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OPTIONS FOR GENERATING POLYCYSTIC OVARY SYNDROME BASED ON EXPERIMENTAL FINDINGS IN ANIMAL MODELS

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▪ Polycystic ovary syndrome (PCOS) is a common endocrine pathology that affects 8–14% of women of reproductive age. The leading signs of the disease are hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Over the past decades, a variety of animal models have been developed to study the etiology and pathogenesis of PCOS, including chemical, hormonal, and genetic interventions. However, a large number of experimental techniques differ even in the framework of a single model. In this review article, we summarized PCOS animal models using both direct hormonal effects and indirect methods.

▪ **Keywords:** polycystic ovary syndrome; animal models; ovaries; pathogenesis.

ВАРИАНТЫ ФОРМИРОВАНИЯ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ НА ОСНОВАНИИ ЭКСПЕРИМЕНТАЛЬНЫХ МОДЕЛЕЙ У ЖИВОТНЫХ

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▪ Синдром поликистозных яичников — распространенная эндокринная патология, которой страдают 8–14 % женщин репродуктивного возраста. Ведущими признаками заболевания являются гиперандрогения, овуляторная дисфункция, а также поликистозная морфология яичников. В течение последних десятилетий для изучения этиологии и патогенеза синдрома поликистозных яичников были разработаны многочисленные модели на животных, которые включают химические, гормональные и генетические вмешательства. Однако экспериментальные методики различаются даже в рамках одной модели. В данном обзоре рассмотрены модели синдрома поликистозных яичников на животных с использованием как прямого гормонального воздействия, так и опосредованных методов.

▪ **Ключевые слова:** синдром поликистозных яичников; модели животных; яичники; патогенез.

Polycystic ovarian syndrome (PCOS) is a common endocrine pathology characterized by metabolic, endocrine, and reproductive disorders, with the prevalence ranging from 8% to 14% among women of reproductive age. PCOS is diagnosed based on the Rotterdam criteria (2003) [1]:

- oligo-ovulation or anovulation;
- hyperandrogenism (clinical or biochemical);
- polycystic ovarian morphology.

Metabolic disorders in PCOS are manifested as insulin resistance, hyperinsulinemia, impaired glucose tolerance, overweight and obesity, and

subsequently cause type 2 diabetes mellitus and cardiovascular diseases. PCOS is believed to cause a decrease in fertility.

The clinical manifestations of PCOS can develop before or during puberty. Girls with established PCOS are known have an increased secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH), leading to premature expression of LH receptors in growing follicles, excessive secretion of androgens, and arrest of follicle development. In addition, in polycystic ovaries, because of an increase in the number of preantral and antral follicles, the antral section of the ovaries and degeneration of granulosa cells increases, and the surrounding layer of theca cells is hypertrophied [2].

PCOS was first described by Stein and Leventhal in 1930, but the pathogenesis of this syndrome has not been fully understood until date. Nevertheless, PCOS is hypothesized to occur because of various factors, including hormonal imbalances, genetic disorders, and the influence of lifestyle and environmental factors [3]. The primary pathogenetic mechanism of the disease is believed to be the overproduction and impaired pulsatile secretion of LH by the pituitary gland, leading to ovarian hyperandrogenism.

The complex pathogenetic mechanisms of PCOS have been studied in animal models, demonstrating the endocrine, reproductive, and metabolic characteristics of the syndrome. Such animal models are created using various methods involving the use of hormones, psychotropic drugs, and chemicals, and the external environmental factors that influence the development of this disease are assessed.

Animal models using androgens in the prenatal period

It is believed that androgens can alter endocrine homeostasis and cause ovarian dysfunction and metabolic disorders. Because PCOS is manifested as hyperandrogenism, it was aimed to increase the androgen level in the experimental animals when creating the experimental model.

In 1998, D.H. Abbott et al. created an experimental model of PCOS in female rhesus monkeys. Testosterone propionate was injected subcutaneously in pregnant monkeys at different periods of gestation for 15–88 days. Notably, the offspring of females that received testosterone propionate injections during pregnancy had ovarian dysfunction from the onset of puberty. The data obtained were concordant with the clinical manifestations of PCOS, with menarche and peak pubertal growth in the animals delayed by 2.5–3 years. In addition, the offspring had an increase in body weight, an increase in serum testosterone and LH levels, and a decrease in the level of follicle-stimulating hormone (FSH), besides the morphological changes in the ovaries in the form of an increase in the number of preantral and antral follicles. Anovulation was noted in more than half of the prenatally androgenized females [4].

