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Original Research Article

HISTOLOGICAL OBSERVATIONS IN HUMAN OVARIES FROM EMBRYONIC TO MENOPAUSAL AGE

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ABSTRACT

Introduction: Age related changes in the ovaries such as formation, differentiation and growth of follicles and stroma are indicators of reproductive competence. Age related changes in the histological structure of ovary from embryonic to menopausal age was not reported in the literature.

Aim: To observe the age related changes in the histological structure of human ovaries in local population from prenatal to postmenopausal age in the Andhra Pradesh region of india.

Materials and Methods: A total of 79 formaline preserved ovaries collected from aborted embryos, dead fetuses, adult cadavers and during surgical oophorectomy were processed for routine tissue processing, section cutting (5microns) and Haematoxylin and eosin staining. The histological sections of ovaries at various ages were observed for the appearance of germinal epithelium, tunica albuginea, types of follicles and their stage of development / atresia in the cortex, appearance of medulla and cortico-medullary differentiation etc. Representative fields were photographed.

Results: 4 weeks delay of decline in the number of oogonia, 12 weeks delay in cortico-medullary demarcation, 8 weeks delay in the initiation of follicular degeneration were observed. Longer delay in follicularization ie. formation of Graafian follicle at 5 yrs and flat germinal epithelium and whirling pattern at 40 years were observed.

Conclusion: When compared to literature there is delay in the formation, maturation and degeneration of follicles and cortico-medullary demarcation in the present study. This study forms the database for the age related histological appearance of human ovaries in the wide age range of embryonic to menopausal age in the local population.

KEY WORDS: Ovaries, Embryonic Stage, Menopausal Age, Follicles, Haematoxylin.

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INTRODUCTION

Female fertility depends on supply and maturation of ovarian germ cells i.e. oocytes and proliferation of ovarian somatic cells i.e. granulosa and theca cells [1]. The term folliculogenesis or follicular histology was proposed to the process of interaction between oocytes and somatic cells [2]. This marks the last step of ovarian differentiation and occurs during fetal life in the human female [1,2].

Several studies on histogenesis of ovaries in prenatal periods of development were reported

in literature [3-8]. Studies on ovaries in childhood [9] and histological classification of growing follicles in postnatal ovaries into primordial, antral and pre ovulatory stages were described [10 – 13] in literature.

There is no single study in the literature on histological aspects of human ovaries from embryonic to menopausal age. There are no reported studies on pre and postnatal ovaries of local population. Hence, the present study was under taken as a sample study.

MATERIALS AND METHODS

This work was conducted at the department of Anatomy with the cooperation of the departments of Obstetrics and Gynecology, Forensic medicine and Pathology, S. V. Medical College, Tirupati, Andhra Pradesh, India. A total of 79 ovaries were collected from aborted embryos, dead fetuses, adult cadavers and during surgical oophorectomy during the study period September 2004 to November 2006 after approval of Institutional ethics committee. The ovaries were preserved in 10% formalin and processed for routine tissue processing, section cutting and staining with Haematoxyline and eosin [14]. Sections of 5 microns thicknesses were observed for the appearance of germinal epithelium, tunica albuginea, types of follicles and their stage of development / atresia in the cortex, appearance of medulla and cortico-medullary differentiation etc. The stained slides were photographed using Leica DS 280 digital camera mounted on Leica DMIRB inverted microscope. Images were transferred to a computer and analyzed as needed.

Table 1: Categorization of Prenatal and Postnatal Ovaries.

Type and number of Specimen	Right ovaries	Left Ovaries	Total
Embryonic (8-12 wks)	2	2	4
Early foetal (13-28 wks)	8	8	16
Late foetal (29 – 40 wks)	5	5	10
Pre pubertal (< 15 yrs)	3	3	6
Reproductive(16- 45 yrs)	16	19	35
Menopausal (>46 yrs)	4	4	8
Total	38	41	79

RESULTS

In the present study developmental histology of ovaries in the prenatal period were described under embryonic, early fetal and late fetal stages. In postnatal ovaries the histological observations were described into those belonging to pre pubertal, reproductive and menopausal groups (Table.1).

