Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: A meta-analysis

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ABSTRACT

Bovine viral diarrhea virus (BVDV) is an important reproductive pathogen of cattle worldwide. The reproductive outcome of BVDV infection is largely dependent on the immune status of the dam and the stage of gestation at the time of infection. Potential sequelae include failure of conception, abortion, a variety of congenital malformations, and fetal infection. Vaccination is a possible tool in the control of BVDV, and there has been a recently renewed focus on providing fetal protection through vaccination. Consequently, the aim of this study was to evaluate the efficacy of BVDV vaccination to prevent reproductive disease by performing a quantitative synthesis of previously published studies. Pertinent articles to be included in the analysis were identified by performing a search in four relevant scientific databases (PubMed, CAB abstracts, National Agricultural Library catalog, and Web of Science) and examining the reference lists of 10 germane review articles. Inclusion criteria for the meta-analysis mandated that the studies were controlled, primary studies that included necessary data for use in the meta-analysis (e.g., group size, number of abortions). Forty-six studies in 41 separate articles matched the inclusion criteria. Risk ratio effect sizes were used in random effects, weighted meta-analyses to assess the impact of BVDV vaccination on three outcomes: risk of fetal infection, abortion risk, and pregnancy risk. Within each outcome, subanalyses were performed to evaluate the effect of a variety of interventions, including modified live, inactivated, polyvalent and monovalent vaccination, homologous, heterologous, or field challenge, and studies with only bovine subjects. The analysis revealed a decrease in abortions of nearly 45% and a nearly 85% decrease in fetal infection rate in cattle vaccinated for BVDV compared with unvaccinated cohorts. Additionally, pregnancy risk was increased by approximately 5% in field trials of BVDV vaccinates. This meta-analysis provides quantitative support for the benefit of vaccination in the prevention of BVDV-associated reproductive disease.

1. Introduction

Bovine viral diarrhea virus (BVDV) is the prototype virus of the *Pestivirus* genus and a principal viral pathogen in both dairy and beef cattle populations. Viral infection leads to a wide array of clinical signs including diarrhea, thrombocytopenia and hemorrhagic diatheses, respiratory disease, and ulcerations of the gastrointestinal tract. However, the largest economic consequence of BVDV infection may be through reproductive losses [1]. Reproductive disease as a result of BVDV infection has been recognized from the time the virus was first reported [2] and remains a major concern on dairy farms, cow-calf ranches, and breeding stock operations. The consequence

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of BVDV infection on reproduction depends largely on the immune status of the dam and the stage of gestation at the time of infection. Exposure of naive cattle to the virus at or near the time of breeding can result in reduced pregnancy rates because of decreased conception rates and early embryonic death [3,4]. Abortion is most common in the first trimester but may occur at any time during gestation, including the third trimester. Viral exposure of the fetus between 18 and 125 days of gestation may lead to immunotolerance and persistent infection. Persistently infected (PI) calves are often weak at birth but may be phenotypically normal and are important to the epidemiologic aspects of viral propagation as they consistently shed high levels of virus in the environment. Infection during crucial times of organogenesis may also result in congenital defects including cerebellar hypoplasia, microphthalmia, hydranencephaly, hypotrichosis, and brachygnathism.

Control of BVDV is currently exerted primarily through strict biosecurity, eradication efforts, vaccination, or a combination of these factors. One of the primary aims of BVDV vaccination is to prevent the creation of PI calves that act as reservoirs of the virus. Although this goal was recognized by the mid-1970s [5,6], the efficacy of early vaccines to prevent fetal infection was often incomplete [7,8]. Improper vaccine usage has also contributed to their limited efficacy [9,10]. More recently, several BVDV vaccines have been licensed that carry fetal protection claims with at least 365 days duration of immunity. Despite this, accounts of fetal infection in calves born to vaccinated dams continue to be reported in the literature [11–13] leading some to question the efficacy of BVDV vaccination to prevent reproductive disease. Consequently, the objective of this study was to analyze the published data in regard to the efficacy of BVDV vaccination to decrease the risk of abortion, the probability of fetal infection, or to prevent a decrease in pregnancy risk.

