PART I

In the present study, 175 infertile females were referred at our bi-weekly clinic for investigations with complaints of different problems regarding infertility from Ahmedabad city and its vicinity.

Endocrine, biochemical studies as well as sonography were carried out in these cases. Moreover chromosome analysis was also done in these females wherever necessary.

The results revealed that among 175 females, majority of them had problems of menstruation. Hence according to diagnosis these females were divided into 6 major groups.

First group included females with primary amenorrhea where there was no onset of menarche with normal chromosome complaints. Most of these females had abnormalities regarding development of gonads as well as endocrine profile and underdeveloped secondary sex characteristics. Majority of females were suffering from primary ovarian failure with small uterus and/or ovaries, or absent uterus and/or absent ovaries. Secondary ovarian failure was also observed in this group. Hyperprolactinemia could be related with stress, psychological trauma and social stigma in these females.
Secondary amenorrhea was also classified under this study where due to some reason menarche stopped in these females. Like primary amenorrheic cases, in this group amenorrhea was related with abnormal development of gonads as well as hormonal imbalance. Secondary amenorrhea was also related with primary ovarian failure and secondary ovarian failure with stress in these females. Chromosome compliment was normal in these cases.

Irregularities of menstruation or oligomenorrhea was classified as the 3rd group in the present study, where gonadal development was found to be normal with normal development of secondary sex characters and wherein 14.28% of patients had normal hormonal profile. These cases had normal Karyotype. However, 52.38% of females had elevated levels of prolactin, gonadotropins with low levels of estradiol which suggested hormonal imbalance in these females with stress and social stigma. Some patients (33.33%) of this group had low gonadotropin with low estradiol hormones which could be the main reason for infertility in these females. Four cases of this group had normal development of secondary sex characters. However, ultrasonography reports showed cystic ovaries on both sides with normal development of uterus. Hormonal profile showed significantly high levels of LH which was related with cyst development in ovaries. The androgen was not converted into estradiol which was evident from the low levels of estradiol in these females. This may be the major reason for their amenorrheic condition.

Group IV and V were included as groups of primary sterility and secondary sterility of females with clinical history of no issue after 2-10 years of married life.
Ultrasound reports showed no changes in gonads or reproductive system in this group. Majority of females in these groups were suffering from "unexplained infertility" which could be related with many causes, i.e. immunological problem, stress, trauma, etc.

MISCELLANEOUS

The VI group comprised of miscellaneous cases where 6 cases were referred with various sexual anomalies.

Two cases had 46,XY chromosome complaints and were phenotypically females. (Case No 979 and Case No. 1205).

Case No. 979 had well formed breast and female phenotype, absence of sexual hair with levels of FSH, LH, T and PRL which were comparable to normal males while Case No. 1205, had also normal development of female secondary sex characteristics with elevated FSH and LH with low E₂ suggesting primary gonadal failure with testosterone levels comparable to that of normal males which is also known as androgen insensitivity syndrome correlated with Mullerian regression.

Turner Syndrome: Case No. 1283, 15 years old girl had short stature, shield shaped chest, cubitus valgus, ptergium colli, hypoplastic nails, low hairline with 45,XO true Turner cell line. Hormonal profile showed elevated gonadotropin levels with subnormal levels of estradiol indicating primary ovarian failure and primary amenorrhea.
XX pseudo hermaphroditism: Case No. 1304 was investigated as a case of pseudo hermaphrodite where the patient was phenotypically male with normal female hair distribution and absence of gynaecomastia. Penis was well developed with poorly developed labia majora. However, vagina and labia minora were found to be absent in this patient. Ultrasound scanning showed well developed ovaries and uterus with normal gonadotropin and low E2 levels. However, testosterone was found to be at higher side as compared to normal females, suggesting abnormal ratio of E/T in this case with 46,XX Karyotype. This condition is known as pseudo-hermaphroditism, which could be related with adrenal hyperplasia.

Delayed puberty: Two patients were found to have delayed development with absence of sexual maturation at puberty and absence of menarche. Hormonal profile showed significantly low serum levels of FSH, LH and E2 which suggested constitutional delay in activation of the hypothalamic-pituitary-gonadotropic axis causing a prolonged pubertal state. Moreover, poor nutrition may also lead to hypogonadotropic delayed growth and development.

Biochemical Evaluation: There were no significant changes in haemoglobin, blood glucose as well as serum cholesterol levels in all groups of females suggesting that no alterations occurred in basal body metabolism in these females. Therefore, from the obtained results, in the present study suggest hormone imbalance was the major cause for infertility in these females. However, primary
amenorrhea was the major cause among amenorrheic patients with abnormal development of reproductive system. Primary and secondary sterility was mostly related with idopathic or unexplained infertility. Chromosome abnormalities was found to be very rare in these patients. Hence, in the present study hormonal imbalance seems to be more prevalent in infertile females.

