PEER REVIEWED

The Repeat Breeder Cow

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Abstract

Cows that fail to become pregnant after 3 inseminations may be termed repeat breeders (RBs). This paper reviews the incidence, economics, etiology and management of the RB cow. The incidence of RB in U.S. dairy herds is approximately 20% and depends on herd conception rate. Factors resulting in repeat breeding are discussed. Repeat breeders experience increased failure of fertilization due to tubal pathology and suboptimal breeding management. Increased embryonic mortality is evident in RBs before maternal recognition of pregnancy. Uterine environment and uterine asynchrony may play important roles in reducing fertility in RBs. Non-specific uterine infections are not major causes of RB but specific viral and bacterial agents known to cause early embryonic death can play roles. Clinical management of RBs should begin with record analysis and thorough reproductive examination. When no specific pathology is detected, prognosis for fertility is guarded but use of GnRH at time of insemination, synchronization of ovulation or uterine lavage may be attempted. In valuable animals, embryo transfer or oocyte aspiration with IVF and IVC has resulted in genetic recovery.

Introduction

Because reproductive efficiency is critical in dairy herd management, cows that fail to become pregnant are a source of concern to farmers. Veterinary service may be sought for these problem animals. While many problem cows have obvious reproductive pathology, Roberts[89] defines the repeat breeder (RB) as a cow that displays normal estrous cycles, has no clinically evident reproductive disease yet fails to become pregnant after 2 or 3 breedings. This paper will review the incidence, economics, etiology and clinical management of RB cows. The scope of this review is directed primarily towards pathophysiology. However, management factors such as heat detection, nutrition, feedbunk management, and cow comfort are of great importance in determining reproductive efficiency and all attempts to decrease the herd incidence of RBs should begin by examining herd management.

Literature regarding RBs is often conflicting. In addition to biological variation, there are several reasons for apparent inconsistencies. Not all authors agree on the definition of a RB. Some investigators reserve the term for cows not pregnant after four services[32,29] while others[4,99] refer to any cow that fails to become pregnant after 2 or 3 breedings. Studies investigating infertile heifers may be less likely to encounter acquired pathology than studies involving multiparous cows. Studies may be based on small numbers of animals, decreasing statistical power. Finally, the etiology of the 'repeat breeder syndrome' is probably multifold, including managerial factors, so RBs from varied management systems may have different characteristics.

Incidence and Economic Impact

The incidence of RB cows has been reported as 10 to 18 percent[97] but herd specific incidence may vary based on conception rate. The relationship between the percentage of cows not pregnant after 3 inseminations and conception rate for a large Dairy Herd Improvement database is shown in Figure 1. Approximately 20 percent of cows are not pregnant after 3 inseminations, and the percentage for high producing Holstein herds is greater.[28] Thus RBs are a significant problem on U.S. dairy farms.

The economic impact of RBs includes decreased milk production (since the less productive later lactation is lengthened), fewer calves for sale, increased veterinary services, extra semen costs, as well as culling and replacement costs.[68] Using an epidemiological model based on a survey of Michigan dairies, Lafi et al.[68] calculated the direct cost of each RB as $168, while cost per 1% incidence rate in the average 86 cow dairy farm

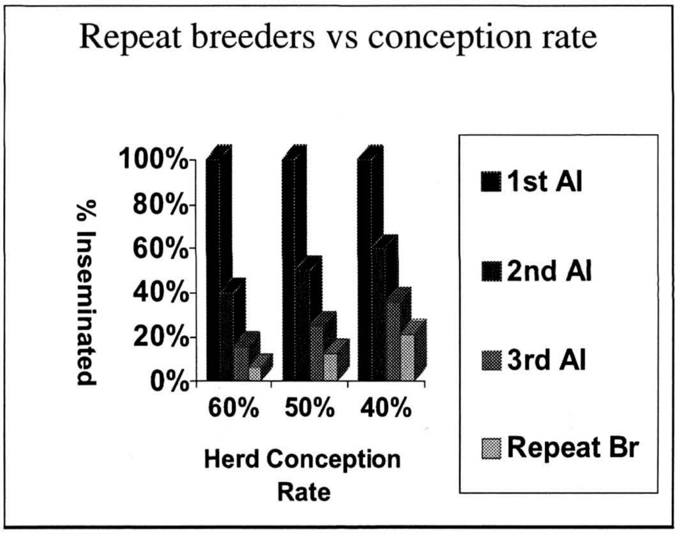

Figure 1. The percent of cows presented for artificial insemination is dependent on conception rate. A herd with a 60% conception rate can expect 6.4% repeat breeders while a herd with a 40% conception rate can expect 21.6% repeat breeders.

