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ВЕСТНИК

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NAS RK is pleased to announce that Bulletin of NAS RK scientific journal has been accepted for indexing in the Emerging Sources Citation Index, a new edition of Web of Science. Content in this index is under consideration by Clarivate Analytics to be accepted in the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index. The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of Bulletin of NAS RK in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential multidiscipline content to our community.

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НАН РК сообщает, что научный журнал «Вестник НАН РК» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Вестника НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному мультидисциплинарному контенту для нашего сообщества.

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PATHOPHYSIOLOGICAL ASPECTS OF GOAT FALSE PREGNANCY (HYDROMETRA) AND MODERN METHODS OF ITS DIAGNOSIS AND THERAPY

Abstract. The article considers the unique, not described in the domestic scientific and educational literature, the dishormonal pathology of the reproductive sphere of goats. The disease is characterized by prolonged anaphrodisia, the persistence of one or more functionally active corpus luteum in the ovaries and hydrometra - volumetric increase in the size of the uterus due to effusion of sterile serous fluid into its cavity. Hydrometra is a leading diagnostic sign of the disease. The research aimed to analyze the data of foreign literature on epidemiology, pathophysiology, diagnostics, and therapy of false pregnancy (hydrometra) in goats.

Based on the analysis of foreign literature data, the epidemiological characteristics of the disease were determined. It was found that the hydrometra is a fairly common pathology and is recorded on average in 4.2% of goats. The risk group includes goats aged 6...8 years and older. A hereditary (familial) predisposition of milk goats to the development of hydrometra was revealed. Iatrogenic factors also have a significant effect on the frequency of incidence: hormonal treatment of goats during and/or out the estrous season with progestins alone or in combination with gonadotropin in the serum of mares.

The etiology of pseudopregnancy, as well as the cause-effect relationship between the persistence of the corpus luteum and the development of hydrometra have not been fully established. Retention of the corpus luteum always precedes and accompanies the development of hydrometra. Spontaneous regression of the persistent corpus luteum leads to interruption of pseudopregnancy and emptying of hydrometra.

Violation of the external regulation with prostaglandin of the functional activity of the corpus luteum, apparently, plays a pivotal role in the pathogenesis of the disease. According to the profile of progesterone in the blood, it was found that the duration of false pregnancy is an average of 150.3 ± 23.5 days.

Visual echography is the main diagnostic method of false pregnancy. The diagnosis of the disease is based on the detection of hypoechoic fluid in the uterine cavity in the absence of placentas and fetuses in the uterus.

Prostaglandin therapy is a pathogenetically substantiated and quite effective method of treating hydrometra.

Key words: goats, pseudopregnancy, persistent corpus luteum, hydrometra, treatment.

False pregnancy (hydrometra) is a rather common dishormonal pathology and cause of infertility in goats.

This disease is characterized by prolonged anaphrodisia, the persistence of one or more functionally active corpus luteum in the ovaries and a volume increase in the size of the uterus due to transudation (effusion) into its cavity of a sterile serous liquid (hydrometra).

In sheep and goats, the hydrometra is the main clinical and sonographic manifestation and the leading diagnostic sign of false pregnancy. In animals of most other species (for example, females of cattle and carnivores), hydrometra is an independent disease. Pathogenetically, it is not associated with persistent progesteronemia. The basis of its development is relative or absolute hyperestrogenism associated with chronic anovulation and accompanied by glandular cystic endometrial hyperplasia [1].

The literature provides different data on the frequency of spread and risk factors for the development of pseudopregnancy in goats. [2,3,4,5,7,13,15,16,17,18,19,20,21].

