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Prolonged Antibiotic Use and Reproductive Challenges in Dairy Cows: Implications for Ovarian, Uterine, and Overall Reproductive Health

Md. Emran Hossain*

Abstract

The widespread use of antibiotics in dairy farming has raised concerns regarding its potential impact on reproductive performance. Prolonged antibiotic administration can disrupt endocrine regulation, alter ovarian function, impair uterine health, and compromise overall fertility in dairy cows. This review explores the multifaceted consequences of antibiotic exposure on reproductive physiology, highlighting its effects on hormonal balance, follicular dynamics, uterine microbiota, and embryo viability. Antibiotics may induce hormonal imbalances that interfere with estrous cyclicity, leading to anovulation, prolonged postpartum anestrus, and reduced conception rates. Ovarian dysfunction, characterized by impaired folliculogenesis and increased ovarian cyst formation, is another critical consequence. Additionally, prolonged antibiotic exposure alters the uterine microbiome, increasing susceptibility to endometritis and subclinical infections that hinder uterine involution and embryo implantation. The development of antimicrobial resistance in reproductive pathogens further complicates fertility management in dairy herds. Furthermore, antibiotic residues may persist in tissues, affecting fetal development and postnatal growth of offspring. Addressing these challenges requires an integrative approach, incorporating precision antibiotic use, alternative therapeutic strategies, and microbiome-targeted interventions to optimize reproductive efficiency. Future research should focus on understanding microbial-host interactions in reproductive tissues and developing sustainable solutions to minimize antibiotic-associated fertility decline in dairy cows.

Keywords: Antibiotic resistance, dairy cow fertility, embryo viability, hormonal imbalance, ovarian dysfunction, reproductive health, uterine microbiota

INTRODUCTION

The use of antibiotics in dairy farming has been instrumental in controlling infectious diseases and improving herd health. However, concerns have emerged regarding their unintended effects on reproductive performance [1]. Antibiotics can disrupt endocrine regulation, alter reproductive microbiota, and compromise ovarian and uterine function, ultimately reducing fertility rates in dairy cows [2]. Prolonged antibiotic exposure has been linked to hormonal imbalances that impair estrous cyclicity, delay ovulation, and contribute to ovarian dysfunction, such as cyst formation and follicular atresia [3, 4]. Additionally, antibiotic residues may interfere with key reproductive pathways, affecting the secretion of progesterone and estrogen, which are critical for maintaining reproductive efficiency [5–7]. These disruptions collectively contribute to an increase in infertility, reduced conception rates, and prolonged calving intervals, posing significant challenges to dairy production systems [8–10].

***Author for Correspondence**
Md. Emran Hossain
E-mail: emran@cvasu.ac.bd

Professor, Department of Animal Science and Nutrition, Chattogram Veterinary and Animal Sciences University, Khulshi, Chattogram, Bangladesh

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Another major concern is the impact of antibiotics on the uterine environment and embryo viability [11, 12]. The reproductive tract harbors a diverse microbiota essential for immune regulation and uterine health [11–14]. Antibiotic administration alters this microbial balance, increasing the risk of dysbiosis, endometritis, and postpartum infections, which negatively affect uterine involution and embryo implantation [15, 16]. The persistence of antibiotic residues in reproductive tissues may also exert toxic effects on gametes and embryos, leading to early embryonic mortality [4, 15, 16]. Moreover, antimicrobial resistance in reproductive pathogens further complicates fertility management, necessitating repeated interventions that may exacerbate reproductive inefficiencies [17, 18]. These challenges underscore the need to assess the long-term consequences of antibiotic exposure on reproductive outcomes in dairy cows, particularly in intensive farming systems where antibiotic usage is frequent.

This study provides a comprehensive review of the mechanisms through which prolonged antibiotic use influences reproductive health in dairy cows, with a focus on ovarian function, uterine microbiota, and embryo viability. Unlike previous studies that have primarily examined the therapeutic efficacy of antibiotics, this work critically evaluates their unintended reproductive consequences, offering a novel perspective on fertility management in dairy herds. By synthesizing existing knowledge and highlighting emerging concerns, this study aims to inform precision antibiotic use strategies, explore microbiome-targeted interventions, and propose sustainable alternatives to mitigate antibiotic-associated fertility decline. Understanding these interactions is crucial for optimizing reproductive efficiency and ensuring the long-term sustainability of dairy production.

ANTIBIOTIC-INDUCED HORMONAL IMBALANCES

Disruption of Estrous Cycle Regularity

Prolonged antibiotic use disrupts the endocrine balance, leading to irregular estrous cycles in dairy cows [19, 20]. The suppression of beneficial reproductive microbiota and interference with hormonal signaling contribute to inconsistent cycle lengths, unpredictable estrus expression, and suboptimal timing for artificial insemination. These irregularities reduce reproductive efficiency, delaying conception and increasing the number of open days in dairy cows.

Reduced Luteinizing Hormone Secretion

Antibiotics can alter the hypothalamic–pituitary–gonadal axis, leading to reduced luteinizing hormone (LH) secretion. This deficiency disrupts ovulatory processes, causing delayed or failed ovulation [20, 21]. Insufficient LH release also impairs follicular luteinization, leading to prolonged follicular dominance and hormonal imbalances. As a result, cows experience increased incidences of ovarian cysts, poor estrus expression, and lower conception rates, adversely affecting reproductive efficiency in dairy herds.

Impaired Follicular Development

Antibiotic-induced disruptions in ovarian function impair follicular development by altering hormone synthesis and follicular fluid composition [22, 23]. Follicles may experience arrested growth, atresia, or the formation of persistent dominant follicles, leading to reduced oocyte quality. Impaired folliculogenesis results in prolonged inter-estrus intervals and increased infertility risks, ultimately decreasing the reproductive efficiency of dairy cows and extending the time to conception.