During embryonic period fragmentation of sex cords into small islands at the peripheral region of ovary (fig.1) and migration of number of primordial germ cells into the gonad were observed. At 16 weeks of foetal period flat germinal epithelium and clusters of oogonia giving lymphoid appearance to the ovary were identified (fig.2). There is no cortico-medullary differentiation at this stage.

At 20 weeks lymphoid appearance with actively proliferating oogonia and early stage of primordial follicles (oocyte surrounded by flat cells) in the inner zone of cortex and homogenous outer zone could be identified. Blood vessels in the centre of ovary suggesting early stage of medullary differentiation and vascular mesoovarium were observed (fig.3). These findings suggests the initiation of cortico medullary demarcation.

At 24 weeks–clear cut cortico-medullary demarcation, vascular medulla and plenty of primordial follicles in the peripheral cortex were identified (fig.4). At 28 weeks plenty of both developing and degenerating primordial follicles were present (fig.5). The cells lining the follicles were flat to cuboidal in shape.

During late fetal period cuboidal germinal epithelium, clear tunica albugenia and well differentiated cortex and medulla were observed. Plenty of encapsulated primary oocytes(Primordial follicles) giving the appearance of tiny white rings with dark central dots were noted (fig.6) at 30 weeks. Plenty of degenerated follicles were also observed.

At 38 weeks abundant stromal tissue and number of primary follicles were present. Each primary follicle consisted of primary oocyte surrounded by unilaminar cuboidal cells. Degenerating primary follicles were also present (fig.7).

FIG.1. OVARY AT 10 WEEKS GA: SEX CORDS (BOLD ARROWS) AND MIGRATING PGC (THIN ARROWS)

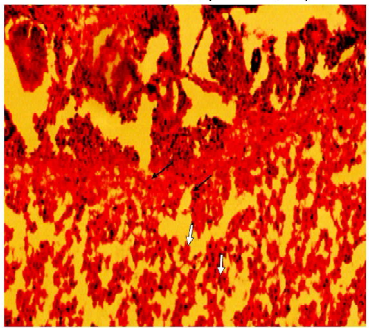


FIG.2. OVARY AT 16 WEEKS GA: NO CORTICO-MEDULLARY DEMARCATION. CLUSTERS OF OOGONIA

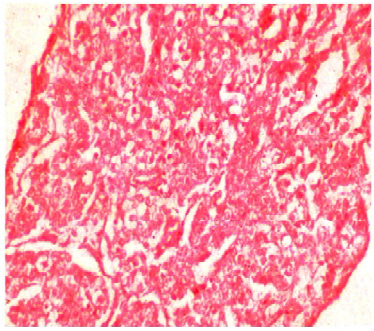


FIG.3. OVARY AT 20 WEEKS GA: LYMPHOID APPEARANCE AND CORTICO-MEDULLARY DIFFERENTIATION. PRIMORDIAL FOLLICLE (ARROW).

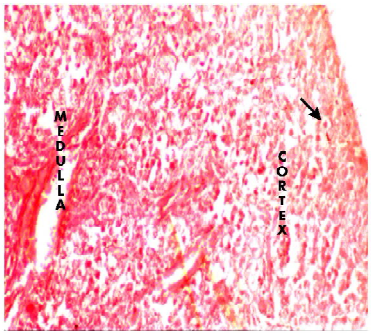


FIG.4. OVARY AT 24 WEEKS GA: CLEAR CORTICO-MEDULLARY DIFFERENTIATION

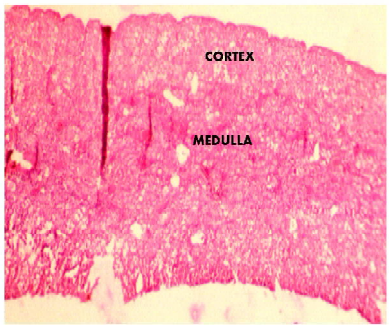


FIG.5.OVARY AT 28 WEEKS GA: PLENTY OF DEVELOPING AND DEGENERATING PRIMORDIAL FOLLICLES (ARROWS)