Table 1 – Frequency of extension of pseudopregnancy (hydrometra) according to ultrasound data

Authors	Number of studied goats	Of them with hydrometra	
		animals	%
R. Duquesnel et al., 1992[5]	11011	271	2,5
J.W. Hesselink, 1993 [7]	550	50	9,0
J.W. Hesselink, L. Elving, 1996 [8]	483	50	10,35
T. Wittek et al., 1997, 1998 [15,16]	2434	143	5,87
M. Batista et al., 2001[4]	1321	43	3,26
J. L. Martel, 2001 [17]	1360	45	3,31
E.S. Lopes Júnior et al. 2004 [13]	23	7	30,4
E.P.B.X. Moraes et al., 2007 [18]	143	13	9,1
G.N. Purohit, J.S. Mehta, 2012 [19]	425	26	6,12
A. Milovanovic et al., 2016 [20]	47	7	10,45
A.L.R.S. Maia, et al., 2017 [21]	2680	268	10,0
T. Barna et al., 2017 [3]	3355	46	1,37
M. Almubarak et al., 2018 [2]	378	40	10,6
Total	24210	1009	4,2

According to transrectal and transabdominal ultrasound examinations on pregnancy and infertility, the frequency of extension of hydrometra in goats ranges from 1.3 to 30.4% and averages 4.2% (table 1).

There are convincing data on the hereditary (familial) predisposition of goats to the development of hydrometra. A study by Dutch scientists [8] showed that risk of developing pseudo-gestation in sexually mature Dutch white milk goats born from mothers with hydrometra is 4.2 times higher (37.8% versus 9.1%) than goats born from mothers with no history of complications in this pathology.

Contradictory results on the effect of dairy productivity on the frequency of extension of hydrometra. According to some materials [7,18], high dairy productivity is one of the risk factors for the development of pseudopregnancy; according to others [2,15,16,20], this factor does not affect the frequency of extension of hydrometra in milk goats.

The development of pyometra is also facilitated by iatrogenic factors: hormonal synchronization of estrus and ovulation [4], induction of estrus out of the season with the use of progesterone or its synthetic analogues alone or in combination with pregnant mare serum gonadotropin (PMSG) [2,3,4,5,20,15,16]. The risk of developing pseudopregnancy in the hormonal-induced reproductive cycle is 4 times higher than in the natural reproductive cycle [2]. However, according to the data of some researchers [13, 18], hormonal treatment is not a risk factor for the development of hydrometra in goats.

The disease is found only in animals of average and above-average fatness. In this case, the risk of developing hydrometra in goats above-average fatness is 3.4 times higher than in animals with an average fatness [2]. The season of the year, the number of lambing, the type of feeding and the housing system do not affect the frequency of extension of hydrometra in goats [2].

The etiology of pseudopregnancy, as well as the causal relationship between the persistence of the corpus luteum and the development of hydrometra are not fully established. Retention of the corpus luteum always precedes and accompanies the development of hydrometra [15,16,22,23,24]. Spontaneous regression of the persistent corpus luteum leads to interruption of pseudopregnancy and emptying of the hydrometra.

There is convincing experimental evidence showing that a violation of the external prostaglandin regulation of the functional activity of the corpus luteum plays a pivotal role in the pathogenesis of the disease. It is proved that the uterus in the absence of pregnancy with prostaglandin F2alpha (PgF2α) controls ovarian function: causes regression of the corpus luteum of the reproductive cycle [1,25]. Active immunization of goats against PgF2α leads in 63.6% of cases to the formation of a persistent corpus luteum with the development of the luteal phase of hydrometra on the 31st... 38th day [12, 24]. According to the profile of progesterone in the blood, the authors found that the duration of false pregnancy is quite comparable with the true one and lasts 150.3±23.5 days on average (with fluctuations from 103 to 168 days).

The corpus luteum of false pregnancy (as well as the true one) is very sensitive to the luteolytic effects of PGF2α and its synthetic analogue, cloprostenol. The effectiveness of the induction of luteolysis when

they are assigned to goats with hydrometra approaches 100%. With almost the same effectiveness, termination of false pregnancy in goats can also be done with oxytocin [26]. It is assumed that oxytocin, produced by the corpus luteum at the end of the luteal phase of the reproductive cycle, binds to special oxytocin receptors in the endometrium, activates prostaglandinogenesis and the release of PGF 2α from its cells [6]. However, it should be noted that the active immunization of goats against oxytocin, although it helps to delay the reverse development of the corpus luteum (by about 10 days), does not lead to the development of hydrometra [6].

