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A Review on Immunological Infertility in Dairy Cows

Kutelo Kussia Muchole*

Department of Veterinary Medicine, Wolaita Sodo University, Ethiopia.

***Corresponding Author(s): Kutelo Kussia Muchole**

Department of veterinary medicine, Wolaita sodo university, Ethiopia.

Email: Dr.Kutelo.Kussia@wsu.edu.et

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Abbreviations: AMH: Anti-Müllerian Hormone; AI: Artificial Insemination; BoLA: Bovine Leukocyte Antigen; CIDR: Controlled Internal Drug Release; CL: Corpus Luteum; DNA: Deoxyribonucleic Acid; ET: Embryo Transfer; ELISA: Enzyme-Linked Immunosorbent Assay; GnRH: Gonadotropin-Releasing Hormone; hcg: Human Chorionic Gonadotropin; IBT: Identification Immunobead test; IBT: Immunobead Test; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IVF: In vitro fertilizationis; mRNA: Messenger Ribonucleic Acid; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PCR: Polymerase Chain Reaction; RFM: Retension of fetal membrane.

Abstract

Immunological infertility in dairy cows is a significant reproductive disorder caused by the immune system's adverse response to gametes (sperm and ova), reproductive hormones, or associated tissues, leading to conception failure or early embryonic loss. This condition arises when the immune system misidentifies sperm or ova as foreign, triggering antibody production (e.g., anti-sperm antibodies) or inflammatory reactions that impair fertilization, embryo implantation, or luteal function. Key risk factors include uterine infections (e.g., endometritis), metabolic stress (e.g., negative energy balance), autoimmune reactions, and improper use of reproductive technologies like artificial insemination. Clinical signs include repeat breeding, abnormal estrous cycles, and suboptimal conception rates. Diagnosis involves uterine cytology, PCR, ELISA, and ultrasonography to detect immune-mediated damage. Treatment strategies focus on immunomodulation (e.g., NSAIDs, antioxidants), hormonal therapy (e.g., $PGF_2\alpha$, GnRH), and advanced reproductive techniques (e.g., IVF, embryo transfer). Preventive measures emphasize improved uterine health, nutritional support, and genetic selection for immune resilience. Immunological infertility poses substantial economic losses due to reduced milk yield, increased veterinary costs, and premature culling. Emerging research explores biomarkers, probiotics, and genomic tools to mitigate this condition, though challenges remain in understanding immune-pathway interactions and optimizing therapies. Addressing immunological infertility requires integrated management to enhance dairy cow fertility and farm profitability.

Introduction

Reproductive health is a cornerstone of livestock production, crucial for farm sustainability, profitability, and meeting the demand for animal products. However, reproductive disorders are common in dairy cows and can significantly reduce reproductive efficiency, offspring survival, and overall herd health [135].

Infertility is a leading reproductive problem in dairy cows. It is broadly defined as the inability to conceive or sustain pregnancy, while subfertility refers to delayed or reduced conception despite repeated breeding. Conception failure, early embryonic death, and repeat breeding contribute to lowered fertility and prolonged calving intervals (Brugo-Olmedo *et al*., 2001). Although infertility has diverse causes physiological, anatomical, nutritional, and managerial a large proportion remains unexplained and is increasingly attributed to immunoinfertility [13,39].

Immunoinfertility arises when the immune system misidentifies gametes or reproductive antigens as foreign and mounts an immune response. This may target hormones (LHRH, GnRH, PGF2α, oxytocin), sperm, seminal Plasma, oocytes, or Zona Pellucida proteins (PZP), resulting in blocked receptors, failure of fertilization, early embryonic loss, endometritis, delayed uterine involution, and repeat breeding (Delves *et al*., 2002) [39,120]. Such immune-mediated disruptions ultimately extend calving intervals and reduce conception rates, leading to higher veterinary costs, culling, and milk production losses.

