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Emerging therapeutic strategies for precision reproductive management of repeat breeder cattle

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ABSTRACT: Repeat breeding in cattle is failure to establish pregnancy after three or more services or artificial inseminations despite cycling and no abnormalities. This causes losses from reduced conception, repeated insemination, prolonged calving interval, maintenance costs, and calf production. This review evaluates mechanisms and management, emphasizing fertilization failure, embryonic death, and uterine function. Evidence shows that it is multifactorial, involving poor oocyte competence, mistimed insemination, endocrine dysfunction, heat stress, sperm transport failure, subclinical endometritis, impaired embryo–maternal communication, endometrial gene expression, and inadequate receptivity. Management requires precise strategies tailored to the pathway.

Keywords:
repeat breeder syndrome, fertilization failure, early embryonic death, endometrial receptivity, subclinical endometritis

■ INTRODUCTION

Repeat breeder syndrome is a reproductive disorder in cattle because affected cows appear normal, return to estrus regularly, and lack tract abnormalities. It is diagnosed when a cow fails to conceive after at least three consecutive services or artificial inseminations while maintaining normal estrous cyclicity (Carbonari *et al.* 2024). This can delay diagnosis because conventional examination may miss ovarian, uterine, endocrine, immunological, or management defects. Repeated inseminations increase semen, labor, veterinary, and treatment costs, while delayed conception extends the calving interval, reduces calves produced during the cow's life (Nowicki 2021), and may increase culling. In Indonesian smallholder dairy farms, previous reproductive disorders, low milk yield, and small herd size increase the risk (Pongkapadang *et al.* 2025). The etiology is multifactorial, with fertilization failure or early embryonic death.

■ CAUSES AND PATHOPHYSIOLOGICAL MECHANISMS

Fertilization failure: Fertilization failure causes repeat breeding. Conception requires estrus, ovulation, and fertilization; disruptions cause return. Oocyte quality from energy balance, stress, parity, and endocrine imbalances alters competence (Pérez-Marín & Quintela 2023). Postpartum ketosis, mastitis, and metritis increase risk (Villar *et al.* 2025). Artificial insemination errors and tropical heat stress reduce fertilization and embryo viability; housing, shade, and ventilation are essential.

Early embryonic death and embryo–maternal communication failure: Embryonic death causes repeat-breeder syndrome. Fertilization occurs, but the embryo fails to survive or elongate. Cows return to estrus after luteolysis, making loss indistinguishable. By days 15–17 after ovulation, interferon-τ prevents luteolysis. Disturbances in interferon-τ signaling and subclinical endometritis may impair embryo–endometrium communication and survival (Kasimanickam & Kasimanickam 2020).

Subclinical endometritis and uterine immune dysfunction: Endometritis is a risk factor for repeat breeding, but not the sole cause; subclinical endometritis is actionable in repeat breeder cows. It increases the risk in primiparous and multiparous cows (Villar *et al.* 2025). Persistent inflammation may disrupt defense and conceptus tolerance. Altered pattern-recognition receptor expression may indicate activation in repeat breeder cows with subclinical endometritis (Ağaoğlu *et al.* 2020).

■ EMERGING DIAGNOSTIC AND MANAGEMENT-BASED APPROACHES

Herd-level risk stratification: Repeat breeding is a herd-level problem, not a cow-level disorder. The assessment included parity, postpartum days, condition score, milk yield, and

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diseases. Evidence has linked condition loss, metabolic disorders, and diseases to repeated breeding (Villar *et al.* 2025). In smallholders, herd size, veterinary access, insemination timing, nutrition, and record keeping influence breeding. Prevention requires monitoring rather than repeated insemination without diagnosis.

Uterine and endometrial assessment: Cows that have failed three inseminations require examination. Palpation/ultrasonography detects pregnancy and fluid but may miss endometritis. Endometrial cytology detects polymorphonuclear neutrophils, indicating inflammation; bacteriological/molecular tests identify pathogens, requiring interpretation. Evaluation classifies fertilization failure, inflammation, luteal/ovulatory dysfunction, embryonic loss, heat-stress-associated infertility, or AI-related failure.

■ THERAPEUTIC PERSPECTIVES

Hormonal synchronization and uterine immune modulation: Hormonal protocols improve estrus synchronization, ovulation, and insemination accuracy in repeat breeder cows. Presynch–Ovsynch may help with estrus detection issues, ovulatory dysfunction, or subclinical endometritis and alter Toll-like and Nod-like expression (Ağaoğlu *et al.* 2020). Effectiveness depends on the diagnosis, postpartum stage, body condition, and herd management.

Antimicrobial-sparing and immunotherapeutic approaches: Antibiotics are used to manage repeat breeding when bacterial endometritis is suspected. However, use may yield inconsistent outcomes in non-bacterial conditions with biofilm, dysbiosis, or inflammation, and stewardship requires diagnosis-based use. Hyperimmune serum improved pregnancy outcomes (Aghamiri *et al.* 2020), but evidence remains limited, requiring trials.

Modulation of uterine contractility: Impaired uterine contractility may contribute to repeat breeding by affecting sperm transport, uterine clearance, inflammatory resolution, and the estrus environment. Scopolamine butylbromide was evaluated to modulate uterine activity in repeat breeders. Administration at estrus increased conception compared to controls in a study (Rizzo *et al.* 2023). However, caution is warranted pending confirmation.

Embryo transfer as a targeted strategy: Embryo transfer for repeat breeder cows can bypass fertilization failure and embryo vulnerability. Morula or blastocyst transfer bypasses oocyte maturation, fertilization, and cleavage, improving pregnancy in cows with poor oocyte competence or early embryo failure (Nowicki 2021). It requires synchronized recipient, functional corpus luteum, and uterine health.

■ PRACTICAL FRAMEWORK FOR MANAGING REPEAT BREEDER COWS

Management confirms diagnosis: cows fail to conceive after three services, show estrous cycles, and lack anatomical abnormalities or pregnancy loss. Then identify pathway. If fertilization failure is suspected, audit estrus detection, insemination timing, semen quality, and inseminator skill. If ovarian dysfunction is suspected, use Presynch–Ovsynch. If embryonic death is suspected, evaluate uterine receptivity, luteal function, heat stress, and metabolic status. If subclinical endometritis is suspected, prioritize cytology and uterine therapy. Persistent failure warrants embryo transfer. Repeat breeding is multifactorial (Carbonari *et al.* 2024).

■ CONCLUSION

Repeat breeder syndrome is multifactorial, involving fertilization failure, embryonic loss, endometritis, embryo–maternal communication, endocrine imbalance, and AI mismanagement. Uterine receptivity is central; management emphasizes diagnosis, estrus/AI, Presynch–Ovsynch-based protocols, immunotherapy, and embryo transfer.

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