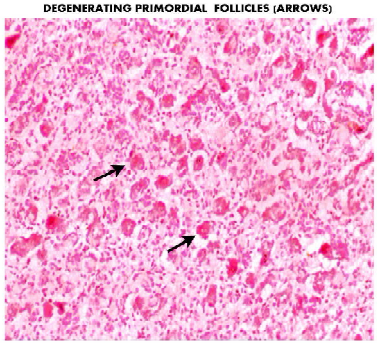


FIG.6. OVARY AT 30 WEEKS GA: CLEARLY DIFFERENTIATED PRIMORDIAL FOLLICLES (ARROWS)

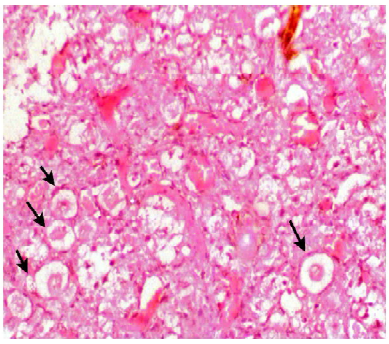


FIG.7. OVARY AT 38 WEEKS: PLENTY OF PRIMARY FOLLICLES LINED WITH CUBOIDAL EPITHELIUM

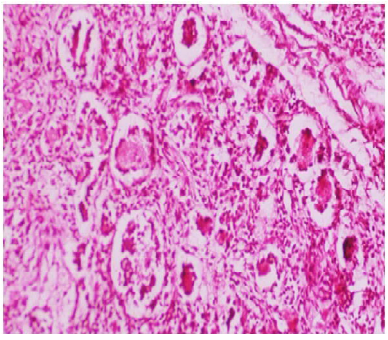


FIG.8 OVARY AT 5YRS AGE: STARRY SKY APPEARANCE OF CORTEX

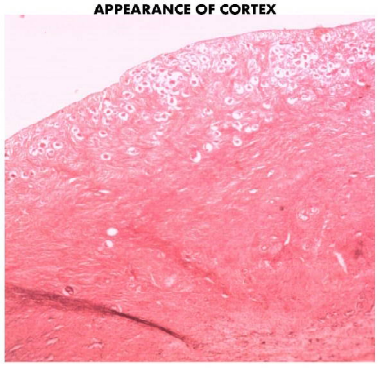


FIG.9. OVARY AT 5 YRS AGE: MATURE FOLLICLE WITH FOLLICULAR FLUID (FF AND THECA INTERNA (TI)

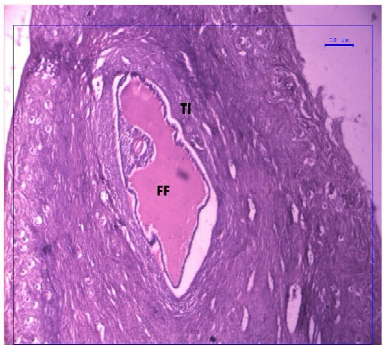


FIG.10.OVARY AT 7 YRS AGE: CYSTIC DEGENERATING FOLLICLE

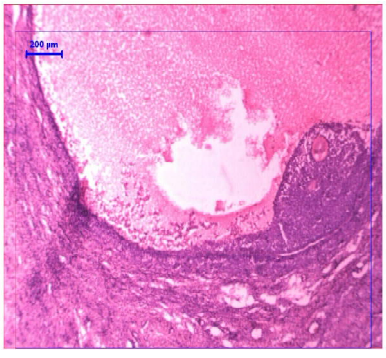


FIG.11. OVARY AT 7 YRS AGE: DEGENERATING SECONDARY FOLLICLE

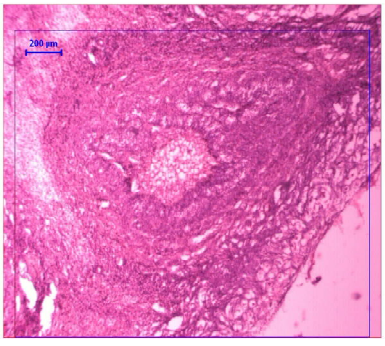


FIG.12. OVARY 13 YRS AGE: MULTIPLE PRIMARY FOLLICLES

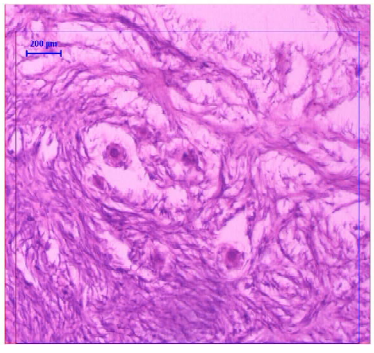


FIG.13. OVARY 30 YRS AGE: CUBOIDAL SURFACE EPITHELIUM (SE), TUNICA ALBUGINEA (TA)