2. Materials and methods

In May 2014, a search for articles was performed in four relevant scientific databases (PubMed, Web of Science, CAB Abstracts, and National Agricultural Library catalog) using the keywords "BVDV vaccine" or "BVDV" and "vaccine." The search results were not restricted by limitations on language or year of publication. The reference lists of several review articles on BVDV and BVDV vaccination [1,14–22] were examined for further pertinent studies. Additional articles were found by cross-referencing citations in retrieved articles. Studies identified from online databases and previous publications were selected for inclusion in the meta-analysis if the following criteria were met: (1) the study was relevant to the objective of the analysis; (2) the study was a controlled, primary study; and (3) data for further analysis could be extracted for at least one of the three outcomes of interest.

From all studies meeting the inclusion criteria, data relating to the outcomes of interest were extracted. To analyze the risk of fetal infection, the number of PI animals and total animals born were noted. Alternatively, precolostral positive antibody titers to BVDV in newborn animals were used as evidence of fetal infection in studies in

which viral challenge occurred following the susceptible window for the creation of PI animals. For the abortion risk, the number of total recorded abortions and the number of pregnant animals were documented. The total number of abortions was used for the analysis rather than only those abortions confirmed to be caused by BVDV as many aborted fetuses were lost to follow-up and the etiologic cause could not be ascertained. For pregnancy risk analysis, the number of recorded pregnancies and the number of animals bred by artificial insemination or exposed to a bull were extracted from each study. Data were analyzed using a commercial meta-analysis software program (Biostat, Englewood, NJ, USA). Studies in which no events were recorded for both the treatment and control groups and studies in which the number of events equaled the group size in both groups were excluded from further analysis by the software. The risk ratio (RR) for each outcome in individual studies was used as the effect size metric. The RR compares the probability of an event occurring in an exposed (i.e., vaccinated) group with the probability of the event occurring in a nonexposed (i.e., unvaccinated) group. When there is no difference in risk between groups, the RR equals 1. If the RR is greater than 1, the event is more likely in the exposed group; when the RR is less than 1, the exposure is deemed to have a protective effect on the measured outcome. Results were presented as means bounded by 95% confidence intervals. Means were statistically different ($P < 0.05$) from the null hypothesis (i.e., no effect of vaccination) when the 95% confidence interval did not include 1. Weighted meta-analysis was performed using a random-effects model to compare mean effect sizes across treatment types. Weighting of the data is performed inherently by the commercial software and is based on the inverse of the sampling variance and by the variability across the population effects.

To examine the effect of certain vaccine and virus factors, additional quantitative syntheses were performed within each outcome of interest using a subset of the identified studies relevant to that outcome. Within each outcome, the effects of modified live (MLV), inactivated, polyvalent or monovalent vaccines, homologous, heterologous, or field challenge, and vaccination studies using only cattle were evaluated. Studies included in the analysis of homologous challenge were those reports in which the challenge genotype was known to be included in the vaccine; studies included in the analysis of heterologous challenge were those investigations in which the challenge genotype was not included in the vaccine. Consequently, studies reporting a field challenge were not included in these subanalyses as the challenge strain could not be ascertained. At least three relevant studies for each subanalysis were deemed necessary to report the results of the meta-analysis.

3. Results

A combined total of 1164 reports were returned by the four databases. After removal of duplicate citations and studies irrelevant to this meta-analysis, a total of 46 studies in 41 reports were identified for meta-analysis. One study using a vaccine subsequently found to contain a BVDV

contaminant and one vaccine safety study with no BVDV challenge were excluded from further analyses, leaving a total of 44 studies in 39 reports included in the final quantitative analyses (Appendix A). Thirty-five of the 44 identified studies contained the necessary data to assess the efficacy of BVDV vaccination to prevent fetal infection. In one study, viral challenge resulted in fetal infection in all study animals, both vaccinates and unvaccinated controls; thus, this study was eliminated from further analyses by the software, leaving a total of 34 included studies in the meta-analysis of the effect of BVDV vaccination on fetal infection. Data on abortion risk was reported in 32 of the 44 studies; five studies were excluded from the analyses concerning abortion risk as no abortion events were recorded in the treatment or control groups. In 23 of the 44 identified studies, vaccination occurred before breeding and pregnancy data was available for analysis. In three studies, all animals in both the vaccinated and unvaccinated groups were pregnant, resulting in exclusion of these studies by the software from further analyses.