Suppression of Progesterone Production

Prolonged antibiotic exposure can suppress progesterone production by interfering with luteal function. Reduced progesterone levels impair endometrial receptivity, increasing embryonic loss and early pregnancy failures [16, 24, 25]. This hormonal imbalance can also cause shortened luteal phases, leading to frequent estrous cycles that reduce insemination success. The resulting fertility decline necessitates increased breeding attempts, elevating economic and management challenges in dairy farming.

Delayed Ovulation Timing

Disruptions in hormonal signaling caused by antibiotics lead to delayed ovulation, reducing synchronization with artificial insemination or natural mating [17, 19, 20, 25, 26]. Poorly timed ovulation results in reduced fertilization rates, lower embryo survival, and increased insemination failures. This delay also leads to extended calving intervals, negatively impacting lactation cycles and overall herd productivity in dairy operations.

Altered Estrogen Levels in the Blood

Antibiotics can disrupt estrogen synthesis and metabolism, leading to fluctuations in circulating estrogen levels. These imbalances impair follicular growth, estrus behavior, and uterine receptivity [16, 24, 25]. Inconsistent estrogen levels can result in poor estrus detection, increased anovulatory cycles, and compromised fertility. Additionally, altered estrogen dynamics negatively influence uterine immunity, increasing susceptibility to reproductive tract infections.

Inhibited Corpus Luteum Formation

Prolonged antibiotic exposure can interfere with corpus luteum (CL) development, leading to inadequate progesterone secretion. A poorly developed CL fails to support early pregnancy, increasing embryonic mortality rates [17, 19, 20, 26]. The absence of a functional CL also prolongs the inter-estrus interval, delaying reproductive recovery and extending calving intervals, ultimately reducing the reproductive efficiency of dairy cows.

Prolonged Postpartum Anestrus

Antibiotic-induced hormonal imbalances contribute to extended postpartum anestrus by delaying the resumption of ovarian activity. Disruptions in estrogen and progesterone signaling impair follicular waves, slowing reproductive recovery after calving [17, 20, 26]. A prolonged anestrus period reduces the number of breedable cows in a herd, leading to lower annual calving rates and decreased milk production efficiency.

Increased Incidence of Silent Heat

Antibiotic use disrupts the hormonal and metabolic pathways that regulate estrus expression, leading to an increased incidence of silent heat. Cows experiencing silent heat do not exhibit overt estrus signs, making estrus detection challenging and reducing successful insemination rates [17, 20, 26]. This results in prolonged open periods, increased calving intervals, and a decline in overall reproductive performance in dairy herds.

Impaired Regulation of Gonadotropins

Gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are essential for ovarian function [17, 20, 26]. Antibiotics interfere with their secretion and signaling pathways, leading to poor follicular recruitment, abnormal ovulation, and reproductive inefficiencies. These disruptions contribute to higher infertility rates, increased embryonic losses, and compromised reproductive success, necessitating improved strategies for sustainable fertility management in dairy cows.

OVARIAN FUNCTION

Inhibited Oocyte Maturation

Prolonged antibiotic use inhibits oocyte maturation by disrupting the hormonal environment essential for follicular development. This interference impairs meiotic progression, leading to the release of immature or dysfunctional oocytes [21, 27]. As a result, fertilization success is reduced, and embryo quality declines, ultimately affecting overall reproductive performance. Delayed or suboptimal oocyte maturation increases the risk of infertility in dairy cows.

Increased Ovarian Cyst Formation

Antibiotic exposure can increase the incidence of ovarian cysts by disrupting the regulation of follicular development [9, 28]. Persistent follicles or luteal cysts may form due to hormonal imbalances induced by antibiotics, leading to dysfunctional ovarian cycles. These cysts disrupt normal reproductive physiology, causing anovulation, irregular estrus, and extended calving intervals, significantly reducing fertility in dairy herds.

Reduced Ovarian Follicle Count

Antibiotics may reduce the total ovarian follicle count by disrupting folliculogenesis and suppressing the recruitment of primordial follicles. Fewer follicles available for ovulation decreases the likelihood of successful fertilization and embryo development [21, 27]. This reduction in follicular reserves results in an overall decline in reproductive efficiency, leading to increased days open and a decrease in milk production.

Altered Ovarian Follicle Size

Antibiotics can disrupt the normal regulation of ovarian follicle growth, leading to irregular follicle size and development. Some follicles may fail to reach the appropriate size for ovulation, while others may grow excessively, resulting in a suboptimal hormonal environment for fertilization [29]. These size discrepancies impair ovulation timing and egg quality, reducing conception rates in dairy cows.

Premature Follicular Atresia

The use of antibiotics accelerates follicular atresia by disrupting hormonal signaling pathways essential for follicular survival [30–32]. Follicles may undergo premature degeneration due to antibiotic-induced imbalances in gonadotropins and growth factors. This early follicular regression reduces the pool of mature oocytes available for ovulation, leading to decreased fertility rates, prolonged anestrus, and suboptimal breeding outcomes.

Lowered Ovulation Rates

Antibiotics adversely affect the signaling required for proper ovulation, leading to lower ovulation rates in dairy cows [30–32]. Disrupted hormonal balances, such as reduced luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, impair the ovulatory process. This results in fewer cows ovulating during each estrous cycle, contributing to extended intervals between calving, reduced conception rates, and overall reproductive inefficiency.

Suppressed Ovarian Sensitivity to Gonadotropins

Prolonged antibiotic exposure suppresses ovarian sensitivity to gonadotropins, which are essential for follicular development and ovulation [33–35]. This suppression impairs the ovarian response to follicle-stimulating hormone (FSH) and luteinizing hormone (LH), reducing the chances of ovulation. As a result, dairy cows experience prolonged anestrus, delayed estrus cycles, and lower fertility rates, compromising reproductive health.