In 2010, X.Y. Wu et al. obtained similar results, as well as researchers from China in 2013, who created an experimental model of PCOS in Sprague-Dawley rats. In an experiment conducted by X.Y. Wu et al., one group of rats received testosterone, and the other received dihydrotestosterone. The experiment results were evaluated 70 days after delivery and compared with the control group of animals. It was observed that in the hypothalamus of rats, under the influence of androgens, the expression of mRNA of progesterone receptors decreased, the basal secretion of LH increased along with the decreased basal secretion of FSH in the pituitary gland. In addition, elevated serum free testosterone and estradiol levels were noted in the offspring. A simultaneous increase in the number of preantral and antral follicles was observed in animals with a decrease in the number of preovulatory follicles. The authors noted that these pathological changes were associated with an increase in the number of anovulatory cycles in the experimental animals [5, 6].

In 2014, A.S. Caldwell et al. created an experimental model using dihydrotestosterone, administered to female mice during pregnancy. Based on the results obtained, oligo-ovulation or anovulation, atretic and cystic follicles were noted in the offspring of the androgenized female mice with unchanged levels of testosterone, estradiol, and gonadotropins. Moreover, the development of obesity, dyslipidemia, hepatic steatosis, and insulin resistance was noted [7].

Table 1 presents the studies on the pathogenetic mechanisms of PCOS in animal models using androgens in the prenatal period.

Table 1 / Таблица 1

Studies on animal models using androgens in the prenatal period
Исследования на моделях животных с использованием андрогенов в пренатальном периоде

Authors	Animals	Number	Drug and duration of administration	Positions under study	Results
D.H. Abbot et al., 1998 [4]	Rhesus monkeys	21	Testosterone propionate, 15–88 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↑ LH; ↓ FSH. 3. ↑ preantral and antral follicles
X.Y. Wu et al., 2010 [5]	Sprague-Dawley rats	45	Testosterone and dihydro-testosterone, 70 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↑ LH; ↓ FSH. 3. ↑ preantral and antral follicles
X. Yan et al., 2013 [6]	Sprague-Dawley rats	44	Dihydro-testosterone, 30 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↓ FSH. 3. ↑ cystic and atretic follicles
A.S. Caldwell et al., 2014 [7]	Mice	–	Dihydro-testosterone, 90 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology. 4. Metabolic disorders	1. =T; =E_2*. 2. =LH; =FSH*. 3. ↑ cystic and atretic follicles. 4. Obesity, dyslipidemia, hepatic steatosis, insulin resistance

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone. * indicators did not change when determined over time.

Animal models using androgens in the postnatal period

In 1983, H. Ota et al. created an experimental PCOS model using testosterone propionate administered in the postnatal period to Wistar rats. The results were evaluated after 200 days. Based on the data obtained, an increase in the levels of free testosterone, LH, and FSH was observed in the blood serum of androgenized rats, besides a decrease in estradiol secretion and an increase in the number of cystic follicles [8].

A similar experimental model was created in 2012 by a group of authors headed by V. Tyndall, but their results were somewhat different from those of H. Ota in 1983. Testosterone propionate was administered for 25–90 days. The authors noted increased serum free testosterone and estradiol levels, decreased FSH level, and increased number of cystic follicles [9].

In 2014, A.S. Caldwell et al. used dehydroepiandrosterone (DHEA) and letrozole (non-steroidal selective aromatase inhibitor) in the postnatal period. The researchers demonstrated that the use of letrozole in animals resulted in pathological changes similar to that using dihydrotestosterone in the prenatal period, namely oligo-ovulation or anovulation, atretic and cystic follicles, obesity, dyslipidemia, hepatic steatosis, and insulin resistance. However, with short-term use of DHEA, ovulation and regular estrous cycles persisted, and with prolonged use of this drug, the number of ovulatory cycles decreased, and insulin resistance developed [7].

Table 2 presents the studies on the pathogenetic mechanisms of PCOS in animal models using androgens in the postnatal period.

Animal models using estrogens

Furthermore, to study the pathogenesis of PCOS, experimental animal models have been developed using estrogens to induce the characteristic signs of the disease.