Pathophysiological factors that block the production of prostaglandin F 2α by the endometrium and cause the development of false pregnancy (the symptom complex “persistent corpus luteum - hydrometra”) remain poorly studied. The specific cause of the appearance of hydrometra in most cases remains undetermined; in 17.9–20.0% of cases, it is associated with intrauterine death of the fetus with a gestational age of 40-90 days [15,16,21].

With the development of false pseudopregnancy, the estrus stops. The general state does not suffer. Biochemical and clinical indicators of blood are within the physiological norm [21]. In blood plasma, the progesterone content is always higher 2 ng/ml [5,7,8,26,24] or 1 ng/ml [21,15,16]. The concentration of estrogen in the blood of goats with hydrometra is higher than in the stage of diestrus, but lower than in animals with a physiologically developing pregnancy [21,15,16].

There were no significant differences in the content of prolactin in the plasma of peripheral blood of goats with a false and physiological pregnancy [12,15,16].

With a pseudo gestation period of approximately 30 days, serous fluid begins to accumulate in the uterine cavity. Its volume can vary from 0.1 or less to 8 or more liters [5,9,26] and on average reaches: according to some data [15,16] – 2.98±2.1 liters, according to others [28] - 13.7±6.0 liters. When a large amount of secretion accumulates in the uterus, a bilateral increase in the volume of the abdomen is observed. At the same time, in lactating goats, a decrease in dairy productivity is noted, in non-lactating goats in the late stages of pseudo gestation, on the contrary, there is breast hypertrophy (gigantomastia) and its preparation for new lactation. At the end of a false pregnancy, spontaneous involution of the persistent corpus luteum occurs. A decrease in the concentration of progesterone in blood plasma (below 1 ng/ml) leads to the disclosure of the cervix, activation of the contractile activity of the myometrium and the emptying of the hydrometra.

During laparoscopic and post-mortem examination of the internal genital organs in pseudopregnant goats, the volume increase in the size of the uterus is diagnosed due to the accumulation of fluid in its cavity. In the ovaries, along with the corpus luteum, vesiculate follicles larger than 5 mm are detected, sometimes ovarian cysts. The walls of the uterine horns are thinner and translucent. A histological examination of the mucous membrane indicates cystic atrophy of the endometrium [16].

The contents of hydrometra is a sterile serous or (extremely rare) mucous transudate produced by the endometrial glands [15,16]. When inoculation, it does not give bacterial growth. In terms of osmolarity, the contents of hydrometra correspond to, and in chemical composition differ from blood plasma, as well as the contents of amnion and allantois (table 2).

Table 2 – Physico-chemical composition of the fluid from the uterine cavity of goats with hydrometra [15,16]

Parameter	M±m
Fluid amount, l	2.98±2.1
pH	7.4±0.1
Osmolarity, mosmol/l	294.0±15.6
Glucose, mmol/l	0.5±0.53
Urea, mmol/l	6.4±2.8
Phosphates, mmol/l	0.03±0.09
Sodium, mmol/l	100.9±28.8
Potassium, mmol/l	9.7±7.5
Calcium, mmol/l	7.6±4.5
Chlorides, mmol/l	123.0±32.2
Total protein, g/l	4.05±3.6
Albumins, g/l	0.9±1.5

Visual echography is recognized as the main and most informative method for the diagnosis of pseudopregnancy, which allows one-time or two-time (with a break of 2 weeks) examination to differentiate false pregnancy from the true one. The optimal time for conducting an echographic study is 40... 70 days after insemination [12,25,15,16]. When researching during these periods at physiological pregnancy, it is possible to visualize its direct signs: the fetus or its body parts, contraction of the cardiac muscle, placenta; at false pregnancy – hypoechoic fluid in the absence of the placenta and fetus in the uterus, respectively [10].

