In the ovaries of cows referred to the third group are also follicles at different developmental stages: primary and secondary. But big changes are experiencing secondary follicles. In some follicles follicular vesicular layer is separated from the inner folder cell forms multiple folds that fill the lumen of the follicle. Observed deformed follicles, and such clearance which is completely filled with follicular cells.

Occasionally there are follicles in which follicular layer was subjected to destruction and necrotic follicular cells are separated from the follicular layer and mixed into the follicular fluid that is experiencing deep destructive changes. In the upper layers of the cortex are located a significant number of atresial yellow bodies of different sizes of round or oval shape.

The medulla of the ovary occupies a small area compared to the cut-off area, and is represented by a network of vessels of all sizes, dispersed in the stroma of the organ.

Key words: ovaries, gistostruktura, sexual cycle, follicles, corpora lutea.

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POSTPARTUM UTERINE DISEASES IN DAIRY COWS

Післяпологові захворювання матки, включаючи неспецифічні маткові інфекції, знижують репродуктивну здатність молочних корів. Їх діагностують і лікують у 55 % корів після пологів. Як правило, інфекції матки призводять до економічних втрат через збільшення витрат на ветеринарний догляд, зниження молочної продуктивності, порушення репродуктивних функцій і вибракування хворих корів. Клінічно захворювання матки характеризуються гнійними виділеннями з піхви, які зазвичай асоціюються з інфікуванням *Escherichia coli* і *Trueperella pyogenes*. Субклінічне захворювання матки асоціюється зі збільшенням числа запальних клітин з або без виявлення патогенних бактерій в матці. Порушення репродуктивної функції опосередковується бактеріальними продуктами обміну речовин (ліпополісахариди, ендотоксини) або запальними медіаторами, які порушують функції сперматозоїдів, яєчників, матки і ембріонів. Методи лікування повинні бути спрямовані на усунення патогенних бактерій в матці, при цьому не порушуючи власних захисних бар'єрів корови в матці. Проте, пропоновані варіанти лікування часто суперечливі. Цей огляд включає критерії для діагностики та класифікації маткових інфекцій у корів, вибору ліків і режимів їх дозування. Також обговорюється проблема стійкості мікробів до протимікробних препаратів та утворення біоплівки. Крім того, з'ясовується роль мікроРНК і її зв'язок з перерванням тільності у корів з патологіями матки.

Ключові слова: захворювання матки, молочна корова, розмноження, інфекції *Escherichia coli* і *Trueperella pyogenes.*

Introduction. The extent of postpartum reproductive diseases in dairy cow includes retained fetal membranes, acute puerperal metritis, clinical endometritis, subclinical endometritis and pyometra. Although, literature suffers from the lack of a reliable definition for uterine diseases, there is agreement that these conditions affect reproductive performances [1−3]. Consistent findings are that uterine disease reduces overall risk of pregnancy, reducing first service conception, prolonging calving interval and increasing risk of involuntary culling. Metritis affects about 20 % of lactating dairy cows, with the incidence ranging from 8 to 40 % in some farms [4−6]. Clinical endometritis affects about 20.0 % of lactating dairy cows, with the prevalence ranging from 5.0 to>30 % in some herds [2, 7]. Subclinical endometritis is the most prevalent of all uterine diseases; it affects approximately 30% of lactating dairy cows, with the prevalence ranging from 11 % to 70 % [3, 5, 8, 9]. The major risk factors for uterine disease are dystocia, twinning including retained placenta. Retained placenta and metritis complex doubles the risk of cows remaining with uterine inflammation at the time of first postpartum insemination [10].

Dominant uterine pathogens. Most pertinent uterine pathogens are *E. coli and T. pyogenes*. A high occurrences of opportunistic pathogens α-hemolytic *Streptococcus* and coagulase-negative *Staphylococcus* (CNS) are also observed. Bacterial species that cause uterine inflammation [11−13]

were classified according to their expected pathogenic potential: a) uterine pathogens associated with uterine lesions (*E. coli, T. pyogenes, Fusobacterium necrophorum, and Prevotella melaninogenica*); b) pathogens frequently isolated from the uterine lumen in cases of inflammatory condition, but not commonly associated with uterine lesions; and c) opportunistic contaminants transiently isolated from the uterine lumen and not associated with uterine lesion.