Creation of models in the postnatal period

In 2012, G. Cruz et al. created an experimental model of PCOS in Sprague-Dawley rats using estradiol valerate, which was administered in the postnatal period. During this experiment, an increase in estradiol level in the blood serum and

Table 2 / Таблица 2

Studies on animal models using androgens in the postnatal period
Исследования на моделях животных с использованием андрогенов в постнатальном периоде

Authors	Animals	Number	Drug and duration of administration	Positions under study	Results
H. Ota et al., 1983 [8]	Wistar rats	55–77	Testosterone propionate, 200 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↓ E_2. 2. ↑ LH; ↑ FSH. 3. ↑ cystic follicles
V. Tyndall, et al., 2012 [9]	Wistar rats	–	Testosterone propionate, 25–90 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↓ FSH. 3. ↑ cystic and atretic follicles
A.S. Caldwell et al., 2014 [7]	Mice	–	Dihydrotesto-sterone, DHEA, letrozole, 90 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology. 4. Metabolic disorders	1. =T; =E_2*. 2. =LH; =FSH*. 3. ↑ cystic and atretic follicles. 4. Obesity, dyslipidemia, hepatic steatosis, insulin resistance

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone. * indicators did not change when determined over time.

a decrease in androstenedione level were recorded, besides an increase in the number of atretic and cystic follicles. However, no reliable data regarding LH secretion changes were observed [10].

In addition to using hormonal drugs and assessing its effects in an experimental PCOS model, several researchers have analyzed the effects of hormone-like substances on the reproductive system. Notably, in 2010, M. Fernandez et al. conducted an experiment regarding the effect of bisphenol A on the endocrine profile and morphological structure of the ovaries. Bisphenol A represents a chemical substance that is part of polycarbonate of plastic, epoxy resin and polystyrene, which can affect the endocrine function of the body. It is an estradiol agonist and an antagonist of androgens and thyroid hormones. An experimental model was created in Sprague-Dawley rats. It was noted that bisphenol A in rats caused an increase in the synthesis of GnRH, free testosterone, and estradiol besides a decrease in progesterone secretion and an increase in the number of atretic and cystic follicles (anovulatory, with a thin layer of granulosis and without a layer of theca cells) [11].

Creation of animal models during puberty

The effect of estrogens and estrogen-like drugs on the occurrence of PCOS-like signs in experimental animals was assessed not only during the postnatal period but also during the pubertal period. A. Schulster, R. Farookhi [12], and J.R. Brawer et al. [13] injected 2 mg of estradiol valerate once to Wistar rats during puberty. After the administration of estradiol valerate, an increase in the number of cystic and atretic follicles with a decrease in the secretion of estradiol and LH was noted. During the experiments, no convincing data related to changes in androgen secretion was obtained.

Creation of models in animals at reproductive age

Development of PCOS-like signs by using estrogens and estrogen-like drugs in experimental animals of reproductive age is a crucial model for studying the pathogenesis of the phenotypic manifestations of this syndrome.

An experimental model on Wistar rats of reproductive age using a single dose of estradiol valerate was developed in 1984 by a group of authors headed by R.K. Hemmings. This study revealed an increase in the number of cystic follicles with a decrease in LH secretion and the absence of changes in androgen levels [14].

A similar model was created in 1993 by L.M. Quandt et al. However, in this work, the model was created in guinea pigs, which received estradiol valerate injections subcutaneously for

Table 3 / Таблица 3

Studies on animal models using estradiol valerate
Исследования на моделях животных с использованием эстрадиола валерата

Authors	Animals	Number	Period	Drug and duration of administration	Positions under study	Results
G. Cruz et al., 2012 [10]	Sprague-Dawley rats	30	Postnatal	Estradiol valerate, single dose	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ E_2; ↓ androstendione. 2. =LH*. 3. ↑ cystic and atretic follicles
M. Fernandez et al., 2010 [11]	Sprague-Dawley rats	30	Postnatal	Bisphenol A, 10 days	1. Steroid hormones. 2. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↑ cystic and atretic follicles
A. Schulster, 1984 [12] J.R. Brawer, 1986 [13]	Wistar rats	65 50	Puberty	Estradiol valerate, single dose	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↓ E_2. 2. ↓ LH; ↓ FSH. 3. ↑ cystic and atretic follicles
R. Hemmings et al., 1983 [14]	Wistar rats	32	Reproductive	Estradiol valerate, single dose	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. =T. 2. ↓ LH. 3. ↑ cystic follicles
L.M. Quandt et al., 1993 [15]	Guinea pigs	32	Reproductive	17β-Estradiol, 2 days	1. Steroid hormones. 2. Ovarian morphology	1. ↑ E_2. 2. ↑ cystic and atretic follicles

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone. * indicators did not change when determined over time.