was $144. This study was based on herds with a rolling herd average of 14,400 pounds per cow. Since 79% of net cost of RB was due to decreased milk production and 23% was due to culling in this study, economic loss in higher producing herds may be increased.

Reproductive failure and mastitis are the most frequent reasons for involuntary culling of dairy cows.[71] Using a computer generated annuity model for culling decisions, Lehenbauer[71] showed that reproductive failure in two cows of similar parity and milk production resulted in a $148 difference in annuity value. Since RBs usually have increased days open they are at increased risk of culling. Herds using recombinant bovine somatotropin lactation may decrease losses from RBs since cows treated with somatotropin exhibit increased lactation persistency and thus may remain profitable for a longer period.

Etiology

The etiology of RBs is complex but may be divided into factors resulting in failure of fertilization or factors causing embryonic death.

Failure of fertilization

The incidence of failure of fertilization is 3.4% in first service heifers, 15 to 17% in normal cows and 29 to 40.8% in RB heifers and cows. These figures are based on studies in which breeding was followed by slaughter and examination of the reproductive tract.[9] A more recent review of fertilization failure suggests the incidence in RBs may be as high as 50%.[58] Graden et al.[41] examined 104 ova from 150 RB cows and heifers and found a fertilization rate of 55%. After inseminating these RBs, failure of fertilization was attributed to ovulation failure in 8.7% of the animals, abnormal ova in 3.3%, endometritis in 3.3%, ovarian adhesions in 2% and uterine tube obstruction in 6.7%. No explanation could be found for fertilization failure in 24.7%.

The importance of uterine tubal pathology was investigated by Kessy and Noakes[63] who examined 2000 bovine reproductive tracts from freshly slaughtered animals. Ovarobursal adhesions were identified in 6.85% of the tracts with an overall prevalence of tubal lesions of 9%. In a more recent review[34] the percentage of tubal disease in cows at slaughter was 6 to 15%, increasing to 36 to 89% in RB or infertile cows. Fertilization failure due to tubal pathology may be a significant cause of RB cows.

Delayed ovulation, failure of ovulation to occur by 36 hours after the onset of estrus,[16] results in failure of fertilization if inseminated sperm are no longer fertile by the time of ovulation. Several studies[29,55,89] have indicated that delayed ovulation is uncommon in RB cows. Hernandez-Ceron et al.[55] found the incidence of delayed ovulation similar in 134 first service and 108 RB Holstein heifers. Furthermore, conception rate for the insemination studied did not differ between the 7.9% of animals with delayed ovulation and heifers with normally timed ovulation. Delayed ovulation is unlikely to be an important factor in RBs.

Management practices can also result in failure of fertilization. Infertile semen, improper artificial insemination technique or poor semen storage can cause fertilization failure.[13] If such problems are common in a herd, overall herd fertility will likely suffer. Insemination of cows during diestrus does not result in fertilization and studies monitoring milk progesterone levels indicate that 20% of cows inseminated are not in estrus.[22,56] When cows fail to get pregnant within a reasonable time after calving, farmers may be more likely to breed on secondary signs of estrus. Frustration with RBs may lead to inappropriately timed and unsuccessful inseminations.