Although *E. coli* is widespread in the environment, specific *E. coli* strains from cows with uterine disease have been isolated [14]. These endometrial pathogenic *E. coli* have been shown to be more adherent and invasive for endometrial epithelial and stromal cells compared with *E. coli* isolated from the uterus of clinically normal animals [14]. It should be noted that these uteropathogenic strain could be entero- or uro-pathogenic.

The composition of uterine microbiota changes substantially at different stage of postpartum period. However, animals infected with *E. coli* or *T. pyogenes* at 10 days after calving (10 days in milk (DIM)) had an increased risk for an infection with the same bacterial species at 24 DIM (*E. coli* relative risk (RR)=3.7 and *T. pyogenes* RR=2.9). Moreover, the risk of being diagnosed with abnormal vaginal discharge at 24 DIM increased in cows with *E. coli* (RR=1.7) or *T. pyogenes* (RR=1.7) at 10 DIM [15].

Association of bovine herpes virus- 4 (BoHV-4) in cows with metritis has also been documented [16, 17]. Monge et al. [16] observed BoHV-4 in 83 % of 12 cases studied and Nak et al., [17] reported that 23 % of the cases studied were positive for BoHV-4.

Definition of uterine disease. The authors rely on generally accepted definition of uterine diseases that goes as follows. Metritis – animal with an abnormally enlarged uterus and fetid vaginal discharge, associated with signs of systemic illness (decreased milk yield, dullness or other signs of toxemia) and fever >39.5 ºC within 14 days postpartum.

Clinical endometritis – presence of mucopurulent or purulent discharge in vagina after 3 and 4 weeks, respectively, from calving. A grading system based on the nature of vaginal discharge is developed to evaluate cows. (Score 1=a few flecks of purulent material; Score 2=mucopurulent material but <50 % purulent material; Score 3=mucopurulent material with >50 % purulent material).

Subclinical endometritis – presence of polymorphonuclear neutrophils exceeding from 6 to 18 % in samples collected by uterine lavage or cytobrush methods.

Effect of uterine disease on fertility. It delays resumption of ovarian cyclicity after calving. It delays time interval from calving to first service (days to first service). It delays interval from calving to conception. It increases voluntary culling.

Lipopolysaccharides (LPS) from *E. coli* impair the function of the hypothalamus-pituitary-ovarian axis. It directly perturbs ovarian granulosa cells steroidogenesis, providing machineries to explain the association between uterine disease and anovulatory anestrus [18]. Once *E. coli* infection is established and LPS is recognized by uterine endometrial and stromal cells, the prostaglandin production by stromal cells is modulated and this in turn may affect luteal phase length. At the ovary, theca cells produce androstenedione, which is aromatized to estradiol by granulose cells. These cells can recognize LPS following which expression of aromatase enzyme is down-regulated and less estradiol is produced [18]. Cows with uterine disease that ovulate have lower peripheral plasma progesterone concentrations that may further reduce the chance of conception associated with endometritis. The presence of LPS in the peripheral circulation also disrupts LH production and release, which may have additional effects on ovarian theca and granulosa cells. Together, these observations may explain the infertility in cattle associated with uterine infection.

An impaired uterine environment is likely to be one of the primary problem of repeat breeder cows [19], which show a high incidence of embryonic death at Day 6 following fertilization (i.e. shortly after entry of the embryo into the uterus) and the increased rate of pregnancy loss continues up until day 19 [20]. Embryos derived from normal cows fail to survive when transferred into the uterus of repeat breeders, whereas embryos derived from repeat breeders showed normal survival rates following transfer into normal cows [21], a result that indicates poor embryo quality is related to a suboptimal uterine environment.

