CHAPTER – I

INTRODUCTION

Prevalence of infertility

It is widely accepted that human existence reaches completeness through a child which is genetically one’s replica and a trail of all transactions. Child bearing and raising of children are extremely important events in every human’s life and are strongly connected with the ultimate goals of completeness, happiness and family integration. The incidence of female infertility differs from 10% to 20% and is increasing constantly by concussions. Childlessness has a multidimensional concussions in one’s life says a report by Romero Ramos et al (2008).

Infertility is seen between the age group of 15 to 49. Infertility affects in many countries and to varied percentage; 10-15% of reproductive age couples is USA 17% to 20% in UK, 21% in Canada. 13% in Denmark, 16% in Scotland and 5.4% in Israel. The incidence in India varies from 5-15% in South India. (Ann et al., 2000).

Types of infertility

Infertility is defined as the unsuccessful waiting period of 12 months for pregnancy. Mc Grath et al., (2005).

Infertility is divided into two groups primary and secondary. The definitions of primary infertility vary between studies but the one proposed by WHO (2001) defines it as the inability to conceive within 2 years of marital life through unprotected intercourse in age among 15 to 49 years. Couples who have previously been pregnant atleast once and who are not able to achieve another pregnancy are termed as secondary infertility. Its rate has been reported to be ranged from 0.6 to
3.4% for the primary infertility and 8.7% to 12.6% for the secondary. (Mescarenhas et al 2012).

**Role of hormones**

The hypothalamo hypophys axis secretes the gonadotrophins namely FSH and LH which causes the follicular maturation and ovulation. Gnoth et al., 2005.

**Reasons for infertility**

Fertility can be postponed and it results in temporary infertility. When it is caused by clinical conditions like chromosomal abnormality that is genetic disorders or hormonal imbalance or due to biochemical (metabolic) disturbances it becomes infertility which needs medical assistance. The reasons for postponing pregnancy in the temporary infertility may be due to time spent in education, time spent in developing career, late marriage or no immediate desire to have a child. Sometimes the reason for secondary infertility may be having an abnormal child and fear of becoming pregnant again. The average age of women in Ireland who bear their first child is 30.6 which is found to be higher than UK (28.7) and Europe (29.6). Also ageing places its limits to fertility. Recent trends towards postponing age at first pregnancy have highlighted the natural limits of fertility and accelerated the development and use of medical technology to overcome such limits. Mc Grath et al (2005).

**Consequences of infertility**

Generally couple face a social stigma especially women. There are many ill effects associated with infertility. The consequences of infertility are grouped as societal repurcussions, psychological disorders and personal suffering according to a
### FSH and LH in females and males

<table>
<thead>
<tr>
<th></th>
<th>FSH</th>
<th>LH</th>
</tr>
</thead>
</table>
| **Female** | • stimulates ovary to produce steroids ovary will produce estradiol during follicular phase and progesterone during luteal phase  
• Surge at midcycle, with LH, triggers ovulation | • stimulation ovary to produce steroids  
• surge at midcycle triggers ovulation  
• remember, luteinizing hormone turns the follicle into the corpus luteum by triggering ovulation |
| **Male**   | • stimulates sertoli cells to produce androgen-binding protein (ABP), thereby stimulating spermatogenesis  
• FSH also stimulates sertoli cells to produce inhibin, which provides negative feedback to the anterior pituitary to decrease FSH secretion | • stimulates Leydig cells to produce testosterone  
• testosterone provides negative feedback to anterior pituitary and hypothalamus |

### In the female

**Estrogen**
- Negative feedback
  - occurs during follicular phases when estrogen levels are still low.
- Positive feedback
  - occurs at high concentrations near the end of the follicular phase, estrogen becomes a positive inducer of the anterior pituitary
  - positive feedback triggers the anterior pituitary to release more FSH and LH
  - more FSH and LH cause the ovary to produce more estrogen
  - the ensuring LH surge is responsible for ovulation

**Progesterone**
- stimulate secretory and vascular activity of the endometrium, preparing for implantation of an embryo
- secreted by the corpus luteum, after ovulation
- when corpus luteum regresses, progesterone levels fallnew vasculature in endometrium regresses and the tissue sloughs off.
FUNCTIONS OF GONODOTROPHINS

1. Beginning at approximately age 8, the hypothalamus increases its production of gonadotropin-releasing hormone (GnRH).

2. GnRH triggers the anterior pituitary to release stimulating hormones (LH) and follicle-stimulating hormone (FSH).

3. LH and FSH trigger testosterone production in the testes and estrogen production in the ovaries.

4. Effects of sex hormone release:
   - Male Secondary Sex Characteristics:
     - Pubic and axillary hair grow
     - Facial hair grows
     - Larynx elongates, lowering voice
     - Shoulders broaden
     - Body, arm, and pubic hair grow
     - Musculature increases body-wide
   - Female Secondary Sex Characteristics:
     - Breasts develop and mature
     - Hips broaden
     - Pubic hair grows

5. Before puberty, the hypothalamus and pituitary are very sensitive to negative feedback signals from testosterone and estrogen. During puberty, the sensitivity of the hypothalamus and pituitary to this negative feedback decreases to levels typically seen in adults. This change allows an increase in the production of testosterone and estrogen that stimulates the development of secondary sex characteristics.

