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ORIGINAL RESEARCH ARTICLE

Oestrogen Induced Ovarian Hyperplasia Leading to Cancer in the Rat Ovary

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ABSTRACT

The present study was aimed to assess the carcinogenic effect of a highly potent semisynthetic oestrogen, ethinyl oestradiol (EO) on the rat ovary. The EO was administered to different groups of rats @ 250, 500 and 750 µg/kg body weight, orally, weekly for 16 and 20 weeks. On the 17th week, the ovarian tissues revealed marked congestion and fibrosis. Degeneration and necrosis of follicular tissues were also noticed. On the 21st week, these changes were more marked. In general, extensive fibrosis, thickening of blood vessel walls, follicular tissue degeneration and necrosis were noticed. At this period, EO (750 µg/kg) caused papillary proliferation in surface epithelium and hyperplasia of follicular cells, which indicated the development of cancer in the rat ovary. The extent and severity of ovarian damage were dose and time dependent, suggesting that the EO at higher dose for prolonged period (750 µg/kg, orally, weekly for 20 weeks) may produce hyperplasia leading to cancer in the ovary.

Key-words: Cancer, Hyperplasia, Oestrogen (EO), Ovary, Rat

INTRODUCTION

Oral contraceptives (OCs) used to prevent fertilization, first became available to American women in the early 1960s. Since then they have influenced the lives of untold millions of women and have had a revolutionary impact on global society. The OCs contains two hormones, viz. oestrogen and progesterone. Oestrogens are also most commonly used as hormonal replacement therapy (HRT) in post-menopausal women.[1] In bitches, oestrogen is used for the treatment of hypogonadal obesity, hormonal urinary incontinence and misalliance.[2] In fact, "oestrogen is the necessity of female because without it female is no more female; however, with excessive and prolonged use, oestrogen may cause cancers of many organs".

Oestrogen has been reported to cause tumours of breast, cervix, endometrium, ovary, pituitary, testicle, kidney and bone marrow.[3] It has been stated that the menopausal women who took HRT or ORT for long periods, particularly for 10 or more years, were at increased risk of the cancer of ovary.[4] It has also been reported to cause many illnesses in human. It is disconcerting to think that a natural hormone (oestrogen) circulating in significant amounts 3through the bodies of half of the world's population (women) is a carcinogen, but it is now official.[5] Enlargement of ovaries leading to cancer was observed after the administration of stilbestrol (a synthetic oestrogen) in rabbits.[6]

Ethinyl oestradiol (EO), a semisynthetic 17 β-oestradiol, is the most highly potent oestrogen. The LD_{50} of EO has been reported to be more than 1000 µg/kg body weight, orally in rats.[7] EO @ 250, 500 and 750 µg/kg, orally, weekly for 8 and 12 weeks caused cytotoxicity in the uterus[8] and ovary[9] of rats. EO also caused liver damage when administered @ 500 µg/kg, orally, weekly for 8 and 12 weeks in female albino rats.[10]

Hence, the present study was aimed to assess the cancerous effect of EO at a specific dose and duration on the ovary of female albino rat. This study has great importance as this is probably the first work in India to produce ovary cancer by EO in rat, and in no Indian literature such research work could be traceable.

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MATERIALS AND METHODS

Forty-two healthy inbred female albino rats (100-150 g) were divided into seven groups, each had six rats. The animals were kept in polypropylene cages under standard laboratory conditions with $25^0 \pm 5^0$C temperature, 45-55% relative humidity and 10 hr light:14 hr darkness in the animal house, and fed on standard pellet diet and clean drinking water. However, before experiment the animals were fasted overnight, but water was given *ad libitum*. The experimental designs in the study received approval of Institutional Animal Ethics Committee.