Delayed Ovarian Rebound Post-Calving

Antibiotic-induced disruptions in ovarian function delay the resumption of normal ovarian activity after calving. The suppression of hormonal signals responsible for follicular development and ovulation leads to a longer postpartum anestrus period [33–35]. This delay in ovarian rebound reduces the number of cows available for breeding, leading to extended calving intervals and reduced annual reproductive output.

Reduced Ovarian Vascularization

Prolonged antibiotic use can decrease ovarian vascularization by impairing the blood supply to the ovaries, crucial for follicular growth and hormone secretion. Reduced blood flow limits the delivery of essential nutrients and oxygen to developing follicles, impairing their growth and maturation [36–38]. This negatively impacts fertility, leading to fewer viable oocytes and poor overall reproductive outcomes in dairy cows.

Decreased Ovarian Enzymatic Activity

Antibiotics reduce the activity of key enzymes involved in steroidogenesis and follicular maturation within the ovaries. Lower enzymatic activity disrupts hormone production, leading to an inadequate endocrine environment for successful ovulation [36–38]. Reduced enzymatic function also impairs the conversion of androgens to estrogens, further compromising reproductive health by inhibiting follicle development and reducing the likelihood of pregnancy.

UTERINE HEALTH

Increased Risk of Endometritis

Prolonged antibiotic exposure can disrupt the normal uterine microbiota, making cows more susceptible to endometritis. Antibiotics may reduce the diversity of protective bacteria, creating an environment conducive to pathogenic bacterial overgrowth [34, 36, 39–41]. This inflammation of the endometrium impairs uterine health, leading to reduced fertility, increased embryonic loss, and prolonged postpartum recovery times.

Delayed Uterine Involution

Antibiotics can delay the natural process of uterine involution by interfering with the normal immune and hormonal signaling pathways [36, 39–41]. The delayed resolution of uterine inflammation impairs tissue remodeling, leading to retained fetal membranes, increased susceptibility to infections, and prolonged postpartum recovery. As a result, dairy cows experience delayed estrus and reduced reproductive efficiency.

Suppressed Uterine Immune Responses

Chronic antibiotic use can suppress the uterine immune system, reducing the ability of the uterus to clear pathogens effectively [36, 39–41]. This impairment compromises the natural defense mechanisms, leading to an increased incidence of uterine infections and inflammation. A weakened immune response can hinder uterine healing postpartum, prolonging recovery times and reducing fertility potential in dairy cows.

Altered Uterine Microbiota Balance

Antibiotic treatments disturb the delicate balance of the uterine microbiota, which is crucial for maintaining reproductive health [29, 36, 39–42]. By killing both pathogenic and beneficial bacteria, antibiotics can lead to dysbiosis, where pathogenic microbes dominate. This imbalance can trigger uterine infections, alter immune responses, and reduce fertility rates, as the uterus becomes more susceptible to inflammation and infection.

Prolonged Uterine Infections

Antibiotics may contribute to prolonged uterine infections by disrupting the natural immune response and promoting the persistence of harmful microorganisms [29, 36, 39–42]. Infected uterine tissues experience prolonged inflammation, which can compromise fertility by affecting embryo implantation, increasing the likelihood of early embryonic mortality, and delaying recovery after calving. These infections necessitate repeated treatments, worsening reproductive health.

Impaired Uterine Clearance Postpartum

Antibiotics may impair uterine clearance mechanisms postpartum, leading to the accumulation of infectious agents, cellular debris, and retained fetal membranes [36, 39–42]. The compromised uterine environment delays the expulsion of these materials, prolonging the recovery process and increasing the risk of uterine infections. This delayed clearance can reduce uterine fertility and increase the risk of postpartum anestrus.

Reduced Uterine Blood Flow

Antibiotic exposure may reduce uterine blood flow by impairing the regulation of blood vessels in the reproductive tract. Reduced blood circulation limits nutrient and oxygen supply to uterine tissues, impairing their ability to repair and regenerate after calving [36, 39–42]. Poor uterine blood flow negatively impacts embryo development and uterine health, reducing overall fertility and reproductive success.

Altered Prostaglandin Synthesis

Prolonged antibiotic use can alter the synthesis and release of prostaglandins, which play a critical role in uterine contraction, immune response, and the luteolysis of the corpus luteum [36, 39–41]. Disruptions in prostaglandin production affect uterine motility and immune responses, leading to poor uterine environment conditions for embryo implantation and survival, reducing conception rates in dairy cows.

Chronic Uterine Inflammation

Antibiotics may contribute to chronic uterine inflammation by disrupting immune pathways and microbiota balance. This ongoing inflammation impairs uterine function and prolongs recovery from calving [36, 39–41]. Chronic inflammation also increases the risk of endometrial fibrosis and scarring, further reducing fertility rates by compromising the uterus' ability to support embryo implantation and gestation.

Reduced Uterine Fertility Rates

The compounded effects of antibiotic-induced uterine infections, dysbiosis, and inflammation lead to a marked decline in uterine fertility rates. A compromised uterine environment impairs embryo development and reduces the chances of successful implantation [36, 39–41]. As a result, dairy cows experience longer intervals between calving, reduced conception rates, and an overall decline in reproductive performance, impacting farm profitability.

SPERM FUNCTION

Reduced Sperm Motility Post-Insemination

Antibiotic exposure can impair sperm motility by altering the physiological environment of the reproductive tract. The disruption of seminal plasma composition and the presence of antibiotic residues can reduce sperm energy metabolism and motility [43]. This decreased motility reduces the sperm's ability to reach and fertilize the egg, leading to lower conception rates and reduced reproductive efficiency in dairy cows.

Altered Sperm Viability in Reproductive Tract

Prolonged antibiotic use can negatively impact sperm viability within the female reproductive tract by altering its biochemical environment. Antibiotic-induced changes in pH and ion concentration may reduce sperm survival [44–48]. As a result, sperm lose their ability to effectively fertilize the egg, increasing the likelihood of infertility and reducing overall fertility rates in dairy cows.

