Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.6, No.6, 2016

Fertility Indices of Rats in Response to Dehydroepiandrosterone (DHEA) Administration

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Abstract
The aim of the present study is to evaluate the effect of oral administration of DHEA on fertility indices in female rats. A total of 18 adult female rats 2.5-3.5 months old and weighting 200-250g were divided into three equal groups: G1-control received saline solution, G2- received 2mg DHEA /kg B.Wt orally and daily for 2 weeks prior to gestation. G3- received the same dose for two weeks prior and during gestation. The was a significant increase in fertility, gestation indeces of rats received DHEA for two weeks prior and during gestation. At the meantime, the gestation length, viability and lactating indeces were decreased in this group as compared with others. In conclusion, administration of DHEA at dose of 2 mg /kg B.Wt for 2 weeks prior to and during gestation seems to be safe as no abortion and fetal abnormalities were recorded.
Keywords: DHEA, Fertility indeces, rats.

1-Introduction

5-Dehydroepiandrosterone (5-DHEA) is 19-carbon endogenous natural steroid hormone. Dehydroepiandrosterone (DHEA) is a hormone that is naturally made by the animal and human body. It can be made in the laboratory from chemicals found in wild yam and soy. However, the body cannot make DHEA from these chemicals, so simply eating wild yam or soy will not increase DHEA levels**.** DHEA and DHEAS are plentiful circulating steroids produced from adrenal gland and gonads. DHEA converted to testosterone or estrogen and show 90% decline by age (Mo *et al*., 2006).

Dehydroepiandrosterone (DHEA) is used for slowing or reversing aging, improving thinking skills in older people, and slowing the progress of Alzheimer's disease. Athletes and other people use DHEA to increase muscle mass, strength, and energy. DHEA is also used by men for erectile dysfunction (ED), and by healthy women and women who have low levels of certain hormones to improve well-being and sexuality (William and Ganong, 2005).

It has been introduced the term of fountain of youth for DHEA (Baulieu, 1996). As it is antiaging hormone. There is an epidemiological evidence that have DHEA and its metabolite DHEAS levels in serum are associated with an increase of metabolite DHEAS levels in serum are associated with an increase of metabolic syndromes related to age like cardiovascular diseases, diabetes mellitus and hypertension (Thijs *et al.,* 2003), (Villareal and Holloszy, 2006). All female animals are born with a definite number of eggs which deceases gradually with age. When the egg supply becomes very low, it is called diminished ovarian reserves (DOR) which is the most common causes of infertility in animals and women. However, one notable cause of DOR is decreased DHEA levels . Thus DHEA is used primarily to treat women with DOR which occurs either as a consequence of female aging or premature ovarian aging (POA). From the other hand, DHEA in used in menopause females which is usually associated with a sudden decline in estrogen one (Puder *et al.,* 2000).

We were interested to find whether DHEA administration before or during gestation has any effect on fertility indices. Therefore, the aim of this experiment was to evaluate the effect of 2 mg DHEA /kg body weight before or before and during pregnancy to female rats on fertility indices.

2-Materials and Methods:

A total of 18 adult female Albino Wistar rats weighting (200-250gm). Their ages ranged between (2.5-3.5 month) were divided after 2 weeks acclimatization into three equal groups as follows: G1-Received orally saline solution daily for two weeks prior to and during gestation time. G2-Received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior to gestation. G3-Received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior and during gestation.

The females of these three groups were subjected to :

Synchronzation of estrus cycle by daily vaginal smears according to the procedure mentioned by **Marcondcs *et al.,* (2002)**. At proestrus phase, females were kept with males for mating which was confirmed after 24 hours by the presence of seminal plug **(Donald, 1984).** To confirm pregnancy, the females were subjected to daily vaginal smears test for five successive days where they stay in the diestrus phase. The following parameters were studied on pregnant female rats and newborns according to **Klaassen *et al* (2008)**:

Fertility index, Gestation index, Gestation length, Growth index, Body weight and number of newborns, Viability index and Lactating index. Date were expressed as mean ± SE and P-value (< 0.05) we considered statistically significant **(SPSS, 2002).**

3-Results

3.1-Effect of DHEA on fertility and gestation indices:

DHEA administration to rats two weeks prior and during gestation time give a clear positive result on fertility index. Table (1) shows that the fertility index in this group is 100% where as that of rats received the same dose of DHEA for two weeks prior to gestation only (G2) was 83.33% compared to control which has fertility index of 100%. Moreover, the infertility is (16.66%) in group of rats received 2mg/kg B.wt DHEA for two weeks prior to gestation (G2) as compared to (0%) for control and G3. The same table reveal that the gestation index for rats received DHEA before and during gestation time (G3) is 100% compared with 80% for these received DHEA for two weeks before gestation only (G2) and 75% for rats administered with saline solution (G1). The non-gestation % is 25, 20 and 0 for rats received saline, 2mg/kg B.wt DHEA two weeks before gestation and group received the same dose for two weeks before and during gestation time respectively.

Table (1): Fertility, infertility, Gestation and non-gestation index (%) of adult female rats received oral daily doses of 2mg/ kg B.Wt DHEA two weeks before and two weeks before + during gestation time.

parameters / Group	Fertility	Infertility	Gestation	Non gestation
G1	**100**	**0**	**75**	**25**
G2	**83.33**	**16.66**	**80**	**20**
G3	**100**	**0**	**100**	**0**

Capital letters indicate a significant ($p< 0.05$) difference between groups.**G1:** control group received orally distilled water daily for two weeks prior and during gestation time, **G2:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior to gestation time, **G3:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior and during gestation.

3.2-Effect of DHEA on gestation length, body weight and growth index of newborns:

There is a significant ($p< 0.05$) decrease in the gestation length of female rats received 2 mg/kg B.Wt before and during gestation time (G3) as compared to those received DHEA before gestation only (G2) and control groups. At the meantime, these rats received DHEA before gestation only (G2) have significantly ($p< 0.05$) shorter gestation length than control. Table (2) also represents the effect of DHEA administration on body weight of newborns. The value are (3.38 ± 0.14), (3.26 ± 0.14) and (3.04 ± 0.14) for control, G2 and G3 respectively. i.e, there is significant ($p< 0.05$) decrease in mean body weight of newborns in G2 and G3 as compared to control. However, the table also shows the growth index of treated and control groups and reveal a significant ($p< 0.05$) increase in rats received DHEA before and during gestation (G3) in comparison to (G2) and control. The mean values of growth index are (0), (3.55) and (10.05) for control, rats received DHEA before gestation only and rats received DHEA before + during gestation time respectively.

Table (2): Gestation length (days) of adult rats received oral daily doses of 2mg/ kg B.Wt DHEA two weeks before and two weeks before + during gestation time and body weight (gm) and growth index (%) of newborns.

Parameters / Group	**Gestation length (days)**	**Body weight of newborns (gm)**	**Growth index (%)**
G 1	**21.33 ± 0.33 A**	**3.38 ± 0.140 A**	**-**
G 2	**21.00 ± 0.00 B**	**3.26 ± 0.143 B**	**3.55**
G 3	**20.00 ± 0.57 C**	**3.04 ± 0.146 C**	**10.05**

Capital letters indicate a significant ($p< 0.05$) difference between groups.**G1:** control group received orally distilled water daily for two weeks prior and during gestation time, **G2:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior to gestation time, **G3:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior and during gestation.

3.3-Effect of DHEA on viability and lactating indices:

Table (3) represents the total a live newborns for the three groups of rats in this experiment. They are (13), (23) and (25) for control, G2 and G3 respectively. However, the viability index for rats received 2 mg/kg B.Wt for two weeks prior and during gestation (G3) was significantly ($p< 0.05$) less than rats received DHEA before gestation only (G2) and control groups. At the meantime, the table reveal a significant increase ($p< 0.05$) in the viability

index of newborns from rats received DHEA for two weeks before gestation time only (G2) in comparison to control and G3.

The lactation index shows a significant ($p< 0.05$) decrease in group of rats received DHEA prior and during gestation time (G3) as compared to control. On the other hand, the lactating index shows higher significant ($p< 0.05$) decrease in group of rats received DHEA before gestation only (G2) as compared to control and G2. The values are (77.77), (50) and (73.33) for control, G2 and G3 respectively. Moreover, the lactating index for newborns from rats received oral administration of 2mg/hg B,wt DHEA two weeks before + during gestation (G3) is significant ($p< 0.05$) higher than those born from rats received DHEA for two weeks before gestation only (G2).