The risk of fetal infection in vaccinated animals regardless of vaccine type or challenge method was approximately one-seventh the risk in unvaccinated animals (Fig. 1). Significant ($P < 0.001$) reductions in the risk of fetal infection were found in all subanalyses performed with the exception of when vaccinated animals were challenged with a heterologous viral genotype (Table 1). The probability of fetal infection was found to be lowest

Table 1
Meta-analysis results for the effect of bovine viral diarrhea virus vaccination on fetal infection showing the risk ratio, 95% confidence interval, and associated P value.

Factor	Risk ratio	Lower	Upper	P value
Overall	0.152	0.103	0.224	<0.001
Cattle studies	0.135	0.091	0.203	<0.001
Field challenge	Insufficient data			
MLV vaccine	0.117	0.074	0.184	<0.001
Inactivated vaccine	0.236	0.131	0.426	<0.001
Heterologous challenge	0.542	0.290	1.014	0.055
Homologous challenge	0.158	0.084	0.296	<0.001
Polyvalent vaccine	0.097	0.056	0.168	<0.001
Monovalent vaccine	0.177	0.096	0.328	<0.001

Abbreviation: MLV, modified live.

when using a polyvalent (RR = 0.10; 95% CI, 0.06–0.17) or MLV vaccine (RR = 0.12; 95% CI, 0.07–0.18). In studies with a known and intentional challenge (field challenge studies excluded), exposure in 353 of 369 (95.7%) unvaccinated animals resulted in fetal infection (data not shown).

In studies included in this meta-analysis, the overall abortion rate was reduced by approximately 40% in animals vaccinated against BVDV (RR = 0.57; 95% CI, 0.46–0.70) (Fig. 2) compared with unvaccinated control groups. The best protection against abortion was provided when the challenge virus genotype was included in the vaccine (RR = 0.29; 95% CI, 0.13–0.66); an insufficient number of
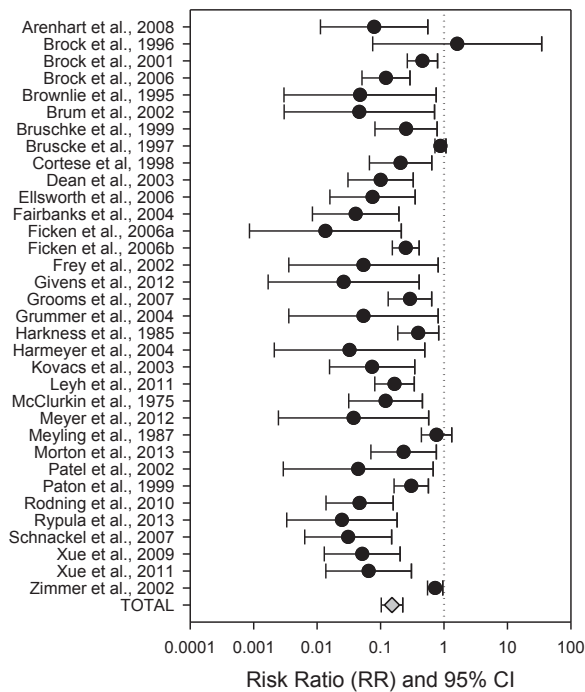

Fig. 1. Forest plot of the meta-analysis of the effect of bovine viral diarrhea virus vaccination on fetal infection. The study names included in the analysis are shown on the left ([2–9,11–27,28–30,32,33,35,37–39] of Appendix A) with their corresponding effect size and 95% confidence interval (CI). The overall effect is shown at the bottom, represented by the shaded diamond. The dotted vertical line represents a risk ratio (RR) of 1, indicating no significant difference between vaccinates and controls.