Increased Sperm DNA Fragmentation

Antibiotics contribute to oxidative stress and inflammation, leading to increased sperm DNA fragmentation. This damage to genetic material impairs sperm quality and decreases the ability to fertilize an egg successfully [44–47]. The presence of fragmented DNA also increases the risk of embryonic loss and reduced pregnancy rates, posing a significant challenge to dairy reproduction.

Disrupted Acrosomal Reaction

The acrosomal reaction, a crucial step for sperm penetration of the egg, can be disrupted by prolonged antibiotic use [44, 45, 47]. Antibiotics interfere with membrane integrity and enzyme release during this reaction, preventing sperm from successfully fertilizing the egg. This disruption reduces fertilization efficiency and significantly decreases the chances of conception in dairy cows following artificial insemination.

Altered Sperm Capacitation Process

Capacitation, the final maturation process required for sperm to fertilize an egg, can be disrupted by antibiotics. Prolonged antibiotic exposure impairs the biochemical and physiological changes required for sperm to undergo capacitation, rendering them incapable of binding with the egg [44, 45, 47]. This interference lowers fertilization rates and overall reproductive success, leading to prolonged calving intervals.

Reduced Sperm-Binding Efficiency

Antibiotic exposure can reduce the sperm's ability to bind to the egg, a crucial step in fertilization. Antibiotics may interfere with the sperm receptors or the zona pellucida of the egg, preventing the sperm from attaching effectively [44, 45, 47]. This reduction in sperm-binding efficiency decreases fertilization success, resulting in reduced pregnancy rates and lower reproductive efficiency.

Increased Oxidative Damage to Sperm

Oxidative stress induced by antibiotic use results in increased free radicals in the seminal plasma. These free radicals damage sperm membranes, proteins, and DNA, reducing sperm integrity and function [44, 45, 47]. The increased oxidative damage impairs sperm motility, viability, and fertilizing capacity, ultimately leading to lower conception rates and diminished reproductive success in dairy cows.

Suppressed Antioxidant Activity in Seminal Plasma

Antibiotics may suppress the natural antioxidant defenses in seminal plasma, increasing the susceptibility of sperm to oxidative damage. A reduction in antioxidants, such as superoxide dismutase and catalase, limits sperm protection from reactive oxygen species, leading to cellular damage and reduced sperm quality [44, 45, 47]. This suppression negatively affects fertility, as damaged sperm are less capable of successful fertilization.

Impaired Sperm Transport in Oviduct

The antibiotic-induced disruption of the uterine and oviduct environment may impair the transport of sperm to the site of fertilization [44, 47]. Antibiotics can alter the viscosity of cervical mucus, hinder sperm motility, and disrupt normal ciliary function in the oviduct, resulting in reduced sperm movement and an increased risk of fertilization failure.

Decreased Fertilization Success Rates

Prolonged antibiotic use affects multiple aspects of sperm function, including motility, capacitation, and binding efficiency, ultimately leading to decreased fertilization success. As sperm quality and the ability to fertilize the egg are compromised, fertilization rates decrease, leading to reduced pregnancy success and prolonged calving intervals [44, 47]. This results in decreased reproductive efficiency and profitability in dairy farming.

EMBRYO VIABILITY

Increased Embryonic Mortality

Antibiotic exposure in dairy cows can increase embryonic mortality by disrupting cellular processes essential for early development. Antibiotics cause oxidative stress and inflammation, damaging both the embryo and uterine environment [47, 49–52]. As a result, the embryo becomes more susceptible to degeneration, leading to early embryonic death and reduced overall fertility rates in dairy cows.

Disrupted Early Embryonic Development

Prolonged antibiotic use can interfere with critical stages of early embryonic development. Antibiotics alter gene expression, reduce cellular integrity, and disrupt protein synthesis, all of which are vital for successful embryo growth [47, 49, 51, 52]. These disturbances can impair cell division and differentiation, delaying or preventing normal embryonic development and increasing the likelihood of early embryonic death.

Altered Maternal-Fetal Signaling

Antibiotics can alter maternal–fetal signaling by disrupting the release of key hormones and signaling molecules essential for embryo survival. These alterations hinder the communication between the maternal and fetal systems, impairing processes like nutrient exchange and immune tolerance [47, 51, 52]. Disrupted signaling increases the likelihood of pregnancy complications, reduced fetal growth, and early pregnancy loss.

Reduced Embryo Implantation Rates

Antibiotics negatively affect the uterine environment, disrupting the conditions necessary for successful embryo implantation. Changes in the endometrial receptivity, inflammatory responses, and immune function reduce the ability of the embryo to properly attach to the uterine lining [47, 51, 52]. As a result, there is a significant reduction in embryo implantation rates, leading to decreased pregnancy success in dairy cows.

Suppressed Embryonic Gene Expression

Chronic antibiotic use can suppress embryonic gene expression, crucial for early development and survival. Antibiotics alter the epigenetic landscape, impacting the regulation of genes responsible for cell growth, differentiation, and immune responses [51–53]. This suppression impairs the embryo's ability to adapt to the maternal environment, increasing the risk of developmental anomalies and embryonic loss.

Increased Risk of Embryonic Deformities

Antibiotics, particularly when administered during early pregnancy, can lead to an increased risk of embryonic deformities [47, 51, 52]. The oxidative stress, gene expression alterations, and hormonal imbalances induced by antibiotics disrupt normal fetal development. This can result in malformations, which not only reduce the chances of a successful pregnancy but also impact the health and viability of the offspring.

Impaired Placental Development

Antibiotics can negatively affect placental development by altering angiogenesis, trophoblast function, and nutrient transport mechanisms [51–53]. A compromised placenta has reduced efficiency in nutrient and gas exchange, which can stunt fetal growth and development. Impaired placental function increases the risk of pregnancy loss and decreases the overall reproductive success and health of dairy cows.