Genetic variation in the Major Histocompatibility Complex (MHC) further influences reproductive immunology, as incompatibility between sires and dams may hinder fertilization and embryo implantation (Pasalic *et al*., 2023) [122]. In advanced reproductive technologies, such as In Vitro Fertilization (IVF), these immune barriers can limit success. Assisted reproductive technologies like Intracytoplasmic Sperm Injection (ICSI) can bypass these barriers by directly injecting sperm into eggs [3,39,69]. Nonetheless, practical application in cattle remains limited due to cost and technical demands.

Several risk factors predispose dairy cows to immunoinfertility, including uterine infections, metabolic stress, autoimmune disorders, and improper use of reproductive technologies. Endometritis, in particular, is a significant contributor, and growing antibiotic resistance complicates its management. Immunomodulators are increasingly considered as promising alternatives to antibiotics for improving uterine health and fertility outcomes (Rashid Dar *et al*., 2019; Kumaresan *et al*., 2024). Despite these advances, diagnosis and control of immunoinfertility remain challenging, and the condition is often underrecognized in field practice.

Overall, Immunological infertility leads to significant economic losses for dairy operations. It causes longer calving intervals, higher veterinary costs, lower milk production, and premature culling. This makes it a serious issue that affects herd fertility and farm profitability. Therefore, the objectives of this seminar paper are:

- To review immunological infertility in dairy cows, including reproductive immunology, causes, risk factors, clinical signs, pathogenesis, diagnosis, differential diagnosis, treatment, prevention, control strategies, and economic impact.
- To discuss recent advances, challenges, and knowledge gaps in understanding and managing immunological infertility in dairy cows.

Literature review

Reproductive immunology of dairy cows

Reproductive Immunology has evolved into an integrated concept of interactions between the endocrine, immune, nervous, and reproductive systems [100,125]. The immune system adapts to daily challenges and is a powerful tool for studying both normal fertility and infertility, functioning by making specific responses against foreign molecules through cells with specific receptors that discriminate between self and non-self [60]. All mammals possess a Major Histocompatibility gene Complex (MHC) coding for unique self-marking cell surface proteins. These glycoproteins recognize foreign antigens via two immune response arms: humoral immunity, involving immunoglobulin production by B lymphocytes, and cellular immunity, mediated by T lymphocytes, both characterized by high specificity [125].

Basic concepts of immunoreproduction

Reproductive immunology is a powerful tool for unlocking normal fertility problems and various forms of infertility or reproductive disorders [122,125. Because antigens appear on hypothalamic cells, pituitary cells, gonads, gametes, placenta, and fetus, the induction of a specific antibody could alter their function. Antibodies can be induced against gonadotropin-releasing factors, gonadotropins, steroidal hormones, and pregnancy-associated hormones, and can be used to quantitate, destroy, neutralize, or enhance specific reproductive events associated with normal fertility and infertility in the bovine [10]. A potential problem is the heterogeneity of immune responses by individuals in inbred and outbred populations along genetic control of antisperm antibodies [12]. The bovine immune response is also influenced by both exogenous factors, such as stress and nutrition, and endogenous factors, such as circulating concentrations of hormone.

Use of immunology to study normal fertility

Immunology is used to study normal fertility through the relationship between the blood-testis barrier and spermatogenesis, epididymal antigens and sperm maturation, seminal antigens and capacitation, immunosuppression, and antigens and antibodies in estrual and cystic follicles and pregnancy recognition [3]. The blood-testis barrier, formed by Sertoli cell tight junctions, masks sperm antigens from immunological surveillance [84]. Its breach exposes immunogenic sperm antigens, leading to autoimmune aspermatogenic orchitis [70].

Immunoinfertility can occur as autoimmunity or isoimmunity, with autoimmunity arising when antibodies are produced against spermatozoa [13]. Ova are less immunogenic than spermatozoa [27]. In the epididymis, sperm are hidden from the immune system, and secretory cells produce antigenic sperm-coating proteins involved in maturation and fertility [25,134]. Seminal antigens are complex, and capacitation involves removing coating antigens to expose intrinsic sperm antigens crucial for fertilization [106]. Monoclonal antibodies study these antigenic sites, and their blockage can prevent fertilization [41].

