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Review Article

PCOS Animal Models: An Approach Induced By Dehydroepiandrosterone

Seda Koçak[1*]

[1]*Ankara University, Faculty of Medicine, Department of Physiology, Ankara, Turkey.*

Abstract

Polycystic ovary syndrome (PCOS) is one of the most common metabolic and endocrine diseases in women. Researchers generally use animal models in order to observe mechanisms of PCOS. One of the PCOS animal model is dehydroepiandrosterone (DHEA)-induced PCOS model. In the present review, DHEA-induced PCOS animal models are investigated according to species, age, number of groups, animal weight, DHEA amount applied, solvent, solvent amount, treatment days and injection way.

Key words: *Dehydroepiandrosterone, Polycystic Ovary Syndrome, Animal models*

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common metabolic and endocrine diseases in women of reproductive age. While the metabolic symptoms of the disease are insulin resistance, obesity and increase in cardiovascular risk factors, endocrine symptoms are hyperandrogenaemia, oligomenorrhea, amenorrhea and hirsutism (1). Mechanisms regulating follicular development are disrupted due to the change in the balance of endocrine system in PCOS patients, morphological changes of ovaries are observed. High luteinizing hormone (LH) level disrupts the interaction between granulosa cells and oocytes, maturation of follicules and oocyte. It also causes antral follicles to remain small (2). International guidelines for the Assessment and Management of PCOS progressed PCOS identification during last three decades. In 1990, National Institutes of Health (NIH) constituted criteria for polycystic ovary syndrome as hyperandrogenism, oligo-ovulation and exclusion for other types of etiologies like Cushing's syndrome, hyperprolactinemia (3). In 2003, Rotterdam criteria are revised again to diagnose polycystic ovary syndrome. The Rotterdam criteria were expanded as oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries. A clinical diagnosis involving at least 2 out of the 3 Rotterdam requirements is supported by the International Guidelines for the Evaluation and Treatment of PCOS (4). Prevalence of PCOS is changing according to populations based on using

*** Corresponding author:** Seda Koçak, Ankara University, Faculty of Medicine, Department of Physiology, Ankara, Turkey, E-mail: sdkocak@ankara.edu.tr, ORCID ID: 0000-0003-1183-4847.

NIH or Rotterdam criteria. Available treatments for PCOS: inhibiting increased androgen secretion, improving menstrual dysfunction, preserving the endometrium, fertility to promote and alleviating metabolic disfunctions (5). Each of these is vital to the health and welfare of PCOS patients. Therefore, treatments mostly relieve symptoms of PCOS. More researches are needed to enlighten molecular and pathophysiological mechanisms of PCOS.

Researchers generally use animal models in order to observe mechanisms of PCOS. One of the PCOS animal model is dehydroepiandrosterone (DHEA)-induced PCOS model.

Dehydroepiandrosterone -Induced PCOS model

DHEA is one of the most common circulating steroid hormones and it acts as a precursor for testosterone. DHEA is primarily produced by the adrenal cortex and to the small degrees by the testes and ovaries (6).

PCOS rodent models are generated to help us understand mechanisms and focus on clinical therapies of PCOS. Their size, life span and physiological resemblance make them favoured organisms for PCOS research. There are agents applied on laboratory animals to produce PCOS. One of the androgen therapies in laboratory animals, DHEA have been commonly used to cause PCOS-like phenotypes. The pathophysiology of human PCOS is currently being investigated using with it. After DHEA treatment, female rats/mice form follicular cysts and become anovulatory like human PCOS features (7, 8). In addition to, DHEA influences the usual function of hypothalamus-pituitary-ovarian axis structure through Luteinizing hormone (9). While DHEA-induced PCOS model demonstrate limitations as PCOS is genetic based disease also, the use of the model enables potential biomarkers and therapies for women with PCOS to be researched and tested.

This review will focus on some characteristics of DHEA-induced PCOS models which have provided comprehensive knowledge of complex mechanisms underlying PCOS.