GONODOTROPHINS NEGATIVE FEEDBACK MECHANISM

1. Hypothalamus
2. GnRH
3. Pituitary
4. LH and FSH
5. Testosterone
6. Estrogens and Progesterone
7. Testes
8. Ovaries
study. Marital discord is also common among infertile couple. Mostly discord in marriage is seen among couple when the recurring medical treatment becomes a failure. (Droszdol et al 2006).

**Management**

The couple attending the infertility clinic are first and foremost counselled and given much hope of conception. Diet regularisation, mineral rich that is iron rich food are recommended. Mostly the couple including the male has to follow the diet pattern to increase the sperm count and quality.

In the regime, next comes the sexual pattern to be followed. The couple are advised to have sex in the oestrus period (heat period) during the 11th to 18th day of menstrual cycle. It is mostly successful. (Wang et al., 1992).

The other method is hormonal treatment through chemical tablets. The recommended tablet is Clomiphene citrate which induces the FSH in the pituitary and regulates the follicular maturation and helps in ovulation. (Release of the mature egg).

If this is not successful then comes IUI (Intra Uterine Insemination) later on next step is IVF if IUI does not answer. The patient has to have much confidence and wait till the treatment. It is quite costly and acquires skilled physicians. It may result in a lot of psychological distress, discord in marriage and society abuse and abandonment. The drugs may also cause adverse effects on health of the mother and issue. Hence to avoid such problems we nowadays seek to the herbal remedy which is quite safe, easily available and gives good results. (Jones et al., 2004).
Menstrual cycle in human female

Menstrual cycle process
Herbs and fertility

Plants have chemical substances medicinal importance that produce a district physiological action on the body of human. Plants provide an important source of pharma and medicine and this has proven to cure diseases (Fan Wilson E.O. 1988).

Plants have served to be an important material for drug development. They have an array of bioactive metabolites the important resource material ones being steroid, tannis, terpenoids, carotenoids, flavanoids, alkaloids and glycosides. (Balaindean and Kinghorn 1993).

According to the WHO (2004), 80% of the word’s population now uses medicinal herbs as drug for their primary health care. Plant based drug is the major area of current research. Herbs form the base for important drugs of this modern world. (Ether 1981)

Medicinal plants are used worldwide because they are cheaper and simple to procure and they have lesser side effects (John 1997).

The oldest repository of human knowledge about medicinal usage of plants in Indian sub-continent has been written in Reg-veda during 4500 BC to 1600 BC, even for treating fertility. (Pushpagandan 1995).

(Rana et al 2010) pointed out that to meet their fertility requirements ethnic people depend on wild plants and each ethnic community have their our ethno medicinal and ethnopharmacological knowledge about the plants in different geographical belts of India.

(Viswanathan 2004) the practice of folk medicines is in rapid decline globally due to life style, secrecy of healers, herbal formulations, negligence of youngsters, therefore ethnobotanical exploitation and documentation of the importance of such
genetic resources is required immediately as this unique indigenous knowledge fade away with the tribal community.

(Lingaiah 2013) Ethnomedicines are used in the form of extracts, paste, juices, powders etc to cure several disease like Asthma, Arthritis, diabets, BP, fever, filaria, Jaundice, paralysis and infections like skin allergy, skin diseases, STD, ringworm etc., Plants are used for fertility improvement in female and male, white discharges in female, tooth ache and other inflammations. Plant material in combination with other parts of same or different plants or substances like curd, honey, oil, milk or turmeric powder. Parts used are bark, roots, leaves, fruit, flower, stem, seeds and the whole plant.

**Alternative medicines**

In Ayurveda, Unani, Homeopathy and Siddha from time immemorial the traditional system of treating infertility and other ailments were followed according to their formulations and prescribed herbs.

Meenakshi Sharma (2014) in her review article has enlisted the herbs that cure infertility problems. *Saraca asoca* is seen to manage ovulation disorders. *Caesalpinia Crista* and guggulu is administered for the treatment of PCOS and for premature ovarian follicle syndrome. Chandraprabha (drug) and *Leptadenia reticulata* is given for treating Pelvic Inflammatory Disease (PID). Katuki (*Picorthizia Kurroa*) and Punarava are used. Under developed is treated with uterus, shatavari, Ashwaganda (*Withania Somnifera*), Bala (*Sida Cordiflia*), *Trapanatas*, *Nagbala* (*Grewia hirsuta*). The herb *Saraca asoca* is useful in menorrhagia, dysmenorrhea and leucorrhea. It exhibits estrogen like activity enhancing ovulation and also heals the endometrium. Thus the pharmacological action of herbs are useful in treating female infertility.
Identification of phytoconstituent through *insilico* analysis

Bioinformatics is a discipline which involves databases formed from organization of data to develop new software and algorithms, which is used for the analysis and interpretation of data. (Nicola et al., 2008)

(Richon, 1994) found that bioinformatics and computational biology has the potential of enhancing drug discovery process therefore it is reducing the cost but also changing the way drugs are designed. Drug designing helps to identify novel compounds. The site at which the drug binds is the receptor or the target and the site for pharmaceutical effect as they are the prime targets for therapeutic agents which regulate biological function via interaction with small molecule.

Molecular docking is a promising technique in computer based drug design by screening small molecules and orienting them in binding site of a protein receptor. This has been routinely used for drug-receptor interactions in modern drug design. (Daisy *et al.*, 2011).

Peptidomimetics small protein-like chains designed to mimic a peptide. Use of them is one of the most recent methods of drug design and development in medicinal chemistry