Immunosuppression in the female reproductive tract is facilitated by seminal plasma and cervical secretions suppressing immune responses [36,81]. Hormones and follicular fluid components regulate immune function, with follicular fluid exhibiting immunosuppressive activity. Ovarian antigens like Thy-1 and OX-2 influence follicular growth and ovulation, with inflammatory-like responses triggered by antigen exposure during estrus [118]. Follicular fluid IgG transports antibodies affecting fertilization and embryonic mortality [15]. Pregnancy relies on immunological balance, with the feto-placental unit avoiding maternal rejection [105]. Pregnancy-specific proteins, detected via immunoassays, aid early pregnancy detection and diagnose infertility causes [5,89].

Use of immunology to study infertility

Immunology is used to study infertility through isoimmunization of females to sperm, where the reproductive tract can generate an immune response to ejaculated sperm, though this is rare in cattle due to infrequent exposure and estrogen-mediated immunosuppression [13,55]. Experimentally, antibodies can cause infertility via agglutination, complement-mediated killing, and inhibition of sperm function and implantation [49]. Isoimmunization with adjuvant-induced sperm antibodies leads to high embryo mortality [8], and repeat breeder cows show elevated agglutinin titers against specific bull sperm [120].

Autoimmune aspermatogenic orchitis occurs when sperm-specific antigens exposed by blood-testis barrier breach trigger immune-mediated testicular damage and aspermatogenesis [109]. Anti-Sperm Antibodies (ASA) impact fertility concentration-dependently, with high levels causing infertility via sperm immobilization, impaired migration, acrosomal inactivation, and embryonic death [110]. Semen extenders containing egg yolk can induce antigenic responses, leading to antibodies that may affect fertility [111]. Freeze-drying semen alters protein structure antigenically, reducing fertility at low moisture levels [50,90]. Infectious genital diseases elicit mucosal IgA or systemic IgG responses, but systemic immunization may not protect the reproductive tract [6]. Uterine infections post-partum, often involving E. coli and Trueperella pyogenes, trigger inflammatory responses via LPS, disrupting follicular function and oocyte competence [72,115]. Immunoinhibitory substances in seminal plasma typically prevent anti-sperm immune responses under natural conditions [62].

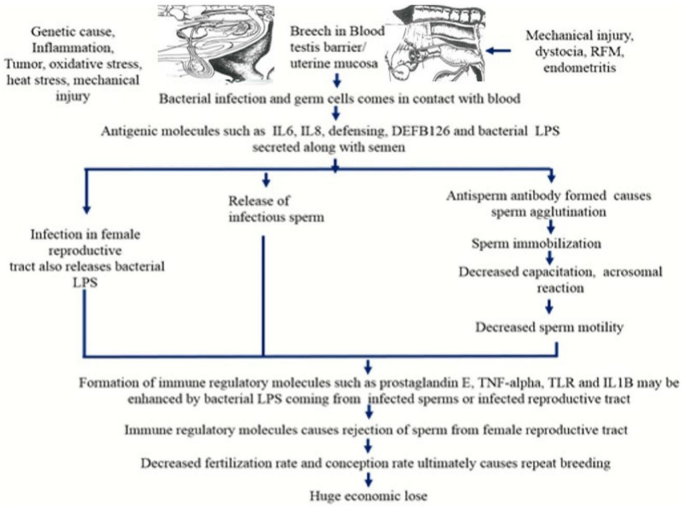

Figure 1: Antisperm antibody production by the immune system and its impact on sperm motility and fertility (RFM, Retension of fetal membrane; IL6, Interleukin 6; IL8, Interleukin 8; LPS, Lipopolysaccharide; TNF-alpha, Tumor necrotic factor-alpha; TLR, Toll like [14].