2 days. During the experiment, an increase in estradiol level in the blood serum and an increase in the number of atretic and cystic follicles were noted. No convincing data was obtained regarding changes in the serum androgen level [15].

Therefore, experimental models of PCOS using estradiol valerate demonstrated an increase in the number of atretic and cystic follicles with no changes in the androgen levels in the blood serum (the results are presented in Table 3).

Creation of genome-modified animal models of polycystic ovarian syndrome

Notably, various techniques are used to modify the genome in animals to develop an experimental model of PCOS.

Some studies have performed genetic modification at the embryonic development stage to create transgenic animals. Notably, scientists have created two experimental models in mice and one experimental model in rats.

Creation of models in the embryonic period

A model for studying genetic modification at the embryonic development stage in female transgenic mice was presented the first time in 1997 by K.A. Risma. The authors created a transgene with the coding region of the bovine β-subunit of LH linked to the coding sequence of the carboxyl-terminal peptide of the β-subunit of chorionic gonadotropin and containing a truncated bovine α-subunit promoter (–315/+45) to direct the expression of this transgene into the gonadotropes. DNA was injected into oocytes from F1 mice (c57BL/6×SJL) and offspring typed by the polymerase chain reaction method using tail DNA. During the experiment, the offspring exhibited an increase in the secretion of estradiol, testosterone, and LH in the blood serum, as well as an increase in the number of cystic follicles [16].

In 2007, J.K. Devin et al. created a PCOS model by using a plasminogen-1 inhibitor (PAI-1) for the first time, the main effect of which is associated

Table 4 / Таблица 4

Studies on genome-modified animal models
Исследования на моделях животных с модификацией генома

Authors	Animals	Number	Period	Drug and duration of administration	Positions under study	Results
K.A. Risma et al., 1997 [16]	Transgenic mice	20	Embryonic	β-LH subunit	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↑ E_2. 2. ↑ LH. 3. ↑ cystic follicles
J.K. Devin et al., 2007 [17]	Transgenic mice	39	Embryonic	PAI-1	1. Steroid hormones. 2. Ovarian morphology. 3. Number of ovulatory cycles	1. ↑ T. 2. ↑ cystic follicles. 3. ↓ number of ovulatory cycles
D. Shi et al., 2009 [18]	Transgenic rats	18	Embryonic		1. Steroid hormones. 2. Ovarian morphology	1. ↑ T; =E_2*. 2. ↑ cystic follicles

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone. * indicators did not change when determined over time.

with the inhibition of serine proteinase activity. Notably, the free testosterone level in the blood serum of transgenic mice increased, along with an increase in the number of cystic follicles and a decrease in the number of ovulatory cycles [17].

In addition to studying the effect of hormonal substances on the formation of clinical signs of PCOS, the effect of metabolic disorders on the reproductive system was studied. In 2009, a group of authors headed by D. Shi developed a PCOS model in transgenic rats with obesity caused by leptin receptor dysfunction. An increase in testosterone secretion without changes in the level of estradiol secretion and an increase in the number of atretic and cystic follicles was observed [18].

Studies on the PCOS pathogenetic mechanisms in genome-modified animal models are presented in Table 4.

Creation of a model of polycystic ovarian syndrome in animals using a non-steroidal aromatase inhibitor

Creating an animal model during puberty

This model was developed on female rats by using a nonsteroidal aromatase inhibitor, letrozole. This drug was administered in three different dosages (0.1, 0.5, and 1.0 mg/kg) for 21 days. The levels of free testosterone and LH increased, with a decrease in estradiol secretion and an increase in the number of cystic follicles [19].

A similar model was created using letrozole in 2013 on female Wistar rats. However, in this case, the dosage of the drug was changed (9.0 or 18.0 mg/kg), and the period of administration was 90 days. Notably, long-term letrozole therapy has been reported to cause metabolic dysfunctions, such as the development of insulin resistance. Insulin resistance is considered a predictor of PCOS development. In addition to insulin resistance, an increase in body weight, a decrease in the number of ovulatory cycles, an increase in the number of atretic and cystic follicles, an increase in LH secretion with a decrease in FSH secretion by adenohypophysis, and an increase in testosterone levels were noted [28].

Creation of a model on animals of reproductive age

In 2016, new data were obtained regarding the use of letrozole during the reproductive period as a drug that potentiates the development of PCOS signs. The results were similar to those of previous studies on puberty in rats (Table 5) [20].