Embryonic mortality

Embryonic death after maternal recognition of pregnancy at day 15 to 16 results in prolonged interestrous intervals.[89] Hawk et al.[52] estimated embryonic mortality in RBs as 42% before day 16 and 51.7% between days 16 to 34. However, studies by Ayalon[10,11] indicated embryonic losses in RBs were significantly greater than in normal cows by day 13 and that by day 7 RBs had approximately half the normal embryos of normal cows. Repeat breeders experiencing embryonic loss at this early stage have normal interestrous intervals.[89]

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With the advent of bovine embryo transfer techniques, investigators researched the role of RB cows and heifers as embryo donors or recipients. Employing reciprocal embryo transfers, Gustafsson and Larrson[43] reported no difference in embryonic death between RB and virgin heifers as either donors or recipients. In a later study, Gustafsson[44] reported more normal day 7 embryos collected from virgin heifers than collected from RB heifers. Gustafsson concluded that retarded embryonic development might be a common factor in RBs. The same laboratory transferred 24 pairs of bisected day 7 embryos to virgin or RB recipients finding normal development in some virgin recipients but no normal embryos in RBs.[2] In contrast, when Tanabe et al.[101] transferred 51 normal day 7 embryos to normal cow or RB cow recipients there was no significant difference in pregnancy rates.

Ayalon[9] found fertility between normal and RB cows diverged by day 6-7 and suggested the transition from morula to blastocyst stage occurring at this time was a critical period for embryonic survival. Almeida[5] supported this theory in studies involving 768 Israeli Friesian cows and heifers. Similar numbers of normal embryos were flushed from normal and RB animals at day 6. However, when virgin heifers were used as embryo recipients, pregnancy rates were higher than when RB cows were recipients, regardless of the type of embryo donor. Almeida concluded that the uterine environment into which the day 6 embryos were transferred was more important than the source of the embryos.

It appears that early embryonic death is a major factor contributing to repeat breeding. Studies investigating embryonic loss in cows have considered genetic factors, immune reactions, aged ova, incompetent ova, hormonal effects and changes in the uterine environment.

Genetics factors include inbreeding, heritability of fertility and chromosomal abnormalities. Inbreeding results in decreased embryo survival,[21,25,74] but RB cows are not more highly inbred than herd cohorts on most farms. Inskeep et al.[59] estimated heritability of fertility as 8.5% in groups of Holstein paternal half sisters. Casida[21] reported that daughters of dams who conceived at first service had higher first service conception rates themselves. However, these animals also had higher rates of embryonic loss than daughters of dams who failed to conceive on first service. A heritable component of cystic ovarian degeneration has been suggested[89] and some farmers may consider cows with cystic ovaries RBs. King[65] reviewed the influence of chromosomal abnormalities on pregnancy failure, reporting an average of 10.4% abnormal embryos. The majority of anomalies were abnormal ploidy found in embryos day 7 or less. Specific chromosomal abnormalities such as 1/29 Robertsonian translocation[45] and deficiency of uridine-5'-monophosphate synthase (DUMPS)[94] result in decreased fertility. In the 1/29 translocation, carrier animals have normal fertilization rates but some embryos have chromosomal imbalance[93] and do not undergo placentation.[27] Mating of cattle heterozygous for DUMPS may result in homozygous recessive embryos not surviving past day 40 of gestation.[111] In 133 RB beef cows that Maurer and Echternkamp[75] examined for chromosomal anomalies, 19 (14.3%) had gross chromosomal abnormalities. Ten of these animals had 1/29 translocations and nine had sex chromosome aberrations. Genetic anomalies represent a small but significant factor in bovine repeat breeding.

Antisperm antibodies may be an important factor in infertility in humans.[67,95] Several studies[14,15,108] found an association between high antisperm antibody titers and infertility in RBs as compared to normal cows. However, Farahani et al.[36] found agglutination and immunoflourescent antisperm antibodies in serum of virgin heifers as well as normal and RB cows. In this study there was no relationship between antisperm antibodies in serum or cervical mucus and fertility status. Since antisperm antibodies may be found in fertile women, and only contribute to some types of infertility,[33] it is possible that the same is true for cattle.

Aged ova retain the ability to be fertilized longer than the ability to develop into viable embryos[12] and there is increased embryonic loss when insemination occurs more than 6 hours after ovulation. Watson et al.[105] found that insemination 24 hours or more after estrous detection resulted in a marked reduction in conception rate. When estrous detection intensity and accuracy are poor, insemination may occur after the optimal period for oocyte competency. Fertilization of aged ova results in polyspermy and embryonic mortality in swine.[47]

Tanaka et al.[102] studied the developmental competency of oocytes taken from RB ovaries immediately after slaughter. The number of oocytes recovered and development to blastocyst stage after *in vitro* maturation, fertilization and culture were normal. After freezing, thawing and transfer the achieved pregnancy rate was also normal. The authors concluded that, in this group of 8 RB cows, oocyte competency was normal.