Reduced Embryonic Nutrient Uptake

Antibiotics disrupt the maternal environment, altering the availability and transport of nutrients to the embryo. Reduced uterine blood flow and impaired placental function hinder the effective transfer of essential nutrients like glucose and amino acids [52, 53]. This limitation in nutrient uptake can negatively affect embryo growth, leading to developmental delays, poor health outcomes, and reduced pregnancy rates.

Altered Blastocyst Quality

Antibiotics interfere with the development and quality of the blastocyst, which is essential for successful implantation and pregnancy [52, 53]. Antibiotic exposure can cause oxidative damage, genetic instability, and altered cellular function in the blastocyst. As a result, the blastocyst's ability to implant properly and continue development is compromised, leading to reduced fertilization and implantation success.

Increased Likelihood of Early Pregnancy Loss

Prolonged antibiotic use increases the likelihood of early pregnancy loss by compromising various stages of embryo development, implantation, and placental function. Antibiotics disrupt the immune system, hormonal regulation, and maternal–fetal communication, all of which are crucial for maintaining pregnancy [52–54]. These disruptions significantly raise the risk of embryonic mortality, early pregnancy loss, and reduced reproductive efficiency in dairy cows.

ANTIBIOTIC-INDUCED STRESS AND INFLAMMATION

Increased Systemic Inflammation Markers

Prolonged antibiotic use can elevate systemic inflammation markers, such as C-reactive protein (CRP) and interleukins, which indicate a heightened immune response [45, 55–57]. This increased inflammation negatively affects reproductive tissues, impairing their function and disrupting normal reproductive cycles. As a result, the inflammatory response can contribute to decreased fertility and reproductive efficiency in dairy cows.

Elevated Oxidative Stress Levels

Antibiotics induce oxidative stress by generating free radicals, which damage cellular components such as proteins, lipids, and DNA. This oxidative damage impairs the function of reproductive tissues, reducing the efficiency of processes such as oocyte maturation and embryo development [45, 55, 56]. Elevated oxidative stress contributes to infertility, pregnancy loss, and overall reproductive health deterioration in dairy cows.

Suppressed Antioxidant Enzyme Activity

Antibiotics can suppress the activity of key antioxidant enzymes, including superoxide dismutase and catalase, which are responsible for neutralizing reactive oxygen species. The depletion of these enzymes increases oxidative damage to reproductive tissues, impairing cell function and leading to a decline in fertility [45, 55–57]. Suppressed antioxidant defenses further exacerbate reproductive challenges and reduce the chances of successful conception.

Altered Immune Function in Reproductive Tissues

Antibiotic-induced changes in the immune function of reproductive tissues can impair the body's ability to combat infections and maintain tissue homeostasis. Disruption of immune responses within the uterus and ovaries increases the risk of infections and inflammatory conditions like endometritis [45, 55, 56]. These immune dysfunctions lead to compromised fertility, extended postpartum anestrus, and higher rates of pregnancy loss.

Chronic Inflammation of Reproductive Organs

Prolonged antibiotic use can lead to chronic inflammation of reproductive organs, including the ovaries and uterus. This persistent inflammation disrupts normal tissue architecture and function, resulting in impaired follicular development, delayed ovulation, and reduced embryo viability [45, 55–57]. Chronic inflammation also compromises uterine receptivity, reducing the likelihood of successful implantation and pregnancy in dairy cows.

Increased Cortisol Levels Impairing Reproduction

Antibiotic use can elevate cortisol levels, which are associated with stress responses. High cortisol concentrations can interfere with reproductive hormone regulation, including the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [45, 55, 56]. Elevated cortisol suppresses the estrous cycle and delays ovulation, negatively affecting fertility and reducing the likelihood of conception in dairy cows.

Stress-Induced Disruption of Estrous Cycle

Antibiotic-induced stress can disrupt the estrous cycle by altering the balance of reproductive hormones. The stress response inhibits normal gonadotropin secretion, preventing ovulation and extending the interestrous interval [45, 55, 56]. This disruption in estrous cycle regularity leads to an increase in anovulation and silent heat, ultimately reducing reproductive success and prolonging calving intervals in dairy cows.

Altered Cytokine Signaling in Reproductive Tract

Antibiotics can interfere with cytokine signaling pathways in the reproductive tract, disrupting immune cell communication and inflammatory responses [45, 55, 56]. This alteration in cytokine production impairs the local immune defense mechanisms and compromises reproductive tissue integrity. The imbalance in cytokine signaling can result in infertility, uterine infections, and increased pregnancy loss in dairy cows.

Compromised Tissue Repair Mechanisms

Prolonged antibiotic use can impair tissue repair mechanisms by disrupting the normal wound healing process in reproductive organs. Antibiotics hinder the regenerative capacity of tissues following inflammation or injury, leading to scarring, reduced uterine contractility, and delayed uterine involution [45, 55, 56]. This delayed repair further compromises fertility and extends postpartum anestrus, negatively affecting reproductive health.

Long-Term Damage to Reproductive Health

Antibiotics cause long-term damage to reproductive health by inducing chronic inflammation, altering immune function, and increasing oxidative stress in reproductive tissues. These effects compound over time, resulting in a gradual decline in fertility, impaired ovarian and uterine function, and increased risk of infections [45, 55, 56]. The long-term impact of antibiotic use reduces overall reproductive efficiency, leading to decreased milk production and lower profitability in dairy farming.

MICROBIOTA DISRUPTIONS IN REPRODUCTIVE TRACT

Reduced Diversity of Beneficial Microbiota

Prolonged antibiotic use can reduce the diversity of beneficial microbiota in the reproductive tract, disturbing the delicate balance of microorganisms [58, 59]. This loss of microbial diversity compromises the normal function of the reproductive system, leading to an increased susceptibility to infections and a decline in reproductive health. A less diverse microbiota reduces the body’s ability to resist pathogens and maintain a healthy reproductive environment.