The required Lynoral tablets (each tablet containing 0.05 mg of EO only) were purchased from the medical shop. The suspension of EO was prepared in distilled water mixed with a pinch of *Gum acacia* powder. The rats of groups 2, 3 and 4 were administered with EO @ 250, 500 and 750 µg/kg, orally, weekly for 16 weeks, and the same doses of EO were administered to the rats of groups 5, 6 and 7, respectively for 20 weeks. However, the rats of group 1 were administered normal saline (also containing a pinch of *Gum acacia* powder) to serve as control. After the respective experimental period, the rats were sacrificed and their ovaries were collected and preserved in 10% buffered formalin. Thereafter, the ovarian tissues were processed and stained with Harris's haemotoxylin and eosin (H & E) stain as per the method cited by Culling.[11] On microscopic examination, the pre-cancerous and cancerous lesions in the ovaries of rats of groups 2 to 7 as compared to group 1 (control) were observed.

RESULTS AND DISCUSSION

On the 17th week, the ovaries of group 2 (EO @ 250 µg/kg) and group 3 (EO @ 500 µg/kg) showed marked congestion and fibrosis. Degeneration and necrosis of follicular tissue were also noticed. In group 4 (EO 750 µg/kg, **Fig. 1**), the histopathological changes were more marked. Presence of homogenous mass in the lumen, infiltration of lymphocytes and thickening of blood vascular walls were quite conspicuous. On the 21st week, the histopathological changes were found to be more severe in groups 5 to 7, subsequently. In group 6 (EO @ 500 µg/kg, **Fig. 2**), extensive fibrosis, including severe degeneration and necrosis of follicular tissues were observed**.** In group 7 (EO @ 750 µg/kg, **Fig. 3 & 4**), these changes were quite conspicuous with fibroplasia of interfollicular connective tissues. Interestingly, hyperplasia of follicular cells, papillary proliferation in surface epithelium and other malignant changes were observed, indicating the ovarian carcinogenesis. The extent and severity of ovarian damage were dose and time dependent, suggesting that the EO at higher dose for prolonged period (750 µg/kg, orally, weekly for 20 weeks) may cause hyperplasia leading to cancer in the ovary.

The results of the present study may be correlated with various reports of ovary cancer caused by oestrogen.[1,3-4,12] Excessive intake of oestrogen is troublesome and may cause many illnesses, including polycystic ovary syndrome (PCOS) and ovarian cancer.[5,12] The carcinogenic changes in the rabbit ovary were observed after administration of oestrogen.[6] Ovarian cytotoxicity was observed after administration of EO (250, 500 and 750 µg/kg, orally, weekly for 8 and 12 weeks) in female albino rats.[9,12] All these reports further support our results.

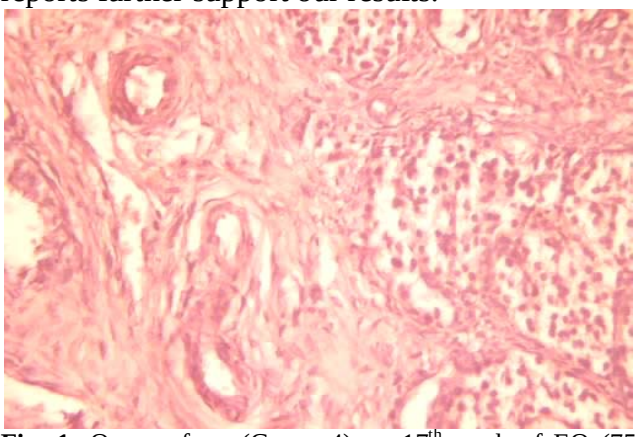

Fig. 1: Ovary of rat (Group 4) on 17th week of EO (750 µg/kg, orally, weekly for 16 weeks) administration showing marked degeneration and necrosis of follicular tissue, infiltration of lymphocytes and thickening of blood vascular walls (H & E, x400).