When interpreting the results of visual echography, it should also be taken into account that an accumulation of fluid contents in the uterine cavity can also be due to pyometra. With pyometra, hyperechoic diffuse inclusions appear in the uterine cavity, due to which its contents become cloudy: the "snowstorm phenomenon" [9]. Hyperthermia, neutrophilia, leukocytosis with a shift of the leukocyte formula to the left also serve as very specific manifestations of pyometra, reflecting the inflammatory nature of the disease.

For therapy of hydrometra, some drugs have luteolytic and uterotonic properties – native prostaglandin F-2 alpha (PgF2α) or its highly active synthetic analogue, cloprostenol (table 3). The latter in its biological (luteolytic) activity is approximately 50 times higher than natural PgF2α and for this reason, preparations based on it are prescribed to goats in much lower doses [1].

The protocols and clinical efficacy of using PgF2α and its analogue cloprostenol in goats with hydrometra are given in table 3.

The analysis of the data given in table 3 indicates that the effectiveness of prostaglandin therapy depends on the administration regimen of drugs based on natural PGF2α and cloprostenol. When administered once, they get very unstable and unacceptable for practice results. So, according to L.R.S. Maia et al. [21], after the first injection of cloprostenol (in the submucous membrane of the vestibule of

Table 3 – Clinical efficacy of treating hydrometra in goats with preparations of native PgF2α and its synthetic analogue, cloprostenol

Authors	Number of animals	Drugs and treatment regimen	Notes
T. Barna et al., 2017 [3]	25	Cloprostenol - twice with a break of 11-12 days IM at a dose of 250 mcg; Antibiotics were also used for all animals (Baytril - three injections with a break of 2 days) and once in/m 5 ml of vitamin AD3E	All animals recovered. After recovery, experimental goats for 11 days were injected intravaginally with progestogen sponge containing 30 mg of flugestron acetate, as well as (48 hours before removing the sponge) 400 U of PMSG (in/m) and 5 mg of dinoprostum, (in/m). 42 hours after removal of the sponge, the goats were kept in place with billy goats for 2 days. According to the proportion of fertilized animals, the effectiveness of the method was 64%
E.P.B.X. Moraes et al., 2007 [18]	13	Native drug PGF-2alfa (lutalysis, Pfizer) once or twice (according to the clinical situation) with a break of 11 days IM at a dose of 0.5 mg	The therapy's effectiveness was monitored by ultrasound. After the first injection of the drug, 10, or 76.9%, animals recovered and were rutting, after the second, other 3, or 23.1%, goats had estrus. After mating with a billy goat in a spontaneously developed reproductive cycle, all animals became fertile
J.W. Hesselink, 1993 [7]	20	Dinoprostum once IM at a dose of 5 mg	After a single hormonal treatment, 40% of goats had estrus seeded and were naturally inseminated. Of these, only 15% became fertile. At the same time, in 9, or 45%, experimental goats there was recorded a relapse of the disease
	29	Dinoprostum twice with a break of 12 days IM at a dose of 5 mg	After two courses of prostaglandin therapy, 48.3% of experimental animals were fruitfully inseminated and rutting. One goat (3.4%) had a backset of the disease
L.R.S. Maia et al., 2018 [21]	20	Cloprostenol in the submucosa of the vestibule of the vagina at a dose of 37.5 mcg three times with a break of 10 days. On 5 day from the start of treatment, 1 ml (25 mcg) of Gestragan Plus (a highly active synthetic GnRH analog) or 1 ml of 0.9% sodium chlo-ride solution (10 animals in each group) were administered	According to ultrasound investigation, after the first injection of the drug, complete emptying of the uterus from the fluid contents was recorded in 50% of animals, after the second and the third ones - in 95 and 100%, respectively. On 90th day after mating with a billy goat, in 11, or 55%, experimental goats, the echographic signs of normally developing pregnancy were revealed. On 45-90 days after the therapy course, according to the Echographic diagnostics data, in 4, or 20%, experimental goats there was recorded a backset of the disease. The authors concluded that additional hormonal treatment of goats with a highly active GnRH analogue (5 days after the treatment start) does not improve treatment results