Overgrowth Of Antibiotic-Resistant Pathogens

Antibiotic use can foster the overgrowth of antibiotic-resistant pathogens in the reproductive tract. These resistant bacteria are difficult to eliminate with standard treatments, leading to chronic infections that impair fertility [18, 42]. The presence of resistant pathogens in the uterus or ovaries can result in uterine infections, endometritis, and compromised embryo development, ultimately reducing reproductive success.

Altered Vaginal Ph Levels

Antibiotics can alter the vaginal pH, disrupting the normal acidic environment that is essential for maintaining a healthy microbiota [58, 59]. A more alkaline vaginal pH promotes the growth of pathogenic bacteria, which increases the risk of infections such as bacterial vaginosis. This alteration in vaginal pH can negatively affect fertility, embryo development, and overall reproductive health in dairy cows.

Increased Risk of Opportunistic Infections

Antibiotic use suppresses beneficial microbes, allowing opportunistic pathogens to proliferate within the reproductive tract. These pathogens, such as fungi and bacteria, can cause infections that damage reproductive organs and impair fertility [18, 42]. Opportunistic infections increase the risk of uterine inflammation, altered uterine microbiota, and decreased embryo viability, further reducing reproductive efficiency in dairy cows.

Disrupted Microbial-Host Interactions

The use of antibiotics disrupts the interactions between the reproductive tract microbiota and the host, interfering with immune responses and homeostasis. This disruption can impair the body’s ability to detect and respond to harmful pathogens, leaving the reproductive organs vulnerable to infections [18, 42, 51, 60, 61]. It also affects the microbial regulation of local immunity, further reducing the capacity for successful reproduction.

Suppressed Protective Microbiota Functions

Antibiotic use suppresses the protective functions of the microbiota, which are vital for maintaining reproductive health. The beneficial bacteria help to prevent pathogen colonization, regulate inflammation, and support tissue repair [18, 42, 51, 61]. When antibiotics kill these protective microbes, it weakens the natural defense mechanisms of the reproductive tract, increasing the likelihood of infections, inflammation, and fertility issues in dairy cows.

Increased Prevalence of Dysbiosis

Dysbiosis, an imbalance in microbial communities, is a common consequence of prolonged antibiotic use in the reproductive tract [47, 60, 62]. This imbalance allows pathogenic microorganisms to proliferate, leading to infections and disturbances in the uterine environment. Dysbiosis disrupts normal immune function and decreases fertility by altering the vaginal and uterine microbiota, thus contributing to infertility and reproductive inefficiencies.

Altered Microbial Metabolites Affecting Reproduction

Antibiotic-induced disruptions in the reproductive tract microbiota can lead to the production of altered microbial metabolites, which can negatively impact reproductive health [18, 42, 51, 61]. Changes in the metabolites can interfere with hormone regulation, immune responses, and tissue function. These alterations can compromise oocyte maturation, embryo development, and uterine receptivity, ultimately impairing fertility and reproductive outcomes in dairy cows.

Reduced Microbial-Mediated Immune Defense

The beneficial microbiota in the reproductive tract plays a crucial role in enhancing the immune defense by stimulating immune cells and producing antimicrobial peptides. Antibiotics reduce the abundance of these protective microbes, weakening the local immune defense [18, 42, 51, 61]. As a result, the reproductive system becomes more susceptible to infections, inflammation, and reduced fertility, ultimately compromising reproductive success in dairy cows.

Chronic Reproductive Tract Infections

Prolonged antibiotic use can lead to chronic reproductive tract infections due to the suppression of protective microbiota and the overgrowth of pathogenic organisms [18, 42, 51, 60, 61]. These infections, such as chronic endometritis, persist over time and disrupt reproductive function. Chronic infections impair fertility by causing inflammation, scarring of reproductive tissues, and altered hormonal regulation, resulting in prolonged calving intervals and reduced productivity.

RESIDUAL EFFECTS ON OFFSPRING

Altered Fetal Development

Prolonged antibiotic use during pregnancy can affect fetal development by disrupting placental function and nutrient transfer [45–47, 63]. These disturbances lead to impaired organogenesis and altered development of the fetus, potentially causing long-term health issues for the offspring. The lack of appropriate fetal growth can also lead to premature births or underdeveloped calves, negatively impacting their health and productivity.

Increased Risk of Congenital Abnormalities

Antibiotic exposure during pregnancy increases the risk of congenital abnormalities in offspring [45–47, 63]. The disruption of normal fetal development, caused by antibiotics, can lead to malformations, such as deformities in the limbs, organs, and skeletal structure. These abnormalities decrease the survival rate of calves and may result in long-term health complications, affecting their overall growth and productivity.

Suppressed Immune Development in Utero

Antibiotics used during pregnancy may suppress the immune development of the fetus. The disruption of maternal microbiota affects the transfer of immune cells and antibodies to the fetus, impairing its ability to develop a robust immune system [45–47, 63]. This suppressed immune response increases the calf's susceptibility to infections and diseases post-birth, reducing overall calf health and survival rates.

Reduced Birth Weight of Calves

Antibiotic use during pregnancy can reduce the birth weight of calves by affecting placental function and nutrient delivery to the fetus. Lower birth weight is associated with a higher risk of neonatal health complications, such as respiratory issues, weakened immune systems, and poor postnatal growth [45–47]. Reduced birth weight also affects the long-term development of the calves, hindering their future productivity.

Altered Postnatal Growth Patterns

The use of antibiotics during pregnancy can alter postnatal growth patterns in calves by influencing early growth and development. Antibiotic exposure affects gut microbiota, digestion, and nutrient absorption, which are essential for proper growth [45–47], 63]. This disruption can lead to stunted growth, poor muscle development, and a higher risk of metabolic disorders, resulting in lower productivity throughout the life of the calf.