The relationship of circulating progesterone to the outcome of insemination has been studied for both the luteal phase preceding insemination and the post-insemination luteal phase. Diskin and Sreenan[30] found the literature inconsistent regarding the effect of progesterone levels preceding service on conception rate. While several studies[26,38,90] correlated higher progesterone levels in the preceding cycle with fertile breeding, others found a negative correlation[54] or no significant difference.[18] The relationship between conception and postbreeding progesterone levels is less ambiguous. Most evidence suggests an increased peripheral progesterone level by day 13[38,57] after fertile, compared to non-

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fertile, breedings. Recent studies[19,70] found higher peripheral concentrations of progesterone by day 4.5 after breeding in pregnant versus non-pregnant cows. Larson et al.[70] found that, compared to pregnant cows, the mean time to initiate luteal function was delayed in non-pregnant cows having prolonged interestrous intervals and high progesterone at day 21 postbreeding. Larson et al. suggested that suboptimal progesterone concentrations compromise early embryonic development, allowing for maternal recognition of pregnancy, but not pregnancy maintenance.

The local effect of progesterone on the uterine environment of RBs was studied by measuring uterine progesterone receptors.[4,98] Almeida et al. found higher concentrations of cytosolic progesterone receptors in RBs than in normal cows on day 6 post-insemination.[4] In this study, cows bearing abnormal embryos at day 6 had higher levels of cytosolic progesterone receptors than cows carrying normal embryos, irrespective of whether the cow had a history of repeat breeding. Almeida et al. suggested that a local hormonal imbalance can exist in RBs. Stanchev et al.[98] determined concentrations of endometrial nuclear progesterone receptors in virgin and RB heifers at day 15, eight days after receiving day 7 demi-embryos. Nuclear progesterone receptors were higher in uteri carrying normal elongated embryos compared to those with abnormal or retarded embryos. In heifers with elongated embryos, nuclear progesterone receptors were lower in RB recipients than in virgin recipients. Although the results of this latter study may seem to contradict the findings of Almeida et al., Stanchev et al. assayed receptors close to the time of maternal recognition of pregnancy, 9 days later than Almeida et al. Both studies suggest that uterine asynchrony, influenced by progesterone, plays a role in embryonic loss in RBs.

Other studies support the role of uterine asynchrony. Ohtani and Okuda[83] evaluated endometrial histology from 5 RBs, 5 normal cows and 5 normal heifers on days 1 and 8 postestrus. On day 1, RB cows had evidence of secretory activity not seen in normal animals. On day 8 RBs still showed a secretory pattern, now seen in normal animals as well. Almeida et al.[6] found decreased numbers of ciliated cells in the endometrium of RBs on days 6 and 7 post-breeding compared to normal cows.

Synchrony is crucial for successful embryo transfer in cattle. Albihn et al.[3] showed that embryos transferred to synchronous recipients developed normally while asynchronous transfers resulted in embryonic degeneration. Rowson et al.[91] reported a decline in pregnancy rates when recipients were greater than one day out of synchrony with embryo donors. If RBs have uterine asynchrony, decreased embryonic development and increased embryonic mortality are likely.[85] Almeida[5] hypothesized that uterine asynchrony may result in embryonic death at the morula-blastocyst transition in about 30% of embryos which cannot develop in the absence of tight uterine-embryo synchrony. Almeida termed these "environment sensitive" embryos to differentiate them from the 50% of "environment resistant" embryos which are not affected by changes in the pre-morula environment and develop normally into blastocysts.