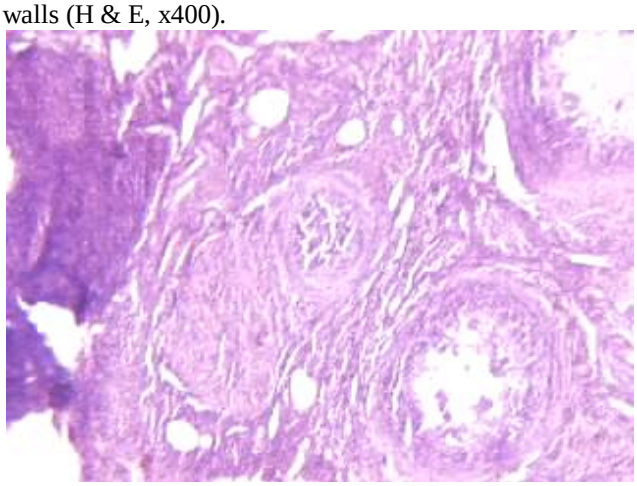

Fig. 2: Ovary of rat (Group 6) on 21st week of EO (500 µg/kg, orally, weekly for 20 weeks) administration showing extensive fibrosis, degeneration and necrosis of follicular tissue (H & E, x100).

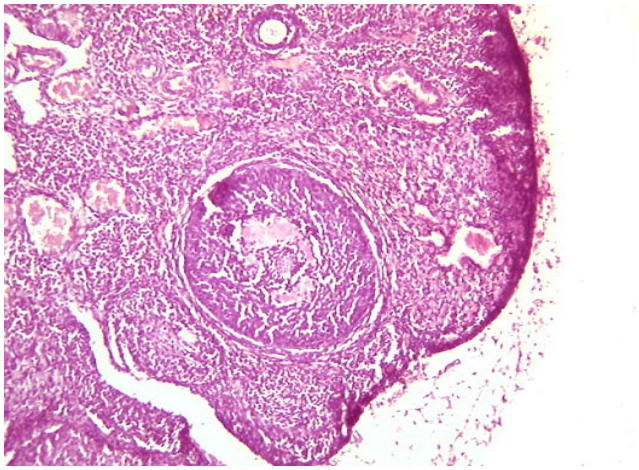

Fig. 3: Ovary of rat (Group 7) on 21st week of EO (750 µg/kg, orally, weekly for 20 weeks) administration showing fibroplasia of interfollicular connective tissues (H & E, x100).

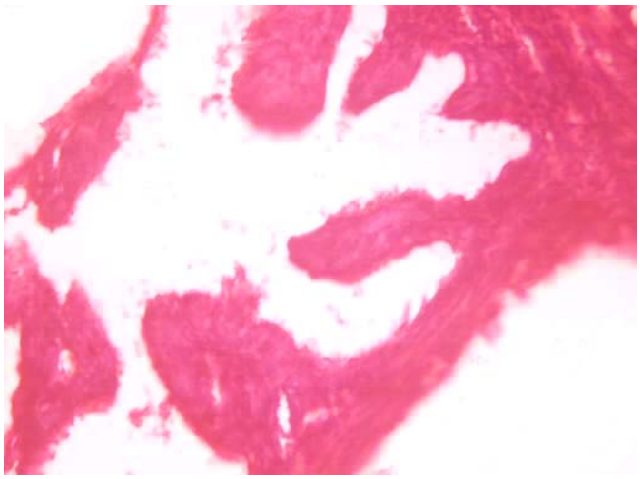

Fig. 4: Ovary of rat (Group 7) on 21st week of EO (750 µg/kg, orally, weekly for 20 weeks) administration showing papillary proliferation in surface epithelium and hyperplasia of follicular cells (H & E, x400)

Excessive oestrogen and its stagnation in the blood circulation may cause cancers of many organs, including breast, uterus and ovary. Oestrogen is believed to cause cancer by helping cells proliferate. After the hormone binds to its receptors in a cell, it turns on hormone-responsive genes that promote DNA synthesis and cell proliferation. In this reaction, 'free oxygen radicals' are produced that can damage the cell's fats, proteins and DNA. Unrepaired DNA damage can turn into a mutation, leading to cancer.[12]

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