An unusual case of uterus didelphys in an infertile mare with mosaic X-chromosome aneuploidy

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A 3 year old Irish Cob maiden mare of normal size was referred at the Centre Hospitalier Universitaire Vétérinaire, University of Montreal, Faculty of Veterinary Medicine because of fertility problems and the possible presence of two cervices. The external genitalia appeared normal. Examination of the internal reproductive tract revealed normally functioning ovaries and two tubular structures compatible with cervices were identified on the pelvic floor. Endoscopic of the cranial vagina confirmed the presence of two cervices. Chromosome analysis revealed mosaic aneuploidy of the X chromosome (mos 63, X/64, XX). No treatment was available for either of the anomalies diagnosed and the mare was discharged. This report highlights the importance of using diagnostic tests in addition to clinical examination in cases of equine infertility.

Key Words: Mare; Uterus didelphys; Mosaicism; Infertility; Karyotype

Abbreviation: UD uterus didelphys

The term Disorder of sexual development (DSD) includes a very broad spectrum of sexual pathologies well described in humans and domesticated animal species. In horses, DSDs are not uncommon and in the clinical context, they are expected to cause reproductive problems and possibly lead to infertility. Normal development of the internal female reproductive tract involves a series of complex molecular and biochemical interactions that lead to differentiation of the Müllerian ducts and the urogenital sinus (1). During this period, the posterior portion of each Müllerian duct undergoes a dynamic process of growth, migration and differentiation and eventually fuses with the corresponding contralateral paramesonephric duct, resulting in formation of the uterine body and cervix as well as the cranial portion of the vagina (2). Congenital abnormalities affecting the uterus and cervix result from abnormal fusion or regression of the posterior portions of the Müllerian ducts (3,4). Varying degrees of these abnormalities, including a complete uterine septum, cervical duplication with a normal or septate uterus, and a blind-ended cervical canal, have been reported in mares (5). Most of the reported cases have involved Clydesdale, Shire and Suffolk Punch draft horses (6-8) and the mares affected were mostly fertile and delivered foals uneventfully (9). However, in none of these reported cases, the cytogenic analysis was performed. The present report describes a uterus didelphys in an infertile mare with mosaic X chromosome aneuploidy.

CASE

A 3 year old Irish Cob maiden mare of normal size was referred at the Centre Hospitalier Universitaire Vétérinaire, University of Montreal, Faculty of Veterinary Medicine, for investigation of fertility problems and the possible presence of two cervices. The mare was not in foal despite being covered by two fertile stallions on four occasions during the same season. On examination, the external genitalia were normal and there was no clitoral enlargement. Transectal palpation and ultrasound examination of the entire reproductive tract using a 7.5 MHz linear probe were performed. The ovaries were of normal size, and examination of their surface and the ovulation fossa revealed no anomaly. The ultrasound examination revealed normal ovarian structures and follicles of various sizes in both ovaries. A dominant follicle (42 mm x 36 mm) was visualized in the left ovary. Uterine edema with a “wagon wheel” appearance was identified on ultrasound examination of cross-sections of the uterine horns and graded as 2/3.

Two tubular structures compatible with the presence of two cervices were identified by transrectal palpation of the pelvic floor. The vagina and uterus were visualized on fiberoptic endoscopy. The caudal vagina and vestibulovaginal fold were normal. Endoscopy of the cranial vagina confirmed the presence of two cervices. Chromosome analysis revealed mosaic aneuploidy of the X chromosome (mos 63, X/64, XX). No treatment was available for either of the anomalies diagnosed and the mare was discharged. This report highlights the importance of using diagnostic tests in addition to clinical examination in cases of equine infertility.