Uterine infection

Farmers often blame insemination failure on infectious disease, requesting veterinarians to address uterine infections when managing RB cows. The role of endometritis in bovine infertility is controversial[76] and confounded by diverse methods of diagnosis.[40,89] Several studies[49,50,84] have found uterine infections of minor importance in RB cows. De Kruif[29] examined 400 RBs and found abnormal vaginal discharges in 16%. Endometrial biopsies taken from 28 of those cows yielded bacteria in only four cases, three of which were *Arcanobacterium* (formerly *Actinomyces* and *Corynebacterium*) *pyogenes*. Hartigan[50] found no increase in uterine infections in RBs compared to normal cows. In a study comparing bacterial isolates from cervicovaginal mucus of 72 normal fertile and 70 RB cows, Panangala et al.[84] found no significant difference in recovery frequency of predominant isolates. However, in this same study, repeat breeder cows did have higher total bacterial counts for *Arcanobacterium* and *Enterobacteriaceae*. It may be that, as in the mare, clearance of non-specific bacteria is impaired in some cows, resulting in higher numbers of resident or opportunistic bacteria.[53]

Infection with specific viral or bacterial agents can result in failure of fertilization or early embryonic death. When BVD virus was infused into the uterus there was decreased embryo survival,[7,107] but when the route of inoculation was oral or nasal, conception was not affected.[42] Intrauterine or intravenous infusion of IBR virus near estrus caused luteal necrosis and infertility[77,103] while recrudescence of latent IBR virus resulted in early embryonic death.[78] Venereal infection with *Tritrichomonas foetus*[89] or *Campylobacter fetus ssp. venerealis*[89] results in early embryonic death and return to service. Endemic infection with *Leptospira interrogans serovar hardjo* has been reported to cause early embryonic death as well as abortion.[35] Although *Haemophilus somnus* may be part of normal genital flora, it has also been associated with abortion and infertility.[62] When *Haemophilus somnus* was infused into the uterus it induced early embryonic degeneration and decreased embryonic survival despite minimal uterine pathology.[62] *Ureaplasma diversum*[31] and *Mycoplasma bovigenitalium*[66] have been implicated as causing early embryonic death although nonpathogenic, as well as pathogenic strains, may be cultured from the bovine reproductive tract.[79]

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Environmental and managerial factors

Most cows are intensively managed animals in the dairy industries of North America and Europe. Under intensive management the interplay of dietary, environmental and reproductive management is complex. Failure or suboptimal performance in any one managerial area is likely to impact all other aspects negatively. On most modern dairy farms management decisions and actions far outweigh infectious pathology in influencing reproductive efficiency.

The role of estrous detection accuracy in insemination success has already been noted. Dairy operations with slippery floors, uncomfortable stalls, or long periods spent in the holding area experience difficulties with intensity and accuracy of estrous detection due to tired cows or high incidence of lameness. The result may be more cows classified as RBs by the farmer.

Management of heat stress can strongly influence reproductive success during warm weather. Studies conducted in Florida[87] and Saudi Arabia[92] showed abnormal early embryonic development and decreased embryonic viability in animals subjected to elevated ambient temperatures. Since fertilization failure[80] as well as abnormal embryo development by day 7 have been reported,[88] cows bred during periods of summer heat may return to estrus normally and be classified as RBs. Heat stress reduction using shades, fans and sprinklers has been recommended[48] to improve pregnancy rates during warmer seasons.

Nutritional factors affecting reproduction are complex, interactive and often poorly understood. Lafi and Kaneene[69] cited poorly balanced dry cow rations as risk factors for the RB syndrome. Imbalanced dry cow rations contribute to the complex of hypocalcemia, dystocia and retained placenta, resulting in more RBs. Negative energy balance affects the days to first postpartum ovulation,[20] is associated with cystic ovarian disease in high producing dairy cows[96] and may decrease fertility at the time of breeding.[106] Britt[17] hypothesized that negative energy balance may also influence preantral follicles, decreasing fertility 60 to 100 days later when these follicles are selected for ovulation. High total dietary protein and high rumen degradable protein have been associated with elevated blood or milk urea nitrogen levels and depressed fertility.[37] Larson et al.[70] found cows with high milk urea nitrogen levels had lower fertility and were more likely to have low progesterone levels 21 days after insemination. They suggested that high milk urea nitrogen concentrations at breeding result in fertilization failure or embryonic mortality prior to maternal recognition of pregnancy. Imbalances in macrominerals, microminerals and vitamins can affect fertility.[106]

Dietary toxins may result in reduced fertility.[60] With the exception of chronic locoweed ingestion, most plant related toxicities cause fetal malformations or abortions, rather than infertility or early embryonic death that would result in repeat breeding. Nitrates and mycotoxins have been implicated in reduced reproductive efficiency but in-depth studies on the affects on early pregnancy are lacking.