Uterine embryo interaction. Luminal portions of the female reproductive tract during the estrous cycle and pregnancy provide a well-synchronized environment for final maturation of

gametes, fertilization, and embryonic and fetal development. In cattle, there is an extended interval of elongation (after blastocyst hatching) of embryo, followed by opposition, attachment, and adhesion of the trophectoderm to the uterine luminal epithelium. The uterine endometrium is a complex tissue, consisting of luminal epithelial cells, superficial and deep glandular epithelial cells, and fibroblast-like stromal cells. These cell types have key roles (via endometrial secretions) in orchestrating elongation.

In addition, alterations to the endometrium are required to establish uterine receptivity to embryo attachment. Because most embryonic loss occurs during the preattachment period, these changes at that period are probably vital to the likelihood of establishing successful pregnancy in cattle. The endometrium is the maternal interface for embryo-maternal communication, which is essential to maintain pregnancy. Endometrial polymorphonuclear neutrophil infiltration is an indicator of uterine disease, and is associated with changes in endometrial gene expression patterns, including genes involved in cell adhesion and immune modulation. Consequently, uterine disease might affect the gene expression in embryos, including expression of genes related to membrane stability, the cell cycle and apoptosis.

Our study indicated that expressions of MUC1 and cytokines genes were significantly different between the endometrium of normal, fertile versus diseased, subfertile dairy cows [22, 23]. We concluded that these altered gene expressions contributed to endometrial inadequacy and consequently to pregnancy wastage. Mucin (MUC) 1 is an inducible innate immune effector and an important component of the first line of defense against bacterial invasion of epithelial surfaces [24]. Expression of MUC1is detected in bovine endometrial epithelial cells and LPS increased the mRNA expression of MUC1 [25]. Functions of MUC1 include cell adhesion, lubrication of epithelial surfaces, and protection from infection, depending on its subunit [26, 27]. Because MUC1 inhibits cell–cell adhesion [28−30], expression of MUC1 in endometrial epithelium has been suggested to create a barrier to embryo attachment that must be suppressed during implantation [29, 30]. Higher MUC1 expression cause embryonic death by preventing or delaying embryonic attachment in these subfertile cows with uterine disease [23].

MiRNA regulation in cows with metritis. MicroRNAs (miRNAs) are naturally occurring small non-coding RNA molecules, approximately 21–25 nucleotides in length. MicroRNAs are partially complementary to one or more messenger RNA (mRNA) molecules, and their main function is to down-regulate gene expression in a variety of manners, including translational repression, mRNA cleavage, and deadenylation. Aberrant miRNA expression is associated with many diseases. In human, abnormal expression of miRNAs has been observed in multiple human reproductive tract diseases including endometriosis and recurrent pregnancy loss.

We identified differential abundance of 34 circulating miRNAs in cows with metritis compared to normal cows. Of those 18 were up-regulated and 16 were down-regulated. Specifically several miRNA families were down-regulated including bta-let-7f, bta-miR-10a, bta-miR-127 and bta-miR-148b-3p and several were up-regulated including bta-let-7a-5p, bta-miR-101, bta-miR-142-3p, bta-miR-150, bta-miR-16b, bta-miR-181a, bta-miR-191, bta-miR-192, bta-miR-21-5p, bta-miR-24-3p, bta-miR-25, bta-miR-26b, bta-miR-30d and bta-miR-30e-5p in cows with metritis compared to normal cows ($P<0.01$) [31]. A considerable number of miRNAs predicted to inhibit the expression of genes functioning as proinflammatory and immune-related response, angiogenesis, cell-cycle progression, and adhesion molecules have been proven to be differently expressed in cows with metritis. In most of the cases, the level of expression of these miRNAs is decreased in cows with metritis compared to those without metritis. The presence of distinct miRNA profiles between inflamed and normal endometrium indicates that miRNA may have a function in the pathophysiology of endometritis which could be used for diagnosis and treatment.

Interestingly, let-7, miR-29, -30, -31, -193A-3p, and -210 have been associated with cell participating in the control of cellular pluripotency, proliferation, and differentiation. Also, let-7, miR-122, -127, -181were implicated in differential expression in placenta of different sources of pregnancy. These differences indicate that these miRNA are transcriptionally not reprogrammed correctly. These aberrant miRNA activities might be associated with genetic and epigenetic modifications in abnormal placentogenesis due to maldifferentiation of early trophoblast cell lineage which may contribute to pregnancy wastage.