Table 5 / Таблица 5

Studies in animal models using a non-steroidal aromatase inhibitor
Исследования на моделях животных с использованием нестероидного ингибитора ароматазы

Authors	Animals	Number	Period	Drug and duration of administration	Positions under study	Results
Kafali H. et al., 2004 [19]	Rats	34	Puberty	Letrozole, 21 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↓ E_2. 2. ↑ LH. 3. ↑ cystic follicles
M.M. Maliqueo et al., 2013 [28]	Wistar rats	46	Puberty	Letrozole, 90 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology. 4. Insulin resistance. 5. Number of ovulatory cycles	1. ↑ T. 2. ↑ LH; ↓ FSH. 3. ↑ cystic and atretic follicles. 4. ↑ IR. 5. ↓ number of ovulatory cycles
C. Li et al., 2016 [20]	Wistar rats	10	Reproductive	Letrozole, 21 days	1. Steroid hormones. 2. Gonadotropins. 3. Ovarian morphology	1. ↑ T; ↓ E_2. 2. ↑ LH; ↑ FSH. 3. ↑ cystic follicles

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone; IR — insulin resistance.

Creation of a model of polycystic ovarian syndrome under the influence of environmental factors

Generally, various environmental factors (hypothermia, light), as well as foods with a high glycemic index, have been considered predictors of PCOS development.

Creating an animal model during puberty

The effect of light on the reproductive system was investigated in 2015 by a group of authors from China. The study was conducted on Sprague-Dawley rats that were exposed to light for 112 days. An increase in blood serum testosterone level and the number of cystic follicles were observed in the rats [23].

Creation of a model on animals of reproductive age

A model on rats of reproductive age was created for the first time in 2008 by M.P. Bernuci et al. to study the influence of environmental factors. The animals were exposed to hypothermia for 60 days. This experiment demonstrated the role of the sympathetic nervous system in the development of hormonal imbalance. Chronic hypothermia leads to activation of the sympathetic nervous system, which contributes to an increase in testosterone and estradiol levels in the absence of changes in LH and FSH secretion. In addition, the number of cystic follicles increases, resulting in a decrease in the number of ovulatory cycles [21].

Furthermore, melatonin is known to influence the secretion of LH and testosterone and stimulate the development of hyperandrogenism. A decrease in melatonin secretion can cause an increase in LH production by activating the kiss1 neuron (kisspeptin 1). Kiss1 is a peptide that increases the activity of hypothalamic cells, thereby stimulating the production of gonadoliberin, which, in turn, affects the secretion of gonadotropins in the adenohypophysis (LH and FSH) [29, 30]. Notably, specialists became interested in the effects of the influence of light on the reproductive system in the 1990s. In 1991, a group of authors headed by S.F. Baldissera published the results of a study on the effects of light on the reproductive system. An experimental model was created using rats that were exposed to light for 74 days. During the experiment, an increase in the number of cystic follicles was noted, but no reliable data were obtained that indicated a change in the hormonal balance [22].

Furthermore, the influence of eating behavior associated with consuming high-calorie foods on the formation of phenotypic signs of PCOS is another area of interest.

K.M. Volk et al. observed irregular, anovulatory menstrual cycles, significant morphological changes in the ovaries with an increase in the number of cystic follicles in rats of reproductive age, which received foods rich in fat and sugar for 14 weeks. During this study, increased insulin and total testosterone levels were determined in the blood serum of the studied rats, besides an increase in adiposity [26].

However, in a similar study by a group of authors headed by J.S. Roberts, wherein the female rats received a high-calorie diet for 11 weeks, hyperinsulinemia was noted without hyperandrogenism and ovarian morphological changes characteristic of PCOS [27].

Creation of a model of polycystic ovarian syndrome using other substances

The effect of psychotropic drugs on the reproductive system was evaluated for the first time in 2003 by Canadian scientists who used valproic acid to create an experimental model of PCOS. Valproic acid is an antiepileptic drug used to prevent migraine headaches.

Sprague-Dawley rats received valproic acid for 30 days. Consequently, the number of atretic and cystic follicles increased, whereas the serum testosterone and estradiol levels were unchanged [24].