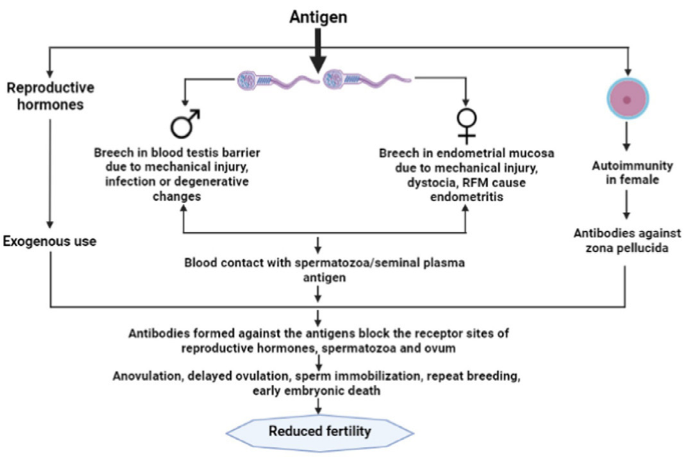

Figure 2: Immunoinfertility caused by exogenous use of reproductive hormones and autoimmunity in female [72].

Risk factors leading to immunological infertility in dairy cows

Immunological infertility in dairy cows' results from the immune system disrupting reproductive processes, influenced by infections, metabolic stress, autoimmune reactions, and modern reproductive technologies [18,32,138]. Uterine infections (endometritis, metritis, pyometra) cause immune-mediated damage through excessive cytokine release (TNF-α, IL-1β, IL-6), oxidative stress, and fibrosis, reducing uterine receptivity [37,66,114]. Dystocia and retained placenta increase inflammation and infection risk, disrupting progesterone production and promoting premature luteolysis [11,63,75,82]. Systemic inflammation from mastitis suppresses GnRH secretion, harms oocytes and embryos via oxidative stress, and reduces progesterone metabolism [102,119,123,129]. Negative Energy Balance (NEB) compromises immunity, with high BHB impairing immune function, low insulin/IGF-1 inhibiting follicle growth, and oxidative stress damaging reproductive tissues [16,58,67,92].

Autoantibodies against sperm, zona pellucida, or ovarian tissues cause fertilization failure and autoimmune oophoritis [3,99]. Stressors like heat stress and overcrowding suppress immunity and increase infection risk [38,43]. High milk production exacerbates metabolic load and uterine disease susceptibility [26,128]. Pathogens such as Coxiella burnetii and Campylobacter fetus cause endometritis, retained placenta, and embryonic death [31,121]. Genetic factors, including immune responder status and genomic susceptibility, affect fertility [20,103]. Reproductive technologies like AI, ET, and hormonal synchronization can lead to uterine contamination, immune rejection, oxidative stress, and hormonal imbalances, further compromising fertility [19,35,42]. Mineral deficiencies (e.g., selenium, zinc) impair immunity and antioxidant capacity, increasing infection risk and embryo mortality [54].

Clinical signs of immunological infertility in dairy cows

Dairy cows with immunological infertility exhibit clinical symptoms indicating immune system dysregulation interfering with reproductive processes [7]. These include abnormal estrous cycles such as anestrus or extended cycles due to suppressed hypothalamic-pituitary-ovarian axis and inhibited GnRH secretion from elevated TNF-α [57]. Repeat breeding syndrome (≥3 conception-free services) occurs due to anti-sperm antibodies hampering fertilization and endometrial fibrosis preventing implantation [137]. Early embryonic death leads to returns to estrus at 18-24 days from IFN-γ and TNF-α interfering with embryonic signaling [112].