2. Materials and Methods

2.1. Species

This review searched data by using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (https://scholar.google.com/). The following words were looked for in the papers:' PCOS',' polycystic ovary syndrome',' animal model', 'Dehydroepiandrosterone' and 'DHEA'. This review excluded studies of animal models with other androgen or agents. All the animals mentioned in this study are female. According to Pubmed and Google Scholar, 90 publication were analysed in terms of species. According to data, all studies focused on rodent family. Results suggest that most used animal type is rats with 52 articles. 38 of the 52 studies were done with Sprague Dawley rats. 37 of the studies chose mice. One data were not available. In fact, it is shown that Sprague Dawley rats were most commonly preferred in PCOS models induced by DHEA. Strain of rats were Sprague Dawley and Wistar albino, strains of mice were ranked as C57BL/6J, BALB/C, Parkes, B6D2F1 and CD1 (Table 1 – 2, Figure 1).

Table 1: Strain of rats in DHEA-induced PCOS models

Strains of rats	Researchers
Sprague Dawley rats	Jong Hee Choi et al (10)
Wistar Albino rats	Takuya Misugi et al (11)

Table 2: Strain of mice in DHEA-induced PCOS models

Strains of mice	Researchers
C57BL/6J mice	Qiyang Shen et al (12)
BALB/c mice	Shabnam Bakhshalizadeh et al (13)
Parkes mice	Anusha Singh et al (14)
B6D2F1 mice	Fatemeh Eini et al (15)
CD1 mice	Shu-Yun Li et al (16)
	Giovanna Di Emidio et al (17)

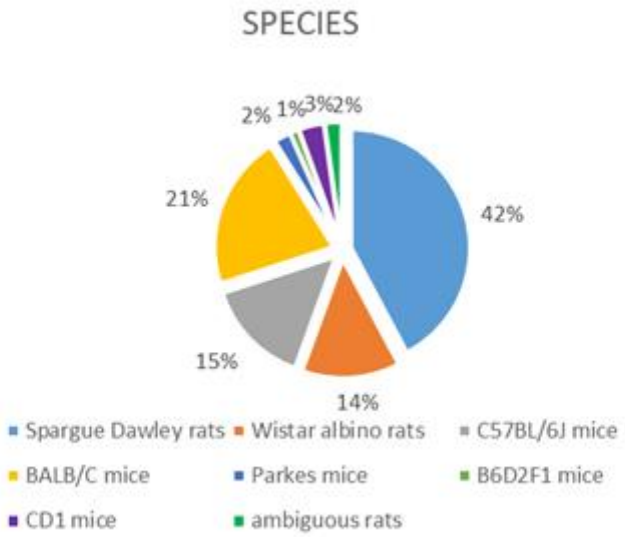

Figure 1: Percentile of species used in DHEA induced PCOS model.

2.2. Age

High DHEA levels during both prenatal and early postnatal life cause a wide variety of PCOS characteristics. In the studies subject to this review showed different age of rodents. From 20 days to 3 months, age of rodents varies. Researchers mostly chose 21 days old animals for research. In 40 of 90 articles, 21-day-old female mice and rats were used. The second most used age was 25 days with 21 publications. The remaining order of the data is 20,22,23,24,28,30,40,42 days and 3 months. Some of the research did not show any age (Table 3, Figure 2).

Table 3: Age range of the rodents used in DHEA induced PCOS model.

Age of rats/mice	Researchers
20-24 days old Sprague-Dawley rats	Lingying Wen et al (18)
21 days old Wistar albino rats	Selenay Furat Rencber et al (19)
28 days old CD1 mice	Giovanna Di Emidio et al (17)
23-30 days old BALB/c mice	María Emilia Solanoa et al (20)
40 days old BALB/c mice	Irene Tessaro et al (21)
42 days old Sprague Dawley rats	Jong Hee Choi et al (10)
3 months Sprague Dawley rats	Hengxia Zhao et al (22)