Impaired Neonatal Immune Responses

Antibiotic exposure during pregnancy impairs the neonatal immune response by disrupting the transmission of maternal antibodies and immune factors through colostrum. This weakened immune system leaves the calf vulnerable to infections in the early stages of life, affecting its health, growth, and ability to thrive [45–47]. Impaired immunity also increases the cost of veterinary care and decreases overall survival rates.

Increased Susceptibility to Diseases in Calves

Calves born to mothers treated with antibiotics during pregnancy have an increased susceptibility to infectious diseases. Disrupted microbiota and a weakened immune system reduce their ability to resist pathogens and recover from illnesses [45–47, 63]. This heightened vulnerability leads to frequent health issues in the early stages of life, affecting growth and development, and potentially reducing their lifetime productivity and fertility.

Delayed Sexual Maturity of Offspring

Antibiotic exposure during gestation can delay the sexual maturity of offspring. The disruption of hormone production and the microbiota-gut-endocrine axis interferes with the normal maturation of reproductive organs [45–47]. As a result, calves may reach puberty later than expected, which delays their first breeding and reduces their lifetime reproductive efficiency, impacting herd productivity and profitability.

Impaired Maternal Bond Formation

Antibiotic use in dairy cows can impair the formation of maternal bonds with their offspring. Disruptions in hormonal signaling, such as reduced oxytocin levels, hinder maternal behavior, including bonding, nursing, and care [45–47, 63]. This impairs the calf's early development, reducing its chances of thriving and affecting the long-term health and productivity of both the mother and offspring.

Altered Milk Composition for Neonates

Antibiotic use during lactation can alter the composition of milk, affecting the transfer of essential nutrients, antibodies, and growth factors to the neonate [45–47]. This alteration in milk quality compromises the nutritional status of the calf, weakening its immune system and impairing growth.

Calves may be at a higher risk for infections, poor development, and lower survival rates, resulting in long-term consequences for their health and productivity.

ECONOMIC AND MANAGEMENT REPERCUSSIONS

Reduced Conception Rates

Prolonged antibiotic use negatively affects reproductive health in dairy cows, leading to reduced conception rates [1, 24, 64]. Disruptions in hormonal regulation, follicular development, and uterine health hinder successful fertilization and implantation. This results in lower pregnancy rates and repeated insemination attempts, increasing the cost of breeding programs and reducing overall reproductive efficiency in dairy farming.

Increased Need for Artificial Insemination

The reproductive challenges caused by antibiotic use increase the need for artificial insemination (AI) in dairy herds. Poor fertility and delayed ovulation necessitate more frequent use of AI to achieve pregnancy [1, 24, 64]. This reliance on artificial insemination increases labor costs, veterinary intervention, and the cost of semen, ultimately driving up the expenses of breeding and lowering the profitability of dairy operations.

Prolonged Calving Intervals

Antibiotic use contributes to prolonged calving intervals by delaying the return to estrus and suppressing normal reproductive processes [1, 24, 64]. Longer intervals between calving reduce the number of calves born each year, which directly impacts milk production and farm income. This extended calving interval also reduces herd replacement rates, leading to fewer productive cows over time, further affecting the farm’s profitability.

Increased Culling of Infertile Cows

Prolonged antibiotic exposure can result in infertility or reproductive disorders in dairy cows, necessitating early culling. As cows that fail to conceive are removed from the herd, the farm incurs additional costs associated with animal replacement [1, 24, 64]. Culling infertile cows not only reduces herd size but also disrupts herd genetics and lowers overall productivity, resulting in financial losses.

Reduced Herd Productivity

Antibiotic-induced reproductive challenges result in decreased herd productivity due to lower pregnancy rates, longer calving intervals, and compromised milk production. Infertility and reproductive health issues mean that fewer cows are in peak lactation at any given time, reducing overall milk output [1, 24, 64]. This lower milk yield translates to reduced farm income and diminished returns on investments in animal care and breeding.

Higher Veterinary Intervention Costs

The reproductive challenges caused by prolonged antibiotic use in dairy cows lead to increased veterinary intervention costs. From diagnostic procedures to treating reproductive infections, hormonal imbalances, and fertility treatments, the need for professional veterinary services rises significantly [1, 24, 64]. These additional costs strain the farm's budget and reduce overall profitability, making it less sustainable in the long run.

Reduced Profitability of Dairy Farming

The compounded effects of reproductive health problems caused by antibiotic use result in reduced profitability for dairy farms [1, 24, 64]. Lower conception rates, prolonged calving intervals, increased veterinary costs, and the need for additional insemination efforts all contribute to a decrease in milk production and the efficiency of the operation. This reduces the farm’s income, making it harder to maintain financial stability.

Increased Antibiotic Residues in Dairy Products

Prolonged antibiotic use in dairy cows can lead to the accumulation of antibiotic residues in milk. These residues can negatively impact milk quality and safety, leading to product recalls, penalties, or market rejection. The presence of residues also raises concerns regarding consumer health and regulatory compliance, potentially harming the reputation and financial viability of the dairy farm.

Reduced Market Value of Affected Cows

Cows that experience reproductive issues due to antibiotic exposure may have a lower market value. Infertile or subfertile cows are less desirable for breeding purposes, reducing their resale potential [1, 24, 64]. Farms may face lower prices for these animals, leading to financial losses when they attempt to sell or replace their affected cows, ultimately reducing the value of their herd.

Compromised Farm Sustainability

The long-term consequences of antibiotic-induced reproductive challenges compromise the sustainability of dairy farming operations. As fertility declines, herd turnover increases, and veterinary intervention costs rise, the ability to maintain a profitable and efficient farm is threatened [1, 24, 64, 65]. These challenges, compounded by potential antibiotic resistance and increased consumer demand for antibiotic-free products, may drive farmers to adopt unsustainable practices, endangering the future viability of dairy farming.