Uterine and vaginal signs include abnormal discharge, thickened uterine walls (>8 mm), fibrosis, pyometra (>25 mm diameter), and persistent corpus luteum infection [34,127]. Ovarian abnormalities feature cysts (>25 mm for >10 days), disrupted LH surge, small corpora lutea (<20 mm) with decreased progesterone, short-lived CL (<14 days), and endometritis-induced PGF2α release [96]. Systemic indications show decreased milk production (10-15% yield drop), poor body condition (BCS <2.5), and worsened immune dysfunction from negative energy balance [65]. Other presentations include antisperm antibodies hindering fertilization without uterine infection, and venereal pathogens like Tritrichomonas foetus causing unusual estrous, embryonic death/abortion, and sticky discharge, or Campylobacter fetus venerealis causing inflammatory early embryonic loss and repeat breeding [107].

Diagnosis immunological infertility in dairy cows

Diagnosis of immunological infertility involves clinical assessment including reproductive history analysis (repeat breeding >3 failed inseminations, extended calving intervals >13 months, past postpartum disorders) [44] and physical inspection revealing mucopurulent discharge, vaginal hyperemia, uterine wall thickening (>8mm), and ovarian abnormalities [95]. Laboratory diagnostics include uterine cytology, PCR/bacterial culture for pathogens (E. coli, T. pyogenes, F. necrophorum) [86], and blood examinations. Imaging methods utilize ultrasonography and Doppler showing decreased uterine blood flow (RI >0.8) indicating fibrosis and assessing ovarian stromal flow [76]. Specialized tests feature anti-sperm antibody detection via Immunobead Test (IBT) for IgA/IgG, ELISA, and oxidative stress markers [80].

New instruments employ metabolomics profiling (LC-MS/MS) identifying inflammatory lipids and energy deficit markers (NEFAs, BHB) [21,124] and transcriptomic analysis via RNA sequencing showing up-regulated TNF-α/IL-8 genes and down-regulated progesterone receptors [139]. Anti-Sperm Antibodies (ASA) are detected through direct (mixed agglutination, immunofluorescence, radiolabeled antiglobulin assay, flow cytometry) and indirect tests (sperm agglutination, immobilization, immuno-bead assay, ELISA). Preventive measures include sexual rest, changing bulls, and serotherapy, with studies showing higher antibody titers against frequently used bulls and improved conception after male change [116].

Table 1: Showing different diagnostic test to detect Antisperm antibodies and their principal in various breed/species [116].

Test	Principle	Species/Breed	R
Sperm agglutination test	Number of clumps with spermatozoa can be seen under the microscope after incubation of semen sample (60 million/ml) with test serum	Cattle serum	
Sperm immobilization test	Guinea pig serum is used as a complement to immobilize the spermatozoa	Cattle serum/ Seminal plasma	
Immunofluorescence test	Fluorescence-labeled secondary antibody is used to detect the Antisperm antibodies	Bull serum	
Immuno-peroxidase test	-	Bull semen	
Mixed antiglobulin reaction	Mixed antiglobulin reaction can detect surface antigens. Based on the coombs test. Mixed clumps of red blood cells and spermatozoa can be seen after agglutination with a slow "shaky" movement under a light microscope. Takes 10min to perform	Human serum	
Flowcytometry	With the use of calibration standards dead sperm from washed and stained samples are excluded with fluorescein-isothiocyanate-conjugated F(ab')2 fragments of anti- IgG and IgA antibodies Sperm-bound antibodies can be quantitated and detected by flow cytometry	Bull serum	
Immunobead binding test	Antibody coated latex beads are used to know the localization proportion and class of antibody attached to spermatozoa 30min takes to perform the test	Human serum	
ELISA	ELISA combines the specificity of the antigen-antibody reaction with the continuous degradation of the chromogenic substrate by an enzyme to amplify the sensitivity of the reaction	Bull serum	

Differential diagnosis of immunological infertility in dairy cows

Veterinarians must methodically rule out other causes of reproductive failure when assessing immunological infertility, including infectious, metabolic, nutritional, genetic, and management-related factors [56,97]. Uterine infections like pyometra, metritis, and clinical endometritis are differentiated via bacterial culture and cytological examination (>5% Polymorphonuclear cells) [126]. Venereal diseases (Tritrichomonas foetus, Campylobacter fetus subsp. venerealis) are identified through preputial washing and PCR testing of vaginal mucus. Metabolic disorders such as ketosis and Negative Energy Balance (NEB) are verified by blood tests showing elevated β-hydroxybutyrate (>1.2 mmol/L) and non-esterified fatty acids (NEFA >0.7 mEq/L) [46,140].