Creation of a model of polycystic ovarian syndrome using anti-Müllerian hormone in the prenatal period

Anti-Müllerian hormone (AMH) is a transforming growth factor that characterizes the ovarian reserve. Therefore, to clarify the possibility of the influence of an increased AMH level during pregnancy on the development of PCOS at a later stage in the offspring, B. Tata et al. (2018) created a mouse model of PCOS using phosphate-buffered saline and a biologically active form of AMH. In the control group, pregnant mice were intraperitoneally injected 0.01 M phosphate-buffered saline (pH 7.4), and the mice of the experimental group received phosphate-buffered saline combined with a biologically active form of AMG. The mice received the preparations from day 17 to day 18 of gestation. The experiment revealed that the offspring of mice that received a biologically active form of AMH exhibited hyperactivation of GnRH secretion in adulthood, which caused an increase in LH levels and consequently increased the testosterone level and anovulation [25].

Table 6 presents the studies on pathogenetic mechanisms of PCOS in animal models using various chemicals, as well as the studies regarding the factors influencing the development of this disease.

Conclusion

Because of the ethical limitations in conducting experimental research on humans, animal models are being developed as the fundamental basis for studying new aspects of the pathogenesis of various diseases. In addition to understanding the mechanisms of the development of pathological processes, experimental models help develop targeted therapy for various diseases. The most significant advantages of using rodents in experimental models include their stable genetic background, ease of handling and care, a shorter reproductive period, and short life cycles.

This review analyzes various experimental animal models of PCOS that have used both direct hormonal action and indirect methods. In most studies cited in the review, changes in ovarian morphology were observed, manifested by an increase in the number of atretic and cystic follicles along with an increased or unchanged androgen level. Notably, convincing evidence for hyperandrogenemia has been obtained only from models using androgens and aromatase inhibitors. Moreover, estrogen-induced intervention is not optimal in creating experimental models of PCOS because of the lack of conclusive evidence for altered androgen secretion.

Moreover, the use of transgenic animals to create an experimental PCOS model can be useful in identifying the pathogenetic mechanisms of endocrine and reproductive disorders.

Nevertheless, animal models that consider the endocrine, reproductive, and metabolic characteristics of the syndrome are required to study the complex pathogenetic mechanisms of PCOS because of the several phenotypes of this disease.

When writing this literature review, it was noted that the formation of the PCOS phenotype depends on the period of life when the effects of

Table 6 / Таблица 6

Studies on animal models using a variety of chemicals and other factors affecting the development of polycystic ovary syndrome

Исследования на моделях животных с использованием различных химических веществ и исследования, в которых изучали факторы, влияющие на развитие синдрома поликистозных яичников

Authors	Animals	Number	Period	Drug and duration of administration	Positions under study	Results
M.P. Bernuci et al., 2008 [21]	Wistar rats	17	Reproductive	Long-term exposure to cold, 60 days	1. Steroid hormones. 2. Ovarian morphology. 3. Number of ovulatory cycles	1. ↑ T; ↑ E_2. 2. =LH; =FSH*. 3. ↑ cystic follicles. 4. ↓ number of ovulatory cycles
S.F. Baldissera et al., 1991 [22]	Rats	15	Reproductive	Long-term exposure to light, 74 days	1. Gonadotropins. 2. Ovarian morphology	1. =LH; =FSH*. 2. ↑ cystic follicles
K.M. Volk et al., 2017 [26]	Sprague-Dawley rats	30	Reproductive	High calorie diet, 14 weeks	1. Insulin. 2. Steroid hormones. 3. Gonadotropins. 4. Number of ovulatory cycles. 5. Ovarian morphology	1. ↑ insulin. 2. ↑ T. 3. ↓ LH. 4. ↓ number of ovulatory cycles. 5. ↑ cystic follicles
X. Kang et al., 2015 [23]	Sprague-Dawley rats	–	Puberty	Long-term exposure to light, 112 days	1. Steroid hormones. 2. Ovarian morphology	1. ↑ T. 2. ↑ cystic follicles
D.S. Lagace et al., 2003 [24]	Sprague-Dawley rats	22	Reproductive	Valporic acid, 30 days	1. Steroid hormones. 2. Ovarian morphology	1. =T; =E_2*. 2. ↑ cystic and atretic follicles
B. Tata et al., 2018 [25]	Mice	–	Prenatal	AMH and phosphate buffer	1. GnRH level. 2. Gonadotropins. 3. Steroid hormones. 4. Number of ovulatory cycles	1. ↑ GnRH. 2. ↑ LH. 3. ↑ T. 4. ↓ number of ovulatory cycles

N o t e. T — testosterone; E_2 — estradiol; LH — luteinizing hormone; FSH — follicle-stimulating hormone; GnRH — gonadotropin releasing hormone; AMH — anti-Mullerian Hormone.

the potentiating factor begin. This information can help in the timely diagnosis of PCOS and the implementation of preventive measures.

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