vagina at a dose of 37.5 mcg), a complete emptying of the uterus from the liquid with restoration of estrous cycle occurs only in 50% of goats with hydrometra, when, after the second and third injection of the drug - in 95 and 100% of animals, respectively. According to J.W. Hesselink [7], a single administration of dinoprostum intramuscularly at a dose of 5 mg in goats with hydrometra provides restoration of estrus cyclicity in only 40%, and fertility in 15% of animals, respectively. Other disadvantages of the single injection method are the high recurrence rate of the disease – 45.0% [7].

Good, suitable for practice results were obtained with two-, three-fold or differentiated, under the control of ultrasound investigation, one/two-fold (according to the clinical situation) administration of drugs based on natural PGF_{2α} and cloprostenol.

At two- or three-time administration of these drugs, the effectiveness of prostaglandin therapy in the proportion of fertilized animals reaches 48.3-77.8% [3,10,14,23,24].

Conclusions. Pseudopregnancy, or false pregnancy, is a dishormonal pathology, the leading diagnostic feature of which is hydrometra - the accumulation of a variable amount of sterile serous fluid in the uterine cavity.

It occurs in goats of reproductive age. The risk group includes goats aged 6...8 years and older. A hereditary (familial) predisposition of dairy goats to the development of hydrometra was revealed. Iatrogenic factors also have a significant impact on the incidence rate: hormonal treatment of goats during and/or out of estrus with progesterone alone or in combination with pregnant mare serum gonadotropin.

Visual echography (ultrasound) is the main diagnostic method for false pregnancy. The diagnosis of the disease is based on the detection of hypoechoic fluid in the uterine cavity in the absence of the placenta and fetus in the uterus.

Prostaglandin therapy is a pathogenetically substantiated and quite effective method of treating hydrometra.

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ЕШКІДЕ ЖАЛҒАН БУАЗДЫЛЫҚ ПАТОФИЗИОЛОГИЯЛЫҚ АСПЕКТИЛЕРІ (ГИДРОМЕТРЛЕР) ЖӘНЕ ОНЫҢ ДИАГНОСТИКАСЫ МЕН ТЕРАПИЯСЫНЫҢ ҚАЗІРГІ ЗАМАНҒЫ ӘДІСТЕРІ

Аннотация. Мақалада отандық ғылыми және оқу әдебиетінде сипатталмаған бірегей, ешкінің репродуктивті саласының дисгормоналдық патологиясы қарастырылады. Ауру ұзақ анафродизиямен, аналық бездегі бір немесе бірнеше функционалды белсенді сары денелердің персистенциясымен және гидрометрамен сипатталады-жатырдың көлемді ұлғаюымен, оның қуысына стерильді серозды сұйықтықтың түсуі салдарынан сипатталады. Гидрометр-аурудың жетекші диагностикалық белгісі.

Зерттеудің мақсаты – ешкі індеті, патофизиология, диагностика және жалған буаздылықты емдеу (гидрометрлер) бойынша шетелдік әдебиет мәліметтеріне талдау жүргізу.

Шетел әдебиетінің деректерін талдау негізінде аурудың эпидемиологиялық ерекшеліктері анықталды. Гидрометр өте кең тараған патология болып табылатыны және орташа алғанда 4,2% ешкіде тіркелгендігі анықталды. Қауіп тобына 6...8 жас және одан үлкен жастағы ешкілер жатады. Сүт ешкілерінің гидрометрлердің дамуына тұқым қуалайтын (отбасылық) бейімділігі анықталды. Аурушандық жиілігіне ятрогенді факторлар да елеулі әсер етеді: жыныстық маусым кезінде және/немесе одан тыс прогестиндермен өз бетінше немесе құлын биелері сарысуының гонадотропинмен біріктіріп ешкілерді гормональды өңдеу.

