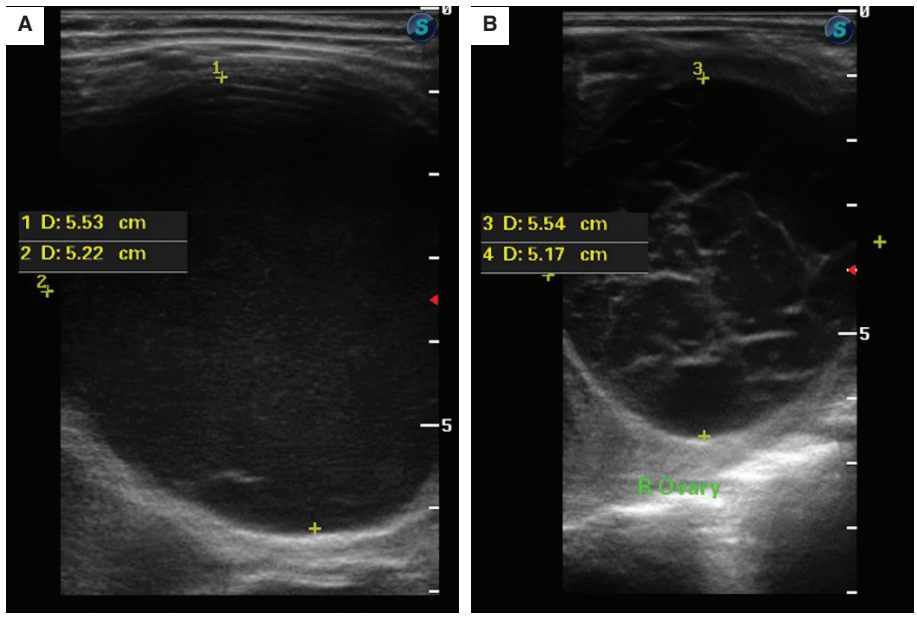

Figure 2. Transrectal ultrasonographic images of left (A) and right (B) ovaries 10 weeks after manual termination of pregnancy (note the decrease in ovarian size)

accessory corpora lutea, and corpora hemorrhagica. These luteal structures lead to additional progesterone and testosterone production.[9-11] Secretary pattern of testosterone in pregnant mares with functional corpora lutea having testosterone concentrations is markedly increased from prostaglandin-treated, altrenogest-supplemented pregnant mares without a functional corpus luteum.[11] This process of excess steroid production occurs at a critical point in equine pregnancy, as the fetoplacental unit does not fully take over production of progestogens until ~ day 120 of pregnancy.

Due to severe, bilateral, ovarian enlargement and ultrasonographic appearance, the possibility of an existing GCT should have been investigated as a cause of hemoperitoneum early in the case management. Endocrine testing revealed extremely elevated testosterone and moderately elevated inhibin B concentrations in the absence of AMH elevation. Testosterone concentrations during the third trimester of pregnancy in mares consistently increase above that of a nongravid mare due to marked steroid hormone production by the fetal gonads. The combination of an elevated inhibin and excessively high testosterone concentrations (517 pg/ml) observed in this case are suggestive of an atypical or early GCT due to the absence of AMH elevation. Analysis of endocrine findings were considered alongside the UC Davis Clinical Endocrinology Laboratory reference ranges for testosterone concentrations: 10-45 pg/ml for normal pregnancy, 45-70 pg/ml 'marginally elevated' 70-100 pg/ml, and > 100 pg/ml 'severely elevated'. One week after pregnancy termination, testosterone concentrations were 74 pg/ml, still warranting a concern for a GCT.