Table (3): Viability index and Lactating index (%) of newborns from rats received oral daily doses of 2 mg/kg B.Wt DHEA two weeks before and two weeks before + during gestation time.

Parameters / Group	Total newborns	Viability index (%)	a live newborns	Lactating index (%)
G 1	13	69.23	9	77.77
G 2	23	69.56	16	50
G 3	25	60	15	73.33

Capital letters indicate a significant ($p< 0.05$) difference between groups.**G1:** control group received orally distilled water daily for two weeks prior and during gestation time, **G2:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior to gestation time, **G3:** received oral doses of 2 mg/Kg B.Wt DHEA daily for two weeks prior and during gestation.

4-Discussion

In order to overcome infertility and improve the live birth rate, attention has been increased at the last few years to involve DHEA (an endogenous adrenal steroid from ovarian theca cells and adrenal cortex) which is an essential pro-hormone in ovarian follicular steroidogenesis (Arlt, 2004). Although, the mechanism of action of DHEA on the ovary remains speculative, some evidence suggests the important role of androgens in normal folliculogenesis and female fertility (Gleicher *et al.,* 2010). Androgens may enhance ovarian function by increasing the follicle recruitment (Ware, 1982). And increasing the intra follicular androgens augments granulosa cell antimullerian hormone (AMH) and inhibin-B production (Andersen and Lossi, 2008). Androgen receptors (ARs) have been described in ovarian stroma and granulosa cells (GC) of primordial follicles, primary follicles (Otala *et al.,* 2004).

It has been demonstrated that ARs are crucial important for normal follicle genesis and development. Higher concentration of ARmRNA and AR protein were detected in pre-antral and early antral follicles which suggested the peak effect of androgens (Weil *et al.,* 1998). Increased expression of AR was detected after treatment of DHEAS compared to cells absence of DHEAS which explained that DHEAS may exert its effect on follicles development through up-regulating AR (ElBeltagy *et al.,* 2007). The expression of ARmRNA in GC and concentration of androgens in follicular fluid were correlated with expression of FSH receptor mRNA (Gleicher and Weghofer, 2008). Therefore, our results could be explained as that administration of DHEA could increase FSH receptors at early stages of folliculogenesis and thus it is benefit for follicle recruitment which is confirmed by the Signiant increase of serum FSH level after DHEA administration in our experiment (un published). According to the two cell-two gonadotrophin theory, androgens play an essential role in ensuring adequate follicular steroidogenesis. At the meantime, DHEA is a crucial precursor steroid to the sex steroid synthesis and is converted to androgens or estrogens. Estrogens promote ovarian follicular growth and granulosa cell proliferation (Sunkara *et al.,* 2012). Estradiol concentration shows a significant increase in rats received 2 mg/kg B.wt DHEA in our study (un published).

The data results from the second experiment in this study show a 100% gestation rate for rats received DHEA prior and during pregnancy i.e. the miscarriage rate was 0% compared to other groups. This could be attributed to the beneficial role of DHEA in reducing the chromosomal abnormalities (aneuploidy) in embryos. A recently published study confirmed low spontaneous miscarriage rates in pregnancies conceived on DHEA supplementation. However, the greatest reduction in aneuploidy (22%) in embryos through preimplantation genetic screening (PGS) was observed with 4-12 weeks of DHEA supplementation to women prior to IVF. The same authors confirmed in their study that most chromosomal abnormalities in embryos result in miscarriages (Stmarys, 2010).

Oral DHEA administration has been proposed to have antiaging effects and may improve ovarian response and pregnancy rats in women with reduced ovarian reserve (OR) during IVF (Casson *et al.,* 2000). However, the association between increasing circulating endogenous maternal testosterone levels during

pregnancy and a decrease in offspring birth weight and gestation length had been supported by human and animal data (Carlsen *et al.,* 2006). Reported in their study an increase in circulating maternal testosterone levels from (25-75%) at week 17 of women gestation corresponded to a decrease in birth weight of 160 g. In sheep, testosterone treatment to the pregnant mother during early to mid-pregnancy reduced birth weight and height in the offspring of other gender (Manikkam *et al.,* 2004). We conclude that we may want to pay more attention to DHEA levels in our bodies because it relates to so many aspects of overall health.

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