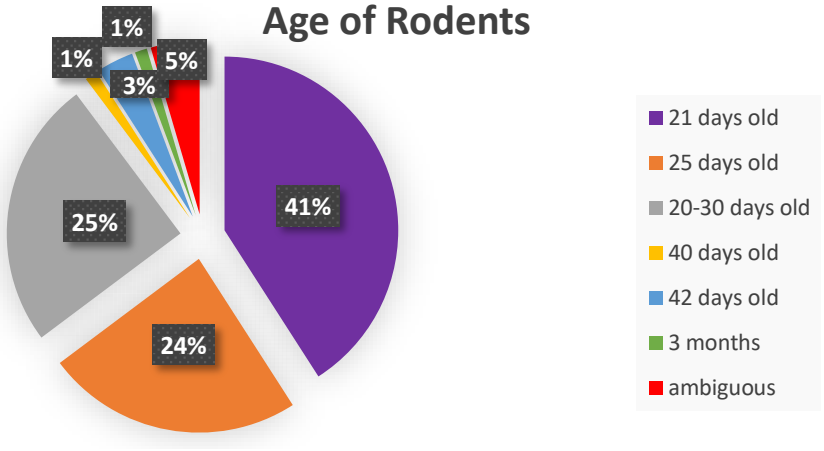

Figure 2: Percentile of rodents used in DHEA induced PCOS model in different age groups.

2.3. Number

According to searched articles, number of animals varies significantly. Range of number in each group is 6-109. Therefore, this study suggests that researchers have not used any specific number of rodents (Table 4).

Table 4: Numbers of animals used in DHEA induced PCOS model.

Numbers of groups	Researchers
6 C57BL/6 mice	Ya-Li Yang et al (23)
15 Sprague Dawley rats	Yanhua Shi et al (24)
56 and 109 Sprague Dawley rats	Eun-Jeong Kim et al (8)
48 BALB/c mice	Gordon Kyei et al (25)
30 Wistar albino rats	Wei Wang et al (26)
10 CD1 mice	Shu-Yun Li et al (16)

2.4. Animal Weight

According to 90 articles, 60 articles did not mention about any rodent weight. The initial weight in rats was at least 16 grams, while the highest weight was 200 grams. When looking at the mice, the lowest weight was 12 grams, and the highest weight was 20 grams (Table 5).

Table 5: Weight of rodents used in DHEA induced PCOS model.

Animal weight	Researchers
12-13gram mice	Gordon Kyei et al (25)
50-70gram rats	Wei Wang et al (26)
120-180gram rats	Ahmed Kabel et al (27)
50-105gram rats	Abeer M. Rababa'h et al (28)

2.5. DHEA amount

PCOS was induced by administration of dehydroepiandrosterone according to body weight of rats and mice. Developing a PCOS model in animals experimentally with DHEA application was attempted for the first time in the 1960s. Roy et al tried different doses of DHEA subcutaneously on female rats. These doses were 1,5 mg/kg, 3 mg/kg, 4 mg/kg, 6 mg/kg. 3 mg/kg and 6 mg/kg dose were similar after administration according to follicule stimulating hormone, luteinizing hormone, and prolactin levels (29). In 1978, Ward et all found out that 6 mg/100 g body weight of DHEA application demonstrated significantly improved levels of FSH, elevated levels of prolactin and depressed serum LH (30). Anovulation, polycystic ovaries and hyperandrogenism, features of PCOS, have been observed after administration of 6 mg/100 g (60 mg/kg) body weight (BW) DHEA. (31-33). Therefore 78 out of 90 articles chose 6mg/100 g body weight DHEA to apply rodents. 6 out of 90 articles used 6 mg/kg DHEA on rodents. Two articles used 2,2 mg/day and 7.5 mg/day in DHEA subcutaneous implantation. 30 mg/kg body weight DHEA was used in one article. Rest of the data were not available (Figure 3).