Equine fetal gonadal development begins ~ on day 40 of pregnancy and is complete by day 60. Steroid hormone production by the formed fetal gonad increases thereafter to reach its peak in mid pregnancy. Currently, there is no convincing literature to suggest that fetal androgen development can influence increases in maternal testosterone concentrations. Although maternal testosterone concentrations during male cotwin pregnancy have not been investigated formally, it is unlikely that fetal testosterone would be produced in sufficient quantities to escape placental aromatization to estrogens. In this case it is possible that prostaglandin treatment prior to termination allowed some degree of luteolysis or ovulation of follicular structures present on both ovaries. This could cause a resultant drop in testosterone concentrations if production by luteal tissue had a substantial role in steroid elevation. In a case of confirmed GCT, testosterone concentrations (> 1,000 pg/ml) decreased 10 fold within 30 days after the removal of affected ovary.[12] Currently, we can only speculate that the patient had ovarian pathology that contributed to normal physiologic rises in androgen production during early pregnancy. Lack of ultrasonographic images and laboratory work after the 10 week follow up examination prevented us to further elucidate the endocrine findings. A follow up GCT panel is highly desired as this is the only reported case of testosterone elevation to that degree during pregnancy in the absence of a GCT. Examination and aforementioned diagnostics performed after regression of the endometrial cups might have provided further endocrinological explanation to this unique case.

Learning points

- Pregnancy should always be considered in mares with ovarian enlargement despite no breeding history
- Hemoperitoneum is a rare complication arising from ovarian stimulation related to eCG secretion and presumed rupture of a corpus hemorrhagica/hematomas
- Androgen synthesis by luteal tissue as a result of eCG secretion may cause increases in maternal testosterone above concentrations expected of a pregnant mare

Conflict of interest

None to declare.

Acknowledgement

Authors thank Alan Conley of UC Davis Clinical Endocrinology Laboratory for his invaluable assistance in the interpretation of endocrinological results.

References

1. Beachler TM, McKelvy KA, Bailey CS, et al: Haemoperitoneum in a pregnant mare with an ovarian haematoma. Eq Vet Edu 2016;28:359-363. doi: 10.1111/eve.12211
2. Pauwels FE, Wigley SJ, Munday JS, et al: Bilateral ovarian adenocarcinoma in a mare causing haemoperitoneum and colic. N Z Vet J 2012;60:198-202. doi: 10.1080/00480169.2011.647607
3. Conwell RC, Hillyer MH, Mair TS, et al: Haemoperitoneum in horses: a retrospective review of 54 cases. Vet Rec 2010;167: 514-528. doi: 10.1136/vr.c4569
4. Dechant JE, Nieto JE, Le Jeune SS: Hemoperitoneum in horses: 67 cases (1989-2004). J Am Vet Med Assoc 2006;229:253-258. doi: 10.2460/javma.229.2.253
5. Murase H, Endo Y, Tsuchiya T, et al: Ultrasonographic evaluation of equine fetal growth throughout gestation in normal mares using a convex transducer. J Med Vet Sci 2014;76:947-953. doi: 10.1292/jvms.13-0259
6. Scott C, Christensen B, Pritchard W, et al: Hemoperitoneum in a mare following rupture of a granulosa-theca cell tumor. Clinical Theriogenology 2015;7:425-429.
7. Worsman FCF, Barakzai SZ, Rubio-Martinez LM, et al: Treatment of haemoperitoneum secondary to ruptured granulosa theca cell tumors in two mares. Equine Vet Edu 2020;32:71-77. doi: 10.1111/eve.12929
8. Squires EL, Ginther OJ: Follicular and luteal development in pregnant Mares. J Reprod Fertil 1975;23:429-433
9. Ginther OJ: Reproductive Biology of the Mare, Basic and Applied Aspects. 2nd edition, Cross Plains; Equiservices Publishing: 1992. p. 237-240.
10. Daels PF, Chang GC, Hansen B, et al: Testosterone secretion during early pregnancy in mares. Theriogenology 1996;45: 1211-1219. doi: 10.1016/0093-691X(96)00076-3
11. Tennent-Brown BS: Lactate production and measurement in critically ill horses. Compend Contin Educ Vet 2011;33:E5.
12. Gee EK, Dicken M, Archer RM, et al: Granulosa theca cell tumour in a pregnant mare: concentrations of inhibin and testosterone in serum before and after surgery. N Z Vet J 2011;60:160-163. doi: 10.1080/00480169.2011.645776