Biofilm formation and drug resistance. Reckless use of antibiotics and/or development of biofilm are the rationale for the development of multidrug resistance (MDR) of pathogenic bacteria. We observed 35 % of *T. pyogenes* isolates found were positive for a gene cassette associated with antibiotic resistance against sulfadiazine, bacitracin, florfenicol, ceftiofur, penicillin, clindamycin and erythromycin, and 33 % of the *E. coli* isolates contained genes for the virulence factor associated with biofilm production [32]. Antibiotic resistance and biofilm formation may contribute to treatment failures.

Treatment. It should be noted that the efficacy and benefit of treatments varies considerably among studies. Even though there are different options that are available to clinicians, research results from last 5 decades were inconsistent. Since, antibiotic resistance and biofilm formation may contribute to treatment failures treatment should include consideration of antimicrobial resistance of pertinent uterine pathogens and biofilm formation in persistent cases. Currently available treatment options for metritis include: Ceftiofur hydrochloride 2.2 mg/kg intramuscularly for 5 days; fluid therapy; calcium therapy; uterine lavage with clean water. For clinical and subclinical endometritis: administration of luteolytic dose of Prostaglandin GF2α (intramuscular) particularly where a corpus luteum is present on the ovary of the affected cow. Repeat the treatment every 2 weeks; intrauterine infusion of 200 mL of 50 % dextrose (Pregnancy/artificial insemination (P/AI)=29.8±4 %) is advantageous over control (P/AI=21.1±4 %); intrauterine infusion of platelet concentrate 15 to 50 mL.

Conclusions. Uterine diseases are highly prevalent in high-producing dairy cows. It requires precise diagnosis and timely treatment. A wide variety of treatment modalities for postpartum uterine diseases have been studied, including antibiotics and hormones. The effectiveness of the antibiotics and the administration of PGF2α varied among the studies. Clinicians should consider alternative treatment modalities.

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Послеродовые заболевания матки у молочных коров

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Послеродовые заболевания матки, включая неспецифические маточные инфекции, снижают репродуктивную эффективность молочных коров. Их диагностируют и лечат у 55 % коров после родов. Как правило, инфекции матки приводят к экономическим потерям из-за увеличения расходов на ветеринарный уход, снижения молочной продуктивности, нарушения репродуктивных функций и отбраковке больных коров. Клинически заболевания матки характеризуются гнойными выделениями из влагалища, которые обычно ассоциируются с инфицированием *Escherichia coli* и *Trueperella pyogenes*. Субклиническое заболевание матки асоциируется с увеличением числа воспалительных клеток с или без патогенных бактерий в матке. Нарушение репродуктивной функции опосредуется бактериальными продуктами обмена веществ (липополисахаридом, эндотоксином) или воспалительными медиаторами, которые нарушают функции сперматозоидов, яичников, матки и эмбрионов. Методы лечения должны быть направлены на устранение патогенных бактерий из матки, при этом не нарушая в матке собственных защитных барьеров коровы. Тем не менее, предлагаемые варианты лечения часто противоречивы. Этот обзор включает критерии для диагностики и классификации маточных инфекций у коров, выбора лекарств и режимов их дозирования. Также обсуждается проблема устойчивости инфекта к противомикробным препаратам и образования биопленки. Кроме того, выясняется роль микроРНК и ее связь с прерыванием беременности у коров с патологиями матки.

Ключевые слова: заболевания матки, молочная корова, размножение, инфекции *Escherichia coli* и *Trueperella pyogenes*.