Fig. 2. Forest plot of the meta-analysis of the effect of bovine viral diarrhea virus vaccination on abortion. The study names included in the analysis are shown on the left ([1,2,4–6,11,15,16,18,19,21,23–27,29,32,35,39] of Appendix A) with their corresponding effect size and 95% confidence interval (CI). The overall effect is shown at the bottom, represented by the shaded diamond. The dotted vertical line represents a risk ratio (RR) of 1, indicating no significant difference between vaccinates and controls.
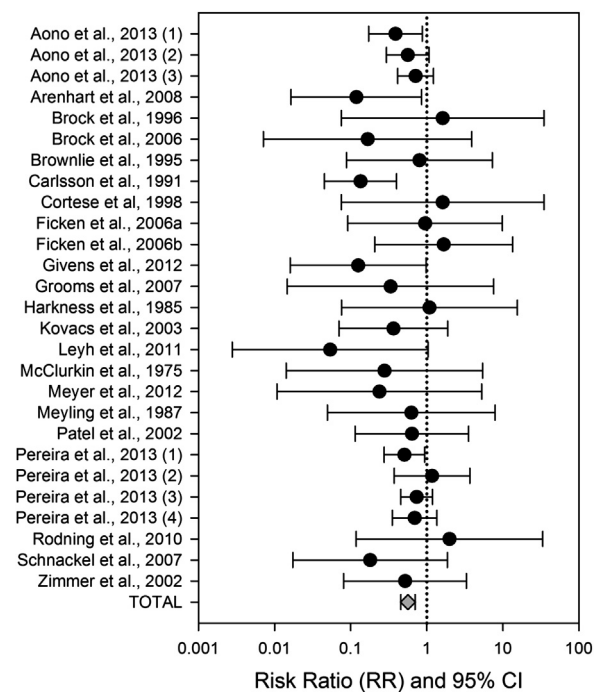
Table 2
Meta-analysis results for the effect of bovine viral diarrhea virus vaccination on abortion rate showing the risk ratio, 95% confidence interval, and associated P value.

Factor	Risk ratio	Lower	Upper	P value
Overall	0.566	0.455	0.702	<0.001
Cattle only	0.600	0.482	0.747	<0.001
Field challenge	0.672	0.535	0.844	0.001
MLV vaccine	0.369	0.185	0.734	0.005
Inactivated vaccine	0.662	0.520	0.842	0.001
Heterologous challenge	Insufficient data			
Homologous challenge	0.287	0.125	0.659	0.003
Polyvalent vaccine	0.314	0.140	0.705	0.005
Monovalent vaccine	0.517	0.360	0.744	<0.001

Abbreviation: MLV, modified live.

Table 3
Meta-analysis results for the effect of bovine viral diarrhea virus vaccination on pregnancy risk showing the risk ratio, 95% confidence interval, and associated P value.

Factor	Risk ratio	Lower	Upper	P value
Overall	1.052	0.987	1.121	0.118
Cattle only	1.052	0.987	1.121	0.118
Field challenge	1.053	1.022	1.085	0.001
MLV vaccine	0.955	0.858	1.062	0.396
Inactivated vaccine	1.069	0.985	1.161	0.108
Heterologous challenge	Insufficient data			
Homologous challenge	1.023	0.878	1.193	0.771
Polyvalent vaccine	Insufficient data			
Monovalent vaccine	1.038	0.954	1.129	0.391

Abbreviation: MLV, modified live.

studies were available for inclusion in the analysis to calculate the RR for abortion in cows challenged with virus heterologous to the vaccinal genotype (Table 2). All other subanalyses demonstrated a significant (P < 0.05) protective effect of BVDV vaccination. The use of MLV vaccines (RR = 0.37; 95% CI, 0.19–0.73) was more effective in reducing the risk of abortion in vaccinates than the use of inactivated vaccines (RR = 0.66; 95% CI, 0.52–0.84).

In this meta-analysis, the overall effect of BVDV vaccination on pregnancy risk (RR = 1.05; 95% CI, 0.99–1.12) was not statistically significant (P = 0.12) (Fig. 3). Pregnancy risk was significantly higher in BVDV vaccinates subjected to field challenge compared with nonvaccinates

(RR = 1.05; 95% CI, 1.02–1.09) (Table 3). Other subanalyses of the included studies did not detect significant differences (P < 0.05) in pregnancy risk based on the type of vaccine or viral challenge.

