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**Review Article**

# Review on methods and mechanisms available for producing poly cystic ovary syndrome (PCOS) in animal models: experimental purpose (pre-clinical studies)

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## ABSTRACT

Poly cystic ovary syndrome (PCOS) is one of the most common endocrine disorder, the cause of PCOS is not accurately understood. So, it's a challenging task for the scientist/researcher for the discovery of new drugs for the treatment of PCOS. Considering with new drug discovery for treatment of PCOS, that drug should undergo pre-clinical studies using animal models, in animal models PCOS was initially induced and treated with testing drug, most commonly four methods were used for induction. (letrazole induced PCOS, Estradiol valerate induced PCOS, prenatal Androgen induced PCOS, Dehydroepiandrosterone (DHEA) induced PCOS). Among these four methods letrazole induced PCOS method is easy and convenient method.

**Key words**: PCOS, letrazole, Estradiol valerate, Prenatal Androgen, DHEA.

## INTRODUCTION

Poly cystic ovary syndrome (PCOS) also known as Stein- Leventhal syndrome [1]. It is one of the most common endocrine disorder [2]. It is caused due to the hormonal imbalance among women of reproductive age. The hormones responsible for normal menstrual cycle are GnRH, FSH, LH and Estrogen. If there are any imbalances in these hormones PCOS may occurs. The most common signs and symptoms of PCOS are female infertility, menstrual irregularities, Type 2 diabetes, obesity etc...[3]

Most commonly there are four types of PCOS they are:

1. INSULIN RESISTANT PCOS – The high levels of insulin that drives up androgen levels which cause issues like excess hair, male pattern hair loss and acne.
2. POST-PILL PCOS - Post-pill PCOS occurs in some people after they stop taking the oral contraceptive pill.
3. ADRENAL PCOS - This type of PCOS is due to an abnormal stress response.
4. INFLAMMATORY PCOS - In inflammatory PCOS, chronic inflammation causes the ovaries to make excess testosterone, resulting in physical symptoms and issues with ovulation. [4]

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Now-a-days traditionally most of the medicines are available for the treatment of PCOS [5] but in allopathy there is a few numbers of medicines were available for that treatment purpose, for treatment purposes that specific medicine should passes all the clinical studies. In clinical studies pre-clinical studies was done. In pre-clinical studies animal models were used. In animal model cysts may induced, it may cause PCOS in animal model. For induction of PCOS in rat models many techniques were available, most commonly four methods were used. (letrazole induced PCOS, Estradiol valerate induced PCOS, prenatal Androgen induced PCOS, Dehydroepiandrosterone (DHEA) induced PCOS). [6]

## METHODS USED IN THE INDUCTION OF PCOS IN RAT MODELS

- Letrazole induced PCOS,
- Estradiol valerate induced PCOS,
- Prenatal Androgen induced PCOS,
- Dehydroepiandrosterone (DHEA) induced PCOS.

These are all the most common method used for the induction of PCOS in rat models. [6]

## LETRAZOLE INDUCED PCOS

### Definition

Letrazole is a non-steroidal aromatase inhibitor, letrazole inhibits the enzyme aromatase in the adrenal glands that produces estrogens. letrazole blocks estrogen production. [7]

### Mechanism of action

Generally, androstenedione is obtained from theca cells as a release of LH hormone. The androstenedione is converted into Estrone\Estradiol with the help of Aromatase. Mainly Letrozole inhibit the action of Aromatase, as a result there is no formation of estrogen, Simultaneously the androgen is increased and it may cause PCOS. [8] [9]

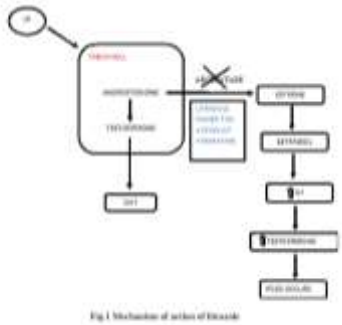


**Fig 1 is added.**

### Method of induction

Non-pregnant female rats (160±20g weight) were selected**,** these rats receive letrozole (21 days continuously)**.** At 21st day vaginal smear examination was done for confirmation of cysts. Treatment was done after 21st day it extends up to 36 days.[10]

## ESTRADIOL VALERATE INDUCED PCOS

### Definition

Estradiol valerate is a naturally producing hormone that circulates with the body. Among all mammalian estrogenic steroids, estradiol is the most effective form, and it is the major female sex hormone.[11]

### Mechanism of action

In normal menstrual cycle the Estradiol helps in the maturation and release of the eggs. The Estradiol (estrogen) releases after the increase release of FSH. When Estradiol valerate is administered in rat model, it inhibits the secretion of FSH and increase the LH level in the body. It may cause the formation of cysts (PCOS). [9] [12]