With intensive management of dairy farms and expanding herd size, influences of managerial and environmental factors on reproduction are compounded. Severe environmental, management or nutritional conditions have a herdwide influence but reproductive or production changes affecting fewer individual animals may occur when marginal problems exist. Ruminal acidosis and lameness decrease estrous expression and cause sufficient stress to influence fertility.[46] When multiple cows are inseminated at one visit, the inseminating technician must avoid prolonged exposure of semen straws to adverse conditions or semen used in the last cows inseminated may have decreased fertility.

Environmental pollution has been shown to affect reproduction in wildlife through endocrine disrupters.[24] The role pollution plays in bovine fertility is unclear although there is a report of increased repeat breeding in water buffalo kept in polluted areas.[1]

Clinical Management of Repeat Breeders

The initial step in confronting a RB problem should be to determine whether there is a herd or an individual cow problem. Examination and analysis of farm records such as on-farm computer programs, Dairy Herd Improvement records or breeding charts should reveal the scope and incidence of the problem. If a herd problem is evident, review of vaccination, nutrition, fresh cow and estrous detection protocols may indicate opportunities to increase breeding efficiency. It is important to note the incidence of postpartum reproductive problems as well as abortion rates in order to focus on risk factors. Analysis of records by cow groupings or season may point to management factors that could be improved.

When record analysis shows the number of RBs to be consistent with reasonable conception rates and days open distributions, individual cow problems, rather than herd problems are likely. The veterinarian and herd manager should discuss the relative value of individual RB cows and whether further diagnostic or treatment efforts are warranted. Treating late lactation cows with excessive body condition is seldom economically sound unless the animal's genetics are exceptional.

Repeat breeders should be identified and examined separately from routine herd reproductive visits so that adequate time can be spent to perform a thorough examination. Epidural anesthesia may facilitate detailed transrectal and vaginal examinations, especially in cows with excessive body condition. If no abnormalities are noted, uterine cytology may aid in detecting

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endometritis.[40] Transrectal ultrasonography helps delineate questionable ovarian structures and small pockets of uterine fluid. In animals with normal interestrous intervals, uterine tube patency tests by starch granule injection may rule out uterine tube obstructions.[64]

Treatment

While cystic ovarian disease, pneumovagina, endometritis, or other abnormalities found on examination should be specifically addressed, many RBs exhibit no evident pathology. Attempts to treat these animals have focused on hormonal or local therapies. When evaluating therapies it should be kept in mind that de Kruif[29] found that 60% of 191 clinically normal cows presented for a fourth insemination became pregnant after that insemination. Thus chance may have a role in the cause and cure of RBs and effectiveness or ineffectiveness of any particular therapy may be masked by chance.

Gonadotrophin-releasing hormone (GNRH) has been administered to cows at the time of insemination in an effort to increase conception rates. Conflicting effects on pregnancy rate have been reported[99,100] but a meta-analysis[81] of 40 trials indicated a 22.5% increased risk of pregnancy in RBs treated with GNRH at insemination. Considering the costs of increased days open, GNRH administration should be advised at third service inseminations.

Exogenous progesterone has been administered to RB cows in an attempt to improve pregnancy rates. When Diskin and Sreenan[30] reviewed studies of progesterone treatment of RBs, they found a significant increase in fertility when studies were combined but no significant effects in any individual study. The data reported for dairy cows of normal fertility did not show any advantage to progesterone administration. After determining that human chorionic gonadotrophin (HCG) administration produced more sustained increases in progesterone than injectable progesterone or a progesterone releasing intravaginal device (PRID), Walton et al.[104] found no effect on pregnancy rates when HCG was administered to RBs 5 days post-insemination. Currently the effects of exogenous progesterone on pregnancy rates of RBs are too ambiguous to recommend routine supplementation.