4. Discussion and conclusions

This meta-analysis provides a quantitative measure of the efficacy of BVDV vaccination to prevent subsequent reproductive disease, namely fetal infection, abortion, and decreased pregnancy risk. Meta-analysis of the results of published trials indicates that the risk of fetal infection in vaccinated cattle is less than one-seventh the risk in unvaccinated controls. Fetal infection resulting in the birth of PI animals represents the most critical step in the control of BVDV on farms. The prevalence of PI animals in US beef cow-calf operations is estimated to be approximately 0.1% to 0.55% [23–25]. Although the prevalence of PI animals is relatively low, their impact on BVDV pathogenesis and transmission is significant. As PI animals may be phenotypically normal, they are often undetected and allowed to remain in the herd, thus propagating the infection cycle. Consequently, vaccination represents a proven method to considerably decrease the number of PI animals that are born and can serve as viral reservoirs.

The percentage of unvaccinated herds seropositive to BVDV may be as high as 53% [26] indicating exposure to the virus through routes other than vaccination is relatively common. Nonvaccinal exposures may be because of contact with other cattle, which are transiently infected or PI. Field exposure of naive cattle to BVDV may result in subsequent protective immunity. Consequently, vaccination of seropositive animals may prove redundant although from an economic standpoint, it is rarely advisable to test for the presence of serum antibodies before vaccination. Additionally, BVDV exposure may occur through contact with infected wildlife, most notably the white-tailed deer (*Odocoileus virginianus*). Evidence of both transient and persistent infections has been reported in wild deer populations [27,28], and the potential for transmission between infected deer and susceptible cattle has been demonstrated experimentally [29]. Data compiled for this meta-analysis show that infection of naive dams during a susceptible period of gestation may result in fetal infection in greater than 95% of exposures. Given the high proportion
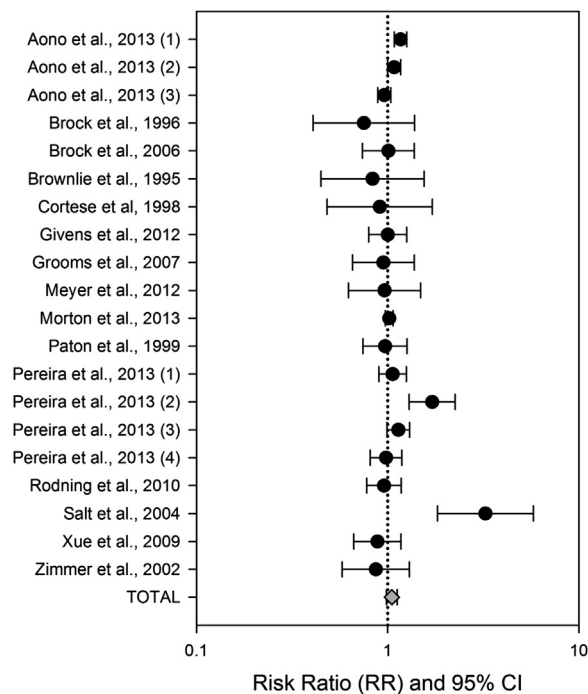

Fig. 3. Forest plot of the meta-analysis of the effect of bovine viral diarrhea virus vaccination on pregnancy risk. The study names included in the analysis are shown on the left ([1,4–6,11,18,19,26,28,30,32,34,38,39] of Appendix A) with their corresponding effect size and 95% confidence interval (CI). The overall effect is shown at the bottom, represented by the shaded diamond. The dotted vertical line represents a risk ratio (RR) of 1, indicating no significant difference between vaccinates and controls.

of exposure in unvaccinated cattle and the efficiency of fetal infection by the virus, the risk of PI cattle formation in naive cattle is likely underestimated.

Genetic analysis of BVDV isolates has led to the recognition of two distinct viral genotypes, BVDV1 and BVDV2; BVDV1 isolates are commonly classified as 1a or 1b sub-genotypes based on sequence homology. Although the genotypes cross-react serologically, antigenic differences exist between the two species [30]. These differences are important clinically because vaccinal protection is maximized when the vaccine strain matches the challenge strain. This was evident in our study by the improved vaccinal protection against fetal infection demonstrated during homologous challenge (RR = 0.16) compared with heterologous challenge (RR = 0.54) and by the decreased risk of abortion after homologous challenge only (RR = 0.29) compared with all studies (RR = 0.56). Evidently, in the field setting, the challenge strains cannot be known with certainty before exposure occurs. In North America, the BVDV1 genotype predominates in clinical samples, although BVDV2 still accounted for greater than 25% of samples in one study [31]. Polyvalent vaccines (RR = 0.10) in this study demonstrated more effective protection against fetal infection than monovalent vaccines (RR = 0.18). Polyvalent vaccines (RR = 0.31) were also more effective in the prevention of abortion after BVDV challenge than were monovalent vaccines (RR = 0.52). For both outcomes, the effect of polyvalent vaccination exceeded the overall effect seen across all studies. Consequently, a multivalent vaccine is recommended to provide maximal coverage against a variety of potential challenge strains.

