Effects of Sulfadiazine and Pyrimethamine and Concurrent Folic Acid Supplementation on Pregnancy and Embryonic Loss Rates in Mares

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The treatment of mares with sulfadiazine and pyrimethamine, with and without concurrent folic acid supplementation, during breeding and early gestation was investigated. No detrimental effects were noted in pregnancy rates or embryonic loss rates up to day 25 of gestation. Reports of abortions and congenital defects in foals from pregnant mares treated for equine protozoal myeloencephalitis warrant caution and further study. Authors’ addresses: College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331 (Brendemuehl) and Dept. of Clinical Sciences, School of Veterinary Medicine, Tuskegee University, AL 36088 (Waldridge and Bridges). © 1998 AAEP.

1. Introduction
Equine protozoal myeloencephalitis (EPM) is a serious and sometimes fatal neurological disease of horses in the Americas. Recent epidemiological studies of horses in Kentucky, Ohio, Pennsylvania, and Oregon have indicated an exposure rate of over 50%. Although the estimated clinical incidence of EPM is less than 1.0%, the condition was recently described by Reed and co-workers at The Ohio State University as the most significant equine disease in the eastern U.S. because of its potential to cause tremendous economic losses. These losses are associated with the direct costs of treatment as well as the loss of earnings or loss of life. Furthermore, recently published reports as well as personal communications with practitioners) indicate that there are substantial reproductive losses in mares treated for EPM. The described losses have included midterm abortions, congenital defects in foals, and early pregnancy losses.

In horses diagnosed with EPM, a prolonged course (≥12 weeks) of the antiprotozoal drug pyrimethamine and a sulfonamide is indicated. These compounds are inhibitors of dihydrofolate reductase, and concurrent supplementation with folic acid is often recommended to minimize the associated toxicity. Embryotoxicity with pyrimethamine administration has been reported in monogastric animals and humans. Additionally, in women a high incidence of neural tube defects are reported in newborns when folic acid inhibitors are administered during pregnancy. Concomitant supplementation with oral folic acid has been shown to augment pyrimethamine toxicity in rats. Recent clinical reports have suggested that the treatment of pregnant mares with sulfonamides, pyrimethamine, and
folic acid can produce abortions\(^6\) and congenital defects in newborn foals.\(^7\)

The objective of this study was to determine if sulfadiazine and pyrimethamine therapy, alone or in conjunction with folic acid supplementation, would alter pregnancy or embryonic loss rates in mares during early gestation.

2. Materials and Methods

Fourteen mares were randomly assigned to one of two treatment groups of seven mares each. All mares were reproductively sound based on routine clinical evaluations and the establishment of a 21-day pregnancy prior to inclusion in the study. Cycles per pregnancy of the untreated mares served as controls for the treated groups. All mares were maintained in dry lots and fed coastal Bermuda grass hay (15 kg/mare) and grain (1 kg/mare) daily. Group 1 and group 2 mares received sulfadiazine (30 mg/kg) and pyrimethamine (1 mg/kg) in a combined dose by mouth once daily. The sulfadiazine-pyrimethamine (SP) combination was administered at 07:00, and grain and hay were fed at least 2 h later. Group 2 mares additionally received 40 mg of folic acid (SPFA) by mouth once daily at 16:00. Mares were monitored every other day by teasing and ultrasonography of the reproductive tract. Once a 35-mm follicle was observed, the mares were inseminated with a minimum of 10\(^9\) progressively motile spermatozoa every other day until ovulation was detected. The evaluation for pregnancy was performed by transrectal palpation and ultrasonography at 14 and 21 days postovulation. The embryonic vesicle height was measured and its appearance was noted at each examination. Upon observation of a normal vesicle and fetal heartbeat at day 25, a luteolytic dose of prostaglandin analog was administered to terminate the pregnancy and return the mares to estrus. Mares were bred a total of three cycles while on their respective treatments. Blood was collected once weekly and serum folate concentrations were determined by bioassay.\(^b\) Comparisons in pregnancy and embryonic loss rates between groups were made by one-way analysis of variance, and a value of \(p \leq 0.05\) was considered significant.

3. Results

Serum folate concentrations were significantly lower in mares not receiving folate supplementation (2.5 ± 1.0 vs. 3.8 ± 1.2 ng/ml) by 60 days of treatment. Pregnancy rates did not differ between treatment groups (\(p > 0.05\)). The overall per cycle pregnancy rate for control mares (16/23; 69.6%) was similar to mares treated with SP alone (21/24; 87.5%) or with SPFA (20/24; 83.3%). There was no significant difference in the number of embryonic losses that occurred between control (1/16; 6.3%) and the treatment groups (SP, 1/21; 4.8%; SPFA, 2/20, 10.0%).

4. Discussion

The results of this study demonstrate that no reduction in pregnancy rate or increase in embryonic loss rate occurs in mares receiving sulfadiazine and pyrimethamine during the first 21 days of gestation. Concurrent supplementation with folic acid likewise had no apparent potentiating embryotoxic effect as has been described in other species. Recent clinical reports\(^6\) and personal communications with practitioners have indicated that mares treated with SP have experienced early pregnancy loss and midgestation abortions. To date, no definitive etiology for these losses has been determined. A possible explanation is that alterations in organogenesis, such as neural tube defects, are occurring that result in fetal demise. The recent report\(^7\) of congenital defects in foals from mares that received folic acid supplementation during late gestation raises concerns regarding the safety of folic acid supplementation during pregnancy.

It should be cautioned that the pregnancies in this study were monitored only by transrectal ultrasonography, and no gross or histologic evaluation was performed. While the embryonic vesicle's height and ultrasonographic appearance were normal, it is possible that abnormalities in development occurred that could result in pregnancy loss at a later stage or in congenital defects in the foals from treated mares. Clearly, further studies are required to determine the safety of folic acid inhibitors and folate supplementation throughout gestation in the pregnant mare.

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References and Footnotes


\(^{b}\)Lactobacillus casei n bioassay, GI Laboratory, College of Veterinary Medicine, Texas A & M University, College Station, TX 77843-4474.