Жалған буаздылық этиологиясы, сондай-ақ, сары дененің персистенциясы мен гидрометрдің дамуы арасындағы себеп-салдарлық өзара байланыс анықталған жоқ. Сары денені ұстау әрдайым гидрометрдің дамуына ықпал етеді. Персистентті сары дененің кенеттен регрессиясы жалған буаздылықты үзуге және гидрометрлерді босатуға әкеледі.

Сары дененің функционалдық белсенділігінің сыртқы простагландинді реттелуінің бұзылуы аурудың патогенезінде жетекші рөл атқарады. Қандағы прогестерон бейіні бойынша жалған буаздылық ұзақтығы орташа 150,3 ± 23,5 тәул.

Визуалды эхография-жалған буаздылықты диагностикалаудың негізгі әдісі. Аурудың диагностикасы жатыр қуысында плацентасы мен ұрығы болмаған кезде гипозоходенді сұйықтықтың анықталуына негізделген.

Простагландин терапиясы патогенетикалық негізделген және гидрометрлерді емдеудің жеткілікті тиімді әдісі болып табылады.

Түйін сөздер: ешкі, жалған буаздылық, персистентті сары дене, гидрометр, емдеу.

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ПАТОФИЗИОЛОГИЧЕСКИЕ АСПЕКТЫ ЛОЖНОЙ БЕРЕМЕННОСТИ (ГИДРОМЕТРЫ) У КОЗ И СОВРЕМЕННЫЕ МЕТОДЫ ЕЕ ДИАГНОСТИКИ И ТЕРАПИИ

Аннотация. В статье рассматривается уникальная, не описанная в отечественной научной и учебной литературе, дисгормональная патология репродуктивной сферы коз. Заболевание характеризуется длительной анафродизией, персистенцией одного или нескольких функционально-активных желтых тел в яичниках и гидрометрой – объемным увеличением матки в размере, вследствие выпота в ее полость стерильной серозной жидкости. Гидрометра является ведущим диагностическим признаком заболевания.

Цель исследования – провести анализ данных иностранной литературы по эпидемиологии, патофизиологии, диагностике и терапии ложной беременности (гидрометры) у коз.

На основании анализа данных иностранной литературы определены эпидемиологические особенности заболевания. Установлено, что гидрометра является достаточно распространенной патологией и в среднем регистрируется у 4,2% коз. К группе риска относятся козы в возраст 6...8 лет и старше. Выявлена наследственная (семейная) предрасположенность молочных коз к развитию гидрометры. На частоту заболеваемости существенное влияние оказывают также ятрогенные факторы: гормональная обработка коз во время и/или вне полового сезона прогестинами самостоятельно или в комбинации с гонадотропином сыворотки жеребых кобыл.

Этиология псевдосукозности, также как и причинно-следственная взаимосвязь между персистенцией желтого тела и развитием гидрометры до конца не установлены. Задержание желтого тела всегда предшествует и сопутствует развитию гидрометры. Спонтанная регрессия персистентного желтого тела приводит к прерыванию псевдосукозности и опорожнению гидрометры.

Нарушение внешней простагландиновой регуляции функциональной активности желтого тела, по-видимому, играет ведущую роль в патогенезе заболевания. По профилю прогестерона в крови установлено, что продолжительность ложной сукозности составляет в среднем $150,3 \pm 23,5$ сут.

Визуальная эхография – основной метод диагностики ложной беременности. Диагностика заболевания основана на обнаружении в полости матки гипозоходенной жидкости при отсутствии плацент и плода в матке.

Простагландиновая терапия является патогенетически обоснованным и достаточно эффективным методом терапии гидрометры.

Ключевые слова: козы, ложная беременность, персистентное желтое тело, гидрометра, лечение.

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