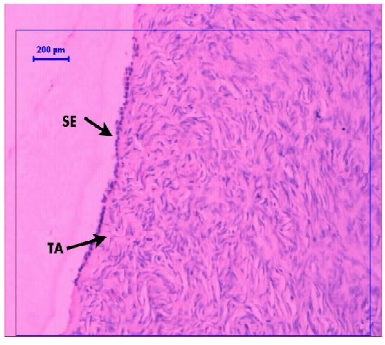


FIG.14. OVARY 41 YRS AGE: WHIRLING OF CORTICAL STROMA

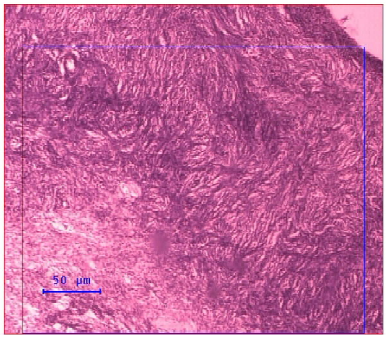
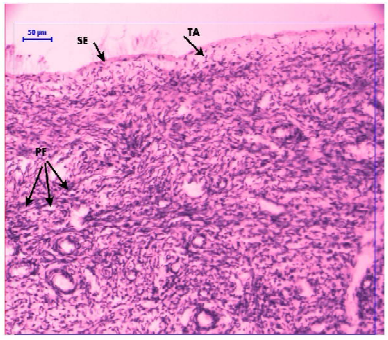


FIG. 15- 55 YEARS SHOWING DEGENERATING PRIMARY FOLLICLES (PF) (ARROWS) THICKENED TUNICA ALBUGINEA (TA) AND SURFACE EPITHELIUM (SE)



At 7yrs plenty of degenerating primordial follicles, growing secondary follicles and many cystic degenerated follicles were seen. One degenerating multi-laminar follicle (Fig.10) and one secondary follicle undergoing degeneration (Fig.11) were observed.

Increase in the cortical stroma with plenty of primordial follicles at the periphery, growing follicles in various stages of development and cystic degenerated follicles in the middle zone were observed at 13 yrs age (Fig.12).

A clear cuboidal surface epithelium and tunica albuginea were observed in the 30 years age section of ovary (Fig.13). Increase in cortical stroma with typical primordial follicles in the outer zone, early primary follicles without zona pellucida and a late primary follicle with clear zona pellucida were seen. Various stages of degenerating unilaminar and multilaminar follicles and corpora albicans were seen. In ovaries of more than 40 years the surface epithelium was flat. Increased stroma, few primary follicles, more number of cystic degenerated follicles and corpora albicans were observed. A large corpus luteum with its foldings and clear granulosa lutein and theca lutein cells was observed in one specimen of 41 years. Increased stroma giving the appearance of whirling pattern was observed at 41 years (Fig.14).In menopausal age group (46 – 55 yrs) thick surface epithelium, tunica albuginea and abundant vascular cortical stroma with no cortico-medullary demarcation (Fig.15) were observed.

DISCUSSION

Age related changes in the ovaries such as formation, differentiation and growth of follicles and stroma are indicators of reproductive competence. Observations on ovarian histogenesis from the time of follicle formation to its full maturation help in understanding the role of follicular cells and oocyte in providing reproductive reserve and competence [11,12,15].

The basis for categorization of prenatal ovaries in to three groups of embryonic, early foeal and late foetal was according to literature by 8 wks gestational age the gonads that were in the indifferent stage to begin with, could be recognized as definitely female gonads and cortex-medulla differentiation also could be observed [16]. Definitive cortex and medulla appear at 4th month of intrauterine life [17]. By 20 weeks gestation the formation of primary oocyte, beginning of granulosa cell interaction with primary oocyte and initiation of meiotic division could be observed [16,18]. According to Gondos [19] oogonia are the predominant cells between 9 -12 weeks of gestation. This period is followed by gradual decrease in oogonial number due to their transformation into oocytes in meiosis and their degeneration. In the present study oogonia were observed up to 16 weeks GA.