Nutritional deficiencies (selenium, copper, vitamin E) are diagnosed via liver biopsy or blood mineral analysis [54], while toxicological causes (mycotoxins like zearalenone, aflatoxin) require liver function tests and feed analysis [53]. Genetic factors, such as Bovine Leukocyte Antigen (BoLA) haplotypes, are identified through genomic testing [68]. Iatrogenic factors (inappropriate AI methods, hormone overuse) are ruled out via reproductive record review [22], and heat stress is assessed through Temperature-Humidity Index (THI) monitoring [101]. A comprehensive diagnostic approach incorporating laboratory testing, ultrasonography, clinical examination, and herd history analysis is essential [73].

Treatment of immunological infertility in dairy cows

Treatment of immunological infertility focuses on reducing inflammation, restoring uterine health, and alleviating immunological disruption [57,117]. For endometritis, Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) is used to induce luteolysis, promote uterine clearance, and cure pyometra [83]. Intrauterine antibiotics (e.g., oxytetracycline) or antiseptics like Povidone-Iodine (PVP-I) infusions improve conception rates and endometrial regeneration [45,136]. Non-antibiotic adjuncts such as 50% dextrose and liquid paraffin are also employed [29]. Immunomodulation with NSAIDs (e.g., flunixin meglumine) and antioxidants (vitamin E, beta-carotene, vitamin C) enhances immune function and fertility [52].

Hormonal therapies, including $PGF_2\alpha$ and GnRH protocols, restore cyclicity and improve ovulation rates [40]. For Anti-Sperm Antibodies (ASA), sperm processing techniques (washing, magnetic bead separation, enzymatic treatment) improve outcomes in assisted reproduction [80]. Novel therapies like Intrauterine Ozone Therapy (IUTO) and probiotics (lactic acid bacteria) reduce inflammation and enhance reproductive outcomes [2]. Nutritional support with antioxidants, omega-3 fatty acids, rumen-protected choline, and propylene glycol addresses metabolic stress and oxidative damage [78]. Advanced reproductive technologies, such as Embryo Transfer (ET), bypass uterine inflammation, while herd-level interventions like vaccination, heat stress abatement, and genomic selection for immune resilience prevent recurrence [30,94].

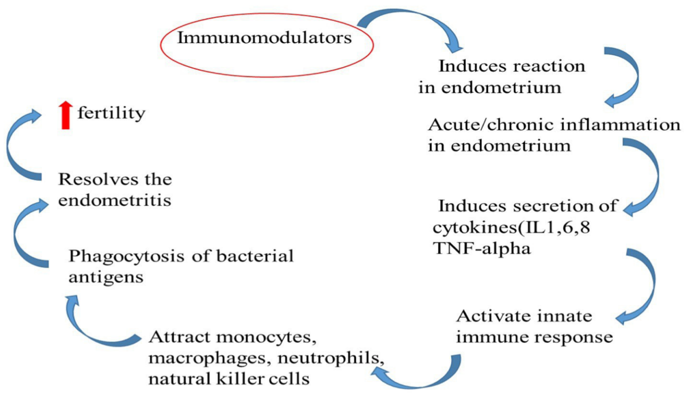

Figure 3: Immune mechanism made by immunomodulators to restore fertility [17].