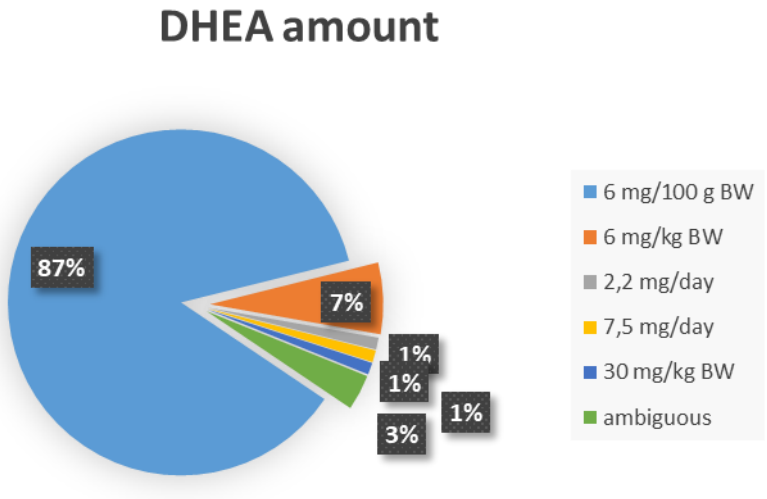

Figure 3: Percentile of dose ranges used in DHEA induced PCOS model.

2.6. Solvent

In experimental groups, PCOS was induced by administration of dehydroepiandrosterone dissolved in different solvents according to body weight of rats and mice. Researchers chose sesame oil, olive oil, peanut oil, corn oil, neutral oil, tea oil, soybean oil, castor oil and phosphate buffer solution. 63 out of 90 articles chose sesame oil as a vehicle. 4 articles have soybean oil, 4 articles used corn oil, 2 articles used olive oil. In some articles, vehicle data is not available (Table 6).

2.7. Solvent Amount

Researchers administered DHEA in different amount of solvents into the study group of rats/mice via different ways of injections. In 34 of the 90 studies, 0.2 ml different types of oil were chosen as solvent. 0.1 ml oil was applied in 22 studies. In 17 studies, oil was diluted with ethanol. Ethanol may have been used to reduce oil viscosity. In these studies, 0.01 ml 95% ethanol was mixed in oil. 3 studies used 0.05 ml oil. Rest of the data were not available (Table 7, Figure 4).

Table 6: Types of solvents applied in DHEA induced PCOS model.

Solvent	Researchers
Sesame oil	Eun-Jeong Kim et al (8)
Olive oil	Gengxiang Wu et al (34)
Peanut oil	Junyu Zhai et al (35)
Corn oil	Olugbemi T. Olaniyan et al (36)
Neutral oil	María Emilia Solanoa et al (20)
Tea oil	Lingying Wen et al (18)
Soybean oil	Lingjun Sun et al (37)
Castor oil	Dan-ni Zhou et al (38)
Phosphate buffer solution	Yan Peng et al (39)

Table 7: Solvent amount applied with DHEA in DHEA induced PCOS model.

Solvent Amount	Researchers
0.01 mL 95% ethanol and corn oil	Vaibhave Ubba et al (40)
0.01 ml 95% ethanol and 0.09 ml sesame oil	Aylin Yaba et al (41)
0.05 ml sesame oil	Ying Huang et al (42)
0.1 ml sesame oil	Lei Dou et al (43)
0.2 ml sesame oil	Yurdun Kuyucu et al (44)

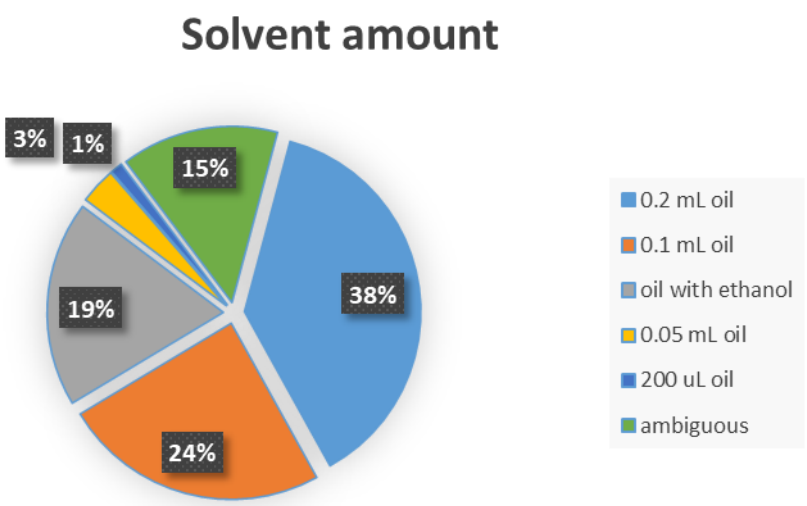

Figure 4: Solvent amounts used in PCOS model to administer DHEA.