**Fig 2 is added.**

### Method of induction

Adults female virgin wistar rats (180-200g weight) were randomly selected. The rats with at least 3 following estrous cycles (4-5 days regular) were selected. These rats receive estradiol valerate (60 days continuously) Daily monitoring of vaginal smear until achieving the stable persistent vaginal cornification (PVC) stage. After 60 days the induction is completed and the treatment is started after the 60th day. [13]

## PRENATAL ANDROGEN INDUCED PCOS

An androgen is a natural (or) synthetic steroid hormone that regulates the development and maintenance of male characteristics in vertebrates by binding to androgen receptors. Androgen is produced by the Leydig cells of the testis and theca cells of the ovary. The testicle produces androgen much higher amount than the ovary. All woman naturally produces a small amount of androgen.[14]

### Mechanism of action

Normally the excess of androgen production in female may leads to PCOS. When the excess of Androgen is administered, there is no development in follicle. It may cause anovulation and PCOS. [9] [15]

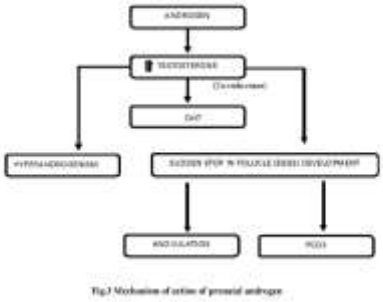


**Fig 3 is added.**

**Method of induction**

Female adult wistar rats. (75-95 days old, 170-190g body weight) were selected Generally pregnant rats are selected for these experiments, pregnancy was confirmed by using vaginal plug. Pregnant rats receive 5mg of free testosterone at 20$^{th}$ day of pregnancy. Vaginal smear was examined between 70- 90 days. After that the treatment protocol was started.[16]

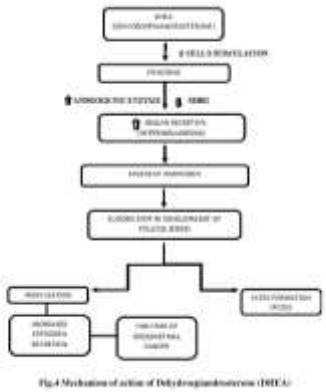
**DEHYDROEPIANDROSTERONE (DHEA) INDUCED PCOS**

**Definition**

DHEA(Dehydroepiandrosterone) is an endogenous steroid hormone, naturally produced from the adrenal gland. Generally, DHEA may alter or affect the levels of other hormones. [6] Synthetically DHEA is produced from diosgenin, a substance found in soy and wild yams.[17]

**Mechanism of action**

When DHEA is administered, the beta cells in the pancreas get stimulated, and secretes insulin continuously, as the result it may causes Hyperinsulinemia. In hyperinsulinemia condition, it may increase androgenic enzymes and decrease SHBG. As a result, there may be the excess production of androgen hormone (male sex hormones). It causes arrest in antral follicle development due to this and anovulation is produced. [9] [18] [15]



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**Method of induction**

Female mice (25 days old) body weight 12-13g balb/C mice were selected for this study. These mice were daily injected with DHEA for 20 days continuously. Daily observation in weight were done throughout the experiment time. Vaginal smear was examined from the 5$^{th}$ day of DHEA injection. After 20 days the DHEA induced rats (45 days old) were randomly selected and experiment were done.[19]

**DISCUSSION**

In letrazole induced rats the volume of ovaries is increased [20] constantly and there may be increase in serum LH , FSH and testosterone concentrations are observed in letrozole induced method thereby it decreases serum oestradiol and progesterone level[21], In estradiol valerate induced rats there is a reduction in body weight , serum level of testosterone was reduced whereas it increases progesterone, LH and glucose levels[22]. Administration of estradoil valerate may causes increase in bone mineral density (BMD) [9]. Administration of DHEA and prenatal androgen may cause decrease in the cortisol, due to the decrease in the cortisol, there is increase in the inflammatory cytokines, it may cause increases in bone resorption (decrease in the bone mass) [9]. Comparing four inducing methods, letrazole inducing PCOS is the most easy and convenient method for the induction PCOS in the rat model. Letrazole directly inhibits the action of aromatase, so it produces the accurate outcome (cyst formation). Compared with other inducing agent the experimental duration was short. Requirements of the experimental animals was less in letrazole induced PCOS method it may be effective compared with other method and letrazole is available in the market.

**CONCLUSION**

Review on the different methods and mechanisms of induction of PCOS, letrazole induced PCOS method is the most convenient, easy and effective method. Generally, letrazole induced PCOS method is more preferable method for the researchers/scientists.

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