Prevention and control strategies of immunological infertility in dairy cows

Prevention of immunological infertility centers on improved management of uterine health and postpartum care, including calving hygiene, early treatment of retained placenta, and selective use of uterine lavage or prophylactic antibiotics to prevent infections [23]. Nutritional strategies involve rumen-protected choline (15–20 g/day), antioxidants (selenium 0.3 ppm, vitamin E 1000–3000 IU/day), and omega-3 fatty acids (100–150 g/day) to reduce inflammation and oxidative stress [108]. Biosecurity measures, vaccination against BVDV, IBR, Campylobacter fetus, and leptospirosis, and experimental vaccines against E. coli and Trueperella pyogenes minimize pathogen exposure [133]. Heat stress mitigation uses cooling systems (THI <68), night feeding, and betaine supplementation (50–100g/day) to reduce cortisol and immune dysfunction [132].

Genetic selection for immune resilience via BoLA haplotypes and High Immune Response (HIR) sires improves fertility [114]. Reproductive management employs timed AI protocols, progesterone supplementation, and post-breeding NSAIDs to enhance pregnancy rates and reduce embryo loss [87]. Prophylactic probiotics (intravaginal lactic acid bacteria) pre-calving reduce metritis and improve conception [2], while optimized dry cow management preserves systemic immunity [61]. Regular monitoring through uterine cytology, Body Condition Scoring (BCS 2.75–3.25), and milk progesterone assays enables early intervention [4]. Judicious use of immunomodulators, antibiotics, and hormones avoids compromising immunity and ensures responsible antimicrobial stewardship.

Economic impact of immunological infertility in dairy cows

Immunodeficiency in cattle leads to significant economic consequences, including increased susceptibility to reproductive diseases, lower conception rates, higher mortality, reduced productivity, elevated veterinary costs, and decreased milk production [9]. Immunological infertility causes substantial financial losses due to direct expenses (treatment, prolonged calving intervals) and indirect costs (premature culling, reduced milk yield), with annual losses per affected cow ranging from $300 to $600, and herd-level impacts exceeding $50,000 annually for a 200-cow operation [42].

These losses stem from: 1) Decreased reproductive performance: Extended calving intervals (>13 months) result in $3–$5 per cow daily milk income loss and higher insemination costs; lower conception rates (20–30% vs. 40–50%) add $150–$200 annually in semen and labor expenses; embryonic mortality (25–40%) causes $250–$400 losses per failed pregnancy [33]. 2) Reduced milk production: Peripartum inflammation decreases peak yield by 2-4 kg/day ($0.50–$0.80/cow/day), and chronic endometritis reduces lactation totals by 500–1,000 kg/cow ($150–$300 loss at $0.30/kg) [26,64].

Increased veterinary costs: Hormonal treatments, NSAIDs, and antibiotics average $80–$120 per case, with diagnostics adding $20–$50 per cow [24]. 4) Early culling: Replacement heifers cost $1,800–$2,500, with 15–25% of infertile cows culled prematurely, reducing productive life from four to two–three lactations and incurring $2,000–$3,000 lifetime profit loss. 5) Hidden expenses: Additional breeding labor (5–10 hours/week) costs $500–$1,000 annually, and delayed genetic progress from reduced AI efficiency lowers herd-wide productivity [130].

Research trends and advances in immunological infertility in dairy cows

Recent research on immunological infertility in dairy cows focuses on identifying immune-endocrine interactions, developing targeted therapies, and utilizing advanced technologies [104]. Key advances include discovering inflammatory biomarkers (haptoglobin, serum amyloid A, IL-6) that predict reproductive failure and mapping immune pathways via omics technologies (genomics, proteomics, metabolomics). Studies show dysregulation of Toll-Like Receptor (TLR4) signaling and NF-κB activation in endometritis cases [91]. Immunomodulatory treatments like pegylated Granulocyte Colony-Stimulating Factor (G-CSF) improve pregnancy rates by 20–25% in repeat breeders [77], while probiotic strains (e.g., Lactobacillus rhamnosus) restore uterine microbial balance [2].