Postpartum uterine diseases in dairy cows

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Postpartum uterine diseases, including nonspecific uterine infections, reduce the reproductive efficiency of dairy cows. Up to 55 % of the postpartum cows are diagnosed with, and treated for, uterine infections. Generally, uterine infections cause economic losses due to increased veterinary care costs, deceased milk production and reproductive efficiency, and culling of the affected cows. Clinical uterine disease is characterized by purulent uterine discharge commonly associated with *Escherichia coli* and *Trueperella pyogenes* infections. Subclinical uterine disease is associated with increased number of

inflammatory cells with or without pathogenic bacteria in the uterus. Impaired reproductive efficiency is mediated by bacterial products (lipopolysaccharide, endotoxin) or via inflammatory mediators that disturb sperm, ovarian, uterine and embryo functions. Treatment modalities are aimed at eliminating pathogenic bacteria from the uterus without inhibiting cow's uterine defense. However, treatment options are often controversial. This review includes criteria for diagnosis, different diagnostic groupings employed to classify uterine infections, choice of drugs and dosing regimens, and antimicrobial resistance and biofilm formation. Further, circulating microRNA dynamics and its association with pregnancy wastage in cows with uterine disease has been discussed.

Key words: uterine diseases, dairy cow, reproduction, *Escherichia coli* and *Trueperella pyogenes* infections.

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ВПЛИВ ПРОБІОТИЧНОГО ЗАХИСТУ СЛИЗОВИХ НА ФУНКЦІЮ ЯЄЧНИКІВ ЛАКТУЮЧИХ КОРІВ

Наведені результати моніторингового дослідження впливу на статеву функцію корів згодовування кормового пробіотичного препарату Агробіобак. Достовірно встановлено, що у корів після закінчення процесу нормофлоризації слизових травного тракту (через 22 дні після початку внесення культур лакто- і біфідобактерій в монокорм), спостерігалось суттєве (в 7 разів) зменшення прояву кістозності гонад порівняно з контролем (без пробіотичного захисту). У дослідних корів відмічено покращення морфофункціонального стану яєчників: у 56% самиць пальпаторно (in vivo) встановлено наявність функціональних жовтих тіл циклу і передовуляторних фолікулів (в контролі – 34 %). В досліді згодовування живих пробіотичних культур в складі раціону не тільки покращило транзит кормів, який знизився до 17 % (в контролі – 36 %), але й дало додатковий біологічно-виробничий ефект оптимізації відтворної функції лактуючих корів.

Ключові слова: корови, яєчники, фолікулярні кісти, полікістоз, пробіотичні культури, *Lactobacillus acidophilus, Bifidobacterium bifidum*, нормофлоризація, транзит кормів.

Постановка проблеми. Впровадження в країнах з розвинутим скотарством промислових технологій виробництва молока призвело до того, що дійні корови утримуються в штучно створеному середовищі, де постійно піддаються дії техногенних стресів. Такі умови експлуатації корів стають чинниками зниження їх природної резистентності, що погіршує здоров'я тварин та негативно впливає на продуктивність і фертильність. У зв'язку з цим лактуючі корови стають дуже вразливими до впливу патогенних і умовно-патогенних асоціацій мікроорганізмів, для інтенсивного розмноження яких умови промислових комплексів з високою концентрацією поголів'я дуже сприятливі.

На значну поширеність змішаних інфекцій (десятки збудників вірусної і бактерійної природи, що формують штучний паратрофний мікробіоценоз промислових тваринницьких приміщень) вказували численні дослідження останніх років [3, 5, 8, 12, 14]. Вирішальною для економіки тваринництва є правильна стратегія зооветеринарних заходів за паразитоценозів: профілактика має бути спрямована на обмеження можливості поповнення числа патогенів новими співчленами і недопущення посилення їх вірулентності.

Аналіз останніх досліджень і публікацій. Серед адекватних засобів наразі набули значної актуальності пробіотики, які на основі антагоністичних властивостей щодо патогенних мікробів зберігають стабільність мікрофлори шкіри, слизових та макроорганізму в цілому і, у випадках дисбіозу, відновлюють нормофлору [1, 2, 3, 12]. Важливим поштовхом для застосування пробіотиків стали вимоги світового агроринку щодо обмеження використання антибіотиків у тваринництві [14, 15].

Біотерапевтичний ефект пробіотиків (представників нормофлори) може бути пов'язаний з прямим антагоністичним впливом на патогенні і умовно-патогенні мікроби, що зменшує їх кількість, а також впливом на метаболізм тварин і появу специфічних антитіл та стимуляцію імунітету [1, 2, 3, 10]. Основна мета їх застосування – утворення метаболічно активної популяції