Use of GNRH and PGF2 alpha in the Ovsynch protocol[86] may be useful in RBs exhibiting poor estrous expression or "missed heats". This protocol calls for injection of GNRH on Day 0, PGF2 alpha on Day 7, GNRH administration on Day 9 and insemination 16 to 20 hours later, thus eliminating estrous detection accuracy or intensity as variables in breeding management.

Narayana and Krishnamurthy[82] evaluated bromocriptine, a dopamine agonist, in one hundred RB cows and found that injection of 1 mg at the time of insemination significantly increased pregnancy rates in both the treated cycle and the subsequent cycle. Further investigations of bromocriptine's effects are warranted.

Local therapy of RBs is by intrauterine infusion or uterine lavage. Various antibiotics, antiseptics and caustics have been infused into the bovine uterus in attempts to improve fertility. The results have been equivocal.[76,110] In light of milk antimicrobial residue concerns, intrauterine antibiotic infusions in RBs without evidence of uterine infection should not be routinely recommended. Uterine lavage is an accepted therapy for treating infectious[8] and noninfectious[61] infertility in the mare. Uterine lavage, as practiced in non-surgical embryo transfer, was used to treat twenty RB cows[23] in conjunction with PGF2 alpha. Ten cows conceived within 30 days of treatment, 2 between 30 and 60 days and one conceived more than 60 days post treatment. In another report[73] 14 of 34 RB cows that were nonsurgically flushed for embryo transfer subsequently became pregnant. Although there are no controlled studies to support the use of uterine lavage in RBs, some have advocated uterine lavage in RBs when no clinical abnormalities can be found.[39]

Genetic Recovery

When valuable RBs fail to become pregnant, it may be possible to recover the animal's genetics prior to culling. Multiple ovulation embryo transfer can be used successfully in many RB cows to produce offspring.[73] When superovulation and embryo transfer fail, ultrasound guided transvaginal oocyte aspiration followed by *in vitro* oocyte maturation, fertilization, embryo culture and embryo transfer have been successfully employed by commercial embryo transfer organizations.[51,72] If valuable cows must be destroyed due to nonreproductive related illness it may be possible to harvest the ovaries upon death and produce pregnancies from aspirated oocytes.[109]

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Baytril® 100
(enrofloxacin)

100 mg/mL Antimicrobial Injectable Solution

For Subcutaneous Use In Cattle Only

Not For Use In Cattle Intended For Dairy Production Or In Calves To Be Processed For Veal

BRIEF SUMMARY: Before using Baytril® 100 (enrofloxacin) injectable solution, please consult the product insert, a summary of which follows.

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian. Federal (U.S.A.) law prohibits the extra-label use of this drug in food producing animals.

INDICATIONS:
Baytril® 100 (enrofloxacin) injectable solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida* and *Haemophilus somnus*.

DOSAGE ADMINISTRATION:
Single-Dose Therapy: Administer once, a subcutaneous dose of 7.5 - 12.5 mg/kg of body weight (3.4 - 5.7 mL/100 lb).
Multiple-Day Therapy: Administer daily, a subcutaneous dose of 2.5 - 5.0 mg/kg of body weight (1.1 - 2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on days 4 and 5 to animals which have shown clinical improvement but not total recovery.

HUMAN WARNINGS: For use in animals only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. To report adverse reactions or to obtain a copy of the Material Safety Data Sheet, call 1-800-633-8405.

WARNING: Animals intended for human consumption must not be slaughtered within 28 days from the last treatment.

Do not use in cattle intended for dairy production.

A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS: The effects of enrofloxacin on bovine reproductive performance, pregnancy, and lactation have not been adequately determined.
Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Baytril® 100 contains different excipients than other Baytril® products. The safety and efficacy of this formulation in species other than cattle have not been determined.
Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures.
Quinolone-class drugs have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. No articular cartilage lesions were observed in the stifle joints of 23-day-old calves at 2 days and 9 days following treatment with enrofloxacin at doses up to 25 mg/kg for 15 consecutive days.

STORAGE CONDITIONS:
Protect from direct sunlight. Do not freeze or store at or above 40° C (104° F).

HOW SUPPLIED:
Baytril® 100 (enrofloxacin) Antimicrobial Injectable Solution:
Code: 0236 100 mg/mL 100 mL Bottle

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Baytril® 100
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