CONCLUSIONS

From the work embodied in this thesis, the following overall conclusions could be drawn:

1. The major cause for amenorrhea was hormonal imbalance.
2. Primary amenorrhea was mostly related with abnormal development of gonads with primary ovarian failure. However, in females with primary amenorrhea, no chromosomal anomalies was detected.
3. Primary amenorrhea was also related with secondary ovarian failure, i.e. significantly low levels of FSH, LH and $E_2$.
4. Secondary amenorrhea was also related with abnormal gonadal development with primary and secondary ovarian failure.
5. Hyperprolactineamia was also found in primary and secondary amenorrhea cases which could be related with stress, social stigma, pressure, etc. in these females.
6. Four females with secondary amenorrhea had polycystic ovarian syndrome with high LH which could be the major cause for infertility.
7. Females with menstruation irregularity (oligomenorrhea) did not present with cytogenetic abnormalities but had changes in endocrine profile as well as primary and secondary ovarian failure.

8. Primary and secondary sterility were mainly related with "idiopathic" or unexplained infertility.

9. XY phenotypic females were related with androgen sensitivity syndrome with Mullerian regression.

10. Case No. 1283 had true Turner cell line of 45,XO with typical Turner characteristics, high gonadotropin and low E₂ which were the main cause of infertility.

11. Case No. 1304, 46,XX genotypical females with male external genitalia caused pseudohermaphroditism in this case, where abnormal E/T ratio was the main cause of this abnormality which could be related with adrenal hyperplasia. Low E₂ levels were also correlated with absence of one X chromosome.

12. Delayed pubertal development could be correlated with constitutional delay in activation of the hypothalamic-pituitary-gonadal axis and with poor nutrition in these females which could lead to hypogonadotropic condition.

13. Biochemical alterations were not found in these infertile females suggesting that basal body metabolism was not affected.

Based on the work embodied in the present study, the following investigations could be carried out to provide further informations:
FUTURE LINES OF WORK

1. Follow up studies of patients which would include monitoring of hormonal levels periodically after therapy which would be beneficial in determining the endocrine changes or response of the patients to the hormonal therapy.

2. The action of hormones is often impaired at the receptor site of the target organ. Receptor assay if carried out would be of utmost importance in determining end-organ response and insensitivity of the target organs to hormone action.

3. Immunological studies would also have been very much useful to determine causes in infertile females.

4. Information regarding diet, life style, food habit, etc. would also be helpful to investigate causes for infertility.

Further investigation of various aspects of sexual dysfunction is of significance in this State (Gujarat) and the neighbouring areas, where the causes and types of sex anomalies are as yet poorly documented.
PART II

Effects of *Carica papaya* seeds benzene and alcoholic extract treatments and withdrawal.

The effects of treatment of rats with benzene and alcoholic extracts of *Carica papaya* seeds for 30 days were studied on the histophysiology of their ovaries and uterus, estrous cycles, fertility rat. Some specific biochemical parameters in ovary and uterus were also carried out. Moreover, to study toxic effects of *Carica papaya* seed extracts, if any, serum GPT and GOT as well as histology and histocytometry of liver, kidney were also done in all groups of animals. The possible reversibility of the induced effects were also investigated.

The results revealed that both papaya seed extracts, i.e. benzene and alcoholic did not affect ovarian steroidogenesis as well as serum hormonal profile of E₂, FSH and LH. Therefore, the extracts do not affect the hypothalamo-pituitary-gonadal axis.

The changes in uterine biochemical profile and alterations in its histology suggested that the extracts affect the internal milieu of uterus in treated rats which might not be conducive for nidation and implantation. Therefore, the extracts manifested anti-implantation effects.

The estrous cycle was irregular with predominance of diestrous in treated females which could be also responsible for 100% negative fertility rate suggesting that the extracts manifested antifertility effects in treated animals.

The two extracts of papaya seeds manifested antiestrogenic effects in treated
animals. However, there were no alterations in serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) in treated animals suggesting that the extracts did not manifest any toxic effects which was also evident by the unaltered histology of liver and kidney as well as histocytometric observations of the same organs.

The withdrawal of treatment helped in recovery of all the induced effects of the treatments in uterus and ovary and restored the fertility. Therefore, functional sterility could be induced in rats by short term treatments with Carica papaya seed extracts.

CONCLUSIONS

From the work embodied in this thesis the following overall conclusions could be drawn:

1. The effects of plant extracts benzene and alcoholic of Carica papaya seeds manifested anti-implantation, anti-fertility as well as anti-estrogenic effects.

2. The two extracts did not affect ovarian steroidogenesis.

3. Benzene as well as alcoholic extracts caused alterations in biochemical profile of uterus which might not be conducive for implantation.

4. Histology and histocytometric studies of uterus and ovary showed alterations in treated animals.

5. The benzene and alcoholic extracts did not manifest any toxic
6. The withdrawal of the treatment caused recovery in the structure and metabolism of ovary and uterus and also restored the fertility.

Based on the work embodied in the present study, the following investigations need to be carried out to provide further informations:

**FUTURE LINES OF WORK**

1. Combinations of extract administration could be used to study antifertility effects of papaya seeds.

2. Fractionation of papaya seed extract will be helpful to know the most effective fraction(s).

3. Ultrastructure studies would be helpful to explain effects of papaya seed extracts at cellular levels.