Nanoparticle-based drug delivery systems reduce endometrial fibrosis [1]. Genetic solutions advance through Genome-Wide Association Studies (GWAS) identifying BoLA-DRB3 alleles linked to enhanced immunity and fertility [141], with immunocompetence genomic testing now available commercially. CRISPR-Cas9 gene editing is explored for embryo disease resistance [47]. Precision Livestock Farming (PLF) tools (automated activity monitors, infrared thermography) enable early detection of subclinical inflammation [85], and machine learning algorithms predict infertility risks with >85% accuracy [74].

Challenges and knowledge gaps in immunological infertility in dairy cows

Despite advancements, understanding and treating immunological infertility remains challenging due to significant knowledge gaps (Moorkens, 2024). The specific immune mechanisms linking ovarian dysfunction and uterine inflammation, including tissue-specific thresholds and temporal dynamics of pro-inflammatory cytokines (TNF-α, IL-1β) during the estrous cycle, are poorly understood. There are no targeted treatments to balance neutrophils' dual roles in bacterial clearance and embryonic harm [71].

Non-invasive biomarkers for subclinical endometritis lack validation; blood-based markers like haptoglobin are non-specific, and cytobrush techniques (>5% PMNs) show variable sensitivity (60–80%) [88]. The vaginal microbiome's role in immune modulation is emerging, with Lactobacillus dominance favoring fertility, but strain-specific treatments are unavailable [93]. Translational gaps persist: G-CSF lacks field-scale protocols for dosage, timing, and cost-effectiveness ($50–100/dose) [51], and nanoparticle drug delivery faces challenges like uterine mucus penetration in cows (Kamothi *et al*., 2025).

Genetic selection is hampered by trade-offs between immunity and milk yield (3–5% reduction in high-immune-response cows) (Pryce *et al*., 2023). Epigenetic regulation via DNA methylation in granulosa cells under chronic inflammation is unexplored [48]. Financial constraints limit adoption, as small farms (<200 cows) cannot afford probiotic regimens ($5,000/year) or genomic testing ($10,000+) [28]. Finally, data on mitigating climate change interactions (e.g., heat stress exacerbating inflammatory infertility) beyond conventional cooling systems are lacking [113].

Conclusion and recommendations

Immunological infertility in dairy cows is a significant reproductive disorder caused by the immune system's adverse response to gametes, reproductive hormones, or associated tissues, leading to conception failure or early embryonic loss. Key contributing factors include uterine infections, metabolic stress, autoimmune reactions, and improper use of reproductive technologies. Clinical signs such as repeat breeding, abnormal estrous cycles, and suboptimal conception rates highlight its impact. Diagnosis involves advanced techniques like uterine cytology, PCR, and ELISA, while treatment strategies focus on immunomodulation, hormonal therapy, and assisted reproductive technologies. Preventive measures, including improved nutrition, genetic selection for immune resilience, and better herd management, are essential to mitigate economic losses from reduced milk yield and increased veterinary costs. Emerging research on biomarkers, probiotics, and genomic tools offers promising solutions, though challenges remain in understanding immune-pathway interactions. Addressing this condition requires an integrated approach to enhance dairy cow fertility and farm profitability.

Based on the above conclusion the following recommendations are forwarded; to mitigate immunological infertility in dairy cows, a multifaceted approach is essential:

- **Enhance uterine health** prioritize postpartum hygiene, prompt treatment of infections (e.g., endometritis) using immunomodulators and targeted antibiotics.
- **Optimize nutrition** supplement diets with antioxidants (vitamin E, selenium) and omega-3 fatty acids to combat oxidative stress and boost immunity.
- **Utilize advanced reproduction** employ Embryo Transfer (ET) to circumvent uterine inflammation in high-risk cows, reducing dependence on artificial insemination.
- **Select for Immune Resilience** Implement genetic selection focusing on BoLA haplotypes to build a more disease-resistant herd with **adopt integrated management.**
- **Mitigate Environmental Stress m**anage heat stress through cooling systems and optimized practices to prevent cortisol-induced immunosuppression.

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