ANTIBIOTIC RESISTANCE AND LONG-TERM IMPACT

Development of Multidrug-Resistant Pathogens

Prolonged antibiotic use in dairy cows contributes to the development of multidrug-resistant pathogens. Overuse and misuse of antibiotics encourage the evolution of resistant bacterial strains, making infections more difficult to treat [3–8, 66]. These resistant pathogens pose a significant threat to both animal and human health, potentially leading to more severe outbreaks and increased veterinary treatment costs.

Reduced Efficacy of Future Treatments

As antibiotic resistance develops, the effectiveness of current and future treatments for reproductive and other infections diminishes [4–8, 66]. This reduced efficacy of antibiotics limits treatment options for dairy cows suffering from reproductive health issues and other infections, leading to prolonged illness and potential complications. In turn, this undermines the overall health management on dairy farms, impacting productivity.

Altered Response to Reproductive Therapies

The emergence of antibiotic-resistant bacteria may alter the response of dairy cows to reproductive therapies, such as hormone treatments and artificial insemination. Resistance to antibiotics can result in persistent infections or ineffective treatment outcomes, complicating efforts to manage fertility and reproductive health [5–8, 66]. This leads to increased veterinary costs, prolonged recovery periods, and decreased reproductive efficiency.

Increased Prevalence of Untreatable Infections

Antibiotic resistance can result in untreatable infections in dairy cows, particularly in the reproductive tract. These infections may become chronic and exacerbate fertility issues, leading to significant economic losses due to decreased milk production and the need for herd culling [6–8, 66]. The inability to treat infections effectively increases the risk of long-term reproductive problems and reduced herd health.

Greater Reliance on Alternative Treatments

The development of antibiotic resistance forces dairy farmers to rely more heavily on alternative treatments, such as probiotics, herbal remedies, or immunomodulators [6–8, 66]. While these alternatives may offer some benefits, they often come with higher costs, less proven efficacy, and potential challenges in ensuring the health and productivity of the herd. This reliance on alternatives complicates herd management and reduces farm profitability.

Risk of Zoonotic Pathogen Transmission

Antibiotic resistance in dairy cows can increase the risk of zoonotic pathogen transmission to humans. Resistant pathogens, transmitted through contaminated milk or direct contact with animals, pose a significant public health risk [6–8, 66]. This exacerbates concerns about food safety, raising potential risks for consumers and increasing regulatory scrutiny on the dairy industry.

Long-Term Damage to Farm Biosecurity

Antibiotic resistance contributes to long-term damage to farm biosecurity. Resistant pathogens may spread across farms, complicating efforts to prevent the spread of disease. The increased difficulty in controlling infections results in higher rates of disease transmission, affecting herd health, productivity, and overall farm biosecurity [6–8, 66]. This ongoing issue weakens the ability to maintain healthy, productive herds and secure farm environments.

Reduced Public Trust in Dairy Products

The emergence of antibiotic resistance and concerns over antibiotic residues in dairy products can lead to reduced public trust in the safety of dairy products. Consumers are becoming increasingly aware of the potential health risks associated with antibiotic use in food production [6, 8, 66]. This diminished trust may result in reduced demand for dairy products, affecting the profitability and reputation of the dairy industry.

Negative Implications for Food Safety

Antibiotic resistance has negative implications for food safety, as resistant pathogens can contaminate milk and other dairy products [6–8, 66]. These pathogens can be transmitted to humans through consumption, leading to foodborne illnesses that are difficult to treat. The rise of antibiotic-resistant bacteria in the dairy industry complicates efforts to ensure the safety and quality of dairy products, posing a significant challenge to public health.

Compromised Global Dairy Trade Standards

Antibiotic resistance poses a threat to global dairy trade standards. Many countries have strict regulations on antibiotic residues in milk, and the development of antibiotic-resistant pathogens in dairy cows can lead to trade restrictions or export bans [6, 8, 66]. This compromises the ability to access international markets, leading to financial losses for dairy producers and potentially affecting global dairy supply chains.

CONCLUSION

Prolonged antibiotic use in dairy farming poses significant challenges to reproductive performance by disrupting ovarian function, altering uterine microbiota, and compromising embryo viability. Hormonal imbalances induced by antibiotics can impair estrous cyclicity and follicular development, leading to reduced fertility. Additionally, antibiotic-induced dysbiosis in the reproductive tract increases the risk of uterine infections, negatively impacting conception rates and pregnancy maintenance. The persistence of antibiotic residues and antimicrobial resistance further complicates fertility management in dairy herds. Addressing these concerns requires precision antibiotic use, alternative therapeutic approaches, and microbiome-targeted interventions. Future research should focus on sustainable fertility management strategies to mitigate antibiotic-associated reproductive decline, ensuring optimal productivity and long-term sustainability in dairy farming systems.

Future Directions

Future research should focus on identifying alternative therapeutic strategies that minimize antibiotic dependence while preserving reproductive health in dairy cows. Probiotics, prebiotics, and phytogenic compounds hold promise in modulating reproductive microbiota and enhancing uterine immunity.

Advanced molecular techniques should be utilized to investigate antibiotic-induced alterations in reproductive gene expression and hormonal pathways. Studies exploring the long-term effects of antibiotic residues on fetal development and postnatal growth are also warranted. Additionally, precision livestock farming tools, such as biomarkers and biosensors, should be developed to monitor reproductive health and guide targeted antibiotic interventions. Expanding knowledge on antimicrobial resistance in reproductive pathogens will be essential for designing sustainable treatment protocols. Collaborative efforts between veterinarians, microbiologists, and nutritionists are needed to integrate microbiome-based interventions into fertility management programs. Strengthening regulatory frameworks to optimize antibiotic stewardship will further support sustainable reproductive performance in dairy farming systems.

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