The choice of vaccine formulation (MLV vs. inactivated) is also one of debate in regard to BVDV vaccination. Inactivated vaccines are generally considered to be safer than their MLV counterparts and for that reason have been used almost exclusively when vaccinating pregnant cattle. However, within the past 10 years several MLV vaccines have been labeled for use in pregnant cattle that have been vaccinated with the same vaccine or vaccine strain within the past 12 months according to label instructions. This study reveals that both vaccine types are effective at preventing abortion and fetal infection because of BVDV. For each outcome, the estimate of the RR was lower for MLV vaccines than inactivated vaccines but vaccination with an inactivated product still resulted in significant decreases in reproductive losses. For this reason, MLV vaccination may be preferable in nonpregnant cattle or when label conditions are met in gestating cows but in situations when this is not possible, inactivated vaccines still provide a notable level of protection against BVDV challenge.

The failure of this study to demonstrate an overall beneficial effect of vaccination on pregnancy risk is likely because of the study design of the individual studies. Because of the concern of fetal infection, intentional viral challenge in reproductive vaccine studies occurs after the cow or heifer has been diagnosed as pregnant, usually between 50 and 100 days of gestation. Interestingly, this meta-analysis demonstrated a statistically significant increase in pregnancy risk (RR = 1.05) in field trials, in which viral challenge was not limited to after conception had occurred. Otherwise stated, a 5% increase in pregnancy risk

was seen in BVDV vaccinates compared with non-vaccinates. The outcome of BVDV infection or vaccination is largely dependent on the timing of the exposure. Exposure of naive heifers to PI cohorts 50 days before breeding provided effective reproductive and fetal protection [32]. Likewise, calves arriving at the feedlot seropositive to BVDV have a decreased risk of subsequent treatment for bovine respiratory disease [33]. Thus, the lack of effect seen in this meta-analysis is likely because of the timing of viral challenge in the study design. These results confirm that BVDV vaccination is safe and does not negatively affect conception when performed appropriately.

Vaccination is one tool that can be used in the control of BVDV infection and disease. The basic tenets of infectious disease control dictate that pathogen reservoirs must be eliminated and transmission of the pathogen between infected and naive animals is minimized. Identification and elimination of PI animals is central to BVDV control as they serve as the major source for viral transmission in cattle herds. After removal of PI animals, herd immunity can be enhanced through the implementation of effective vaccination protocols and biosecurity measures (as reviewed in [18]). Biosecurity programs must focus on the introduction of purchased PI cattle or pregnant dams carrying a PI fetus. All such animals should be quarantined and tested before introduction to the herd. The offspring of pregnant purchased cattle must also be tested to ensure the animals are not PI. Exposure of cattle, especially pregnant cattle, to other animals that serve as potential reservoirs of BVDV (e.g., at livestock shows, through fence-line contact, and wildlife contact) must be limited as much as possible. Alternatively, eradication efforts in several regions or countries have proven successful at eliminating or significantly reducing the effect of BVDV infection [34–37] and should be considered where circumstances allow. Virus eradication provides the most definitive method to prevent BVDV infection and disease.

In conclusion, abortion in BVDV vaccinates is decreased by nearly 45% compared with unvaccinated controls and fetal infection is decreased by almost 85%. Additionally, pregnancy risk is increased by approximately 5% in field trials of BVDV vaccinates. Although polyvalent or MLV vaccines were more efficient in reducing abortion and fetal infection than monovalent or inactivated vaccines, respectively, all vaccine types provided significant protection. The decision to vaccinate is more important than the type of vaccine to be used when a decrease in BVDV-associated reproductive disease is desired. Vaccination, in combination with a sound biosecurity program, will greatly limit the negative reproductive impact of BVDV infection.

Competing Interests

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.theriogenology.2014.09.028.

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Appendix A
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