Gondos [3]observed medulla in ovaries of more than 12weeks gestation. Konishi et.al.,[4] reported hyper cellular cortex packed with germ cells at the periphery and central fibro vascular medulla at 12 weeks with clear corticomedullary demarcation. In the present study only at 24 weeks gestational age well defined Corticomedullary demarcation, vascular medulla and plenty of primordial follicles in the peripheral cortex were identified suggesting a delay of 12 weeks in the local population.

Valdes-Dapena [20] reported the presence of clearly recognizable germinal epithelium and ovarian stroma with lymphoid appearance at 24 weeks gestation. In the present study clearly recognizable germinal epithelium was observed only in late foetal period but lymphoid appearance of ovary could be identified at 16 weeks which is earlier than that reported in literature.

Plenty of encapsulated primary oocytes giving the appearance of tiny white rings with dark central dots that are known as primordial follicles were observed at 30 weeks in the present study. The primary oocytes exhibited vesicular nucleus and clear cytoplasm. Valdes-Dapena[20] reported these finding in the ovary of a dead fetus of 17weeks gestation. According to Gondos [3] formation of primordial follicles takes place between 16 –29 weeks. Nicosia [21] observed primordial follicles at 20 weeks gestational age. According to him primordial follicles and medulla occupy the largest component of ovary between 20 – 25 weeks of development. In the present study this was observed for a wider period of 20 to 38 weeks of GA.

According to Young and Heath and Moore and Persaud [18,22] this encapsulation takes place in 7th month of fetal life there by arresting further development of primordial follicles until the female reaches sexual maturity. Gondos [3] reported beginning of follicular atresia at 16th week with most extensive germ cell degeneration during 16 – 20 weeks. In the present study follicular degeneration started at 24 weeks and most extensive degeneration was observed during 30 - 38 weeks.

The postnatal ovaries were divided into pre pubertal, reproductive and menopausal groups. The basis for this classification was that in the prepubertal group there will be no progress in the follicular development. In the reproductive group follicles in various stages of development and degeneration could be observed. In the menopausal age more of degenerating and atretic follicles, corpora lutea and corpora albicans were observed with no primordial follicles.

Development of vesicular (Graafian) follicles is particularly characteristic of the active sexual years [17]. According to Shaw [23] follicularization i.e. the process by which a primordial follicle is converted into a Graafian follicle begins as early as 32nd week of intra uterine life. In the present study up to formation of primary follicle was observed in prenatal ovaries. Graafian follicle was observed earliest in one postnatal ovary of 5 years age in the present study.

In the literature Valdes-Dapena [20] reported follicular cysts at 36weeks and multilaminar follicle at 40 weeks old prenatal ovaries. Konishi et.al.,[4]observed many primordial follicles in inner cortex at 31 weeks. At 40 weeks they observed growing follicles with several layers of granulosa cells and theca cells in the inner most region while outer region consisted of primordial follicles. Nicosia [21] observed cuboidal germinal epithelium in neonate and a germinal epithelium with few flat and few cuboidal cells at 8th postnatal age. Nicosia and Sforza et.al., [21,24]reported secondary and antral follicles in the neonatal and 8th postnatal ovaries. In the present study follicular cysts, multilaminar follicles were observed only in postnatal ovaries.

CONCLUSION

When compared to the reports in literature there is 6 weeks to 12 weeks delay in the time of appearance, growth and degeneration of follicles and in cortico-medullary demarcation in prenatal group in the present study. In the postnatal group also delay in appearance of Graafian follicles and follicularization was observed when compared to that reported in literature. This discrepancy in observation from different laboratories can be due to racial, geographical or nutritional factors. By conducting studies with larger samples considering these factors will provide the statistically proved basis for these factors. The present study is only a preliminary study including a wider age range in a single study which was not reported in literature.

Conflicts of Interests: **None**

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