Peripheral blood was collected into sterile sodium heparin tubes. Lymphocytes were cultured under conventional conditions (10) and the karyotype was analyzed using fluorescent C-banding and X-chromosome specific fluorescent in situ hybridization. Screening of 86 metaphase spreads using the fluorescent C-banding approach showed that 72 cells (84%) had a normal 64XX chromosome constitution and 14 (16%) had an abnormal 63X karyotype. Fluorescent in situ hybridization of the interphase nuclei of 502 cells revealed that 430 (86%) had a normal two X chromosomes and 72 (14%) had one X chromosome (Figures 5 and 6). On average, the mare had a 14.6% rate of X chromosome monosomy. As a control samples from a normal fertile mare processed in the same way (e.g. fluorescent C-banding analysis) were found to have two X chromosome in 100% of metaphase and interphase spreads (n=200).

DISCUSSION

Uterus didelphys is a congenital anomaly of the female reproductive tract, except in marsupials and lagomorphs, where it is considered normal. The condition results from failure of fusion of the lower segments of the paired Müllerian ducts, resulting in two uteri and two cervices. Very few clinical cases of UD have been published, suggesting a very low incidence of this anomaly. Abnormalities of the female reproductive system are generally not accompanied by clinical signs, unless an anatomic modification or pathology, such as a tumor, is present (11,12). Pregnancy loss during the embryonic stage or later during fetal growth would be a concern in a mare with UD. In a normal mare, movements of the embryo throughout the entire uterine cavity before immobilization at around day 16-17 after ovulation are essential

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Received: March 26, 2018, Accepted: April 17, 2018, Published: May 1, 2018

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for maternal recognition of pregnancy. Any limitation or restriction of these movements would prompt release of luteolysin, which would result in the destruction of the corpus luteum and a return to estrus (13). In a mare with UD, movements of the equine embryo would be limited to only half of the uterus, so the pregnancy would be compromised. There would also be concern about the risk of abortion during subsequent fetal growth, because of the significant reduction in the surface of the placenta (9) and a lack of space for the fetus to grow and develop (7,14). Nevertheless, there are reports of live and healthy foals being delivered by mares with various Müllerian duct disorders (7,9), including a case of a small viable foal born to a Clydesdale mare with UD that was treated with oral progesterone for the full duration of the pregnancy (9).

Uterus didelphys in domestic animals is mostly an incidental finding, and routine transrectal palpation and ultrasound examination of the internal reproductive tract in a mare does not necessarily facilitate the diagnosis of UD. In the present case, the anomaly was diagnosed primarily by transrectal palpation and from the history provided by the referring veterinarian. Additional tests, including vaginoscopy and hysteroscopy, may be more conclusive and vaginoscopy should be routinely included in the assessment of breeding soundness. Three-dimensional ultrasound and magnetic resonance imaging have been reported to aid visualization of UD and other malformations of the internal reproductive system in human patients (15,16); however, implementation of these technologies might be difficult in a practice that treats large animals. While some corrective procedures to improve fertility have been described in human patients with UD (16), the authors are not aware of any such treatments in domestic animals.
The mare described in this clinical report was normal in appearance. The uterine horns were normal in size, and the ovaries had normal follicular activity. The mare had a history of normal estrus cycles but never having been in foal. However, no formal examinations for pregnancy had been performed, and the mare was simply declared not to be in foal each time she came back into estrus following attempts at natural breeding. This could be related to a failure of maternal recognition of pregnancy in response to movements of the embryo being limited to one uterine horn instead of the entire uterus. An ultrasound examination 14 days post ovulation and supplementation with synthetic progesterone would have been suitable in the event of pregnancy. To the author’s knowledge, this is the first case of UD in a mare with mosaicism. Further tests, including a skin biopsy to obtain connective tissue for development of a fibroblast cell culture and explore other possible structural chromosomal abnormalities in this patient were offered but were declined by the owner.

CONCLUSION

In conclusion, UD is a rare congenital disorder of the female reproductive system in mammals, including horses. Diagnosis by transrectal palpation and ultrasound examination is not always conclusive and requires further investigation, such as vaginoscopy or hysteroscopy. When diagnosed, assisted reproduction techniques may be the best option to optimize the chances of obtaining a healthy live foal. When a phenotypically normal mare is presented with a complaint of fertility problems despite thorough clinical examination, karyotyping is strongly recommended to rule out a chromosomal abnormality.

REFERENCES