2.8. Treatment Days

Differences in the timing of DHEA overload exposure contribute to improvements in the expression of PCOS characteristics found in models of this study. DHEA administration triggers cystic changes in the ovaries of female rats/mice in combination with acyclic ovulation and anovulation (7, 8). In 1991, Everett Anderson et al tried different exposure time of DHEA (0, 10,15,20,25, and 30 days) and found out that follicles after 10 days of DHEA treatment were undergoing atresia and the actual number of follicular cysts occurring in a single ovary is in 20-30 days (45). Therefore 52 out of 90 publications chose 20 days of DHEA treatment as developmental stage of follicular cysts is likely to be a key determinant. 21 out of 92 chose 20 – 30 days, most of them were 21 days treatment. 6 publications chose 15 days, and 4 publications were 35 days. Two studies used DHEA subcutaneous implantation for 60 and 90 days. In one article, researchers applied 12 weeks of DHEA treatment. Rest of the data was 7 days and ambiguous (Table 8, Figure 5).

Table 8: Treatment durations conducted with DHEA induced PCOS model.

Treatment days	Researchers
7 days and 15 days of DHEA injection	Hiroyuki Honnma et al (46)
20 days of DHEA injection	Gordon Kyei et al (25)
21 days of DHEA injection	Ya-Li Yang et al (23)
28 days of DHEA injection	Yurdun kuyucu et al (44)
35 days of DHEA injection	Daojuan Wang et al (32)
12 weeks of DHEA injection	Kok-Min Seow et al (47)

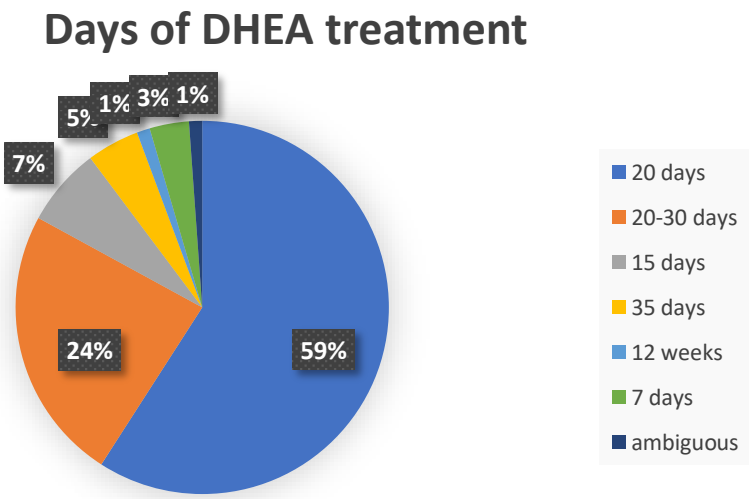

Figure 5: Percentile of different treatment durations conducted with DHEA induced PCOS model.

2.9. Injection Way

Researchers administered DHEA into the study groups of rats/mice via different ways of injections. 83 out of 90 articles used subcutaneous way to produce PCOS. DHEA was injected by unknown way in 3 articles (48-50). While hypodermic injection was used in 2 articles (51, 52), intramuscular injection was used in one article (53). Animals were fed with DHEA in one article (54).

3. Conclusion

Overall, our understanding of PCOS pathogenesis and the development of new PCOS therapeutics is supported by DHEA-induced PCOS models. In the present study DHEA induced PCOS animal models are investigated according to species, age, number of groups, animal weight, DHEA amount applied, solvent, solvent amount, treatment days and injection way. This study might therefore contribute to PCOS research and its development.

4. Conflict of interests

The author declares no conflict of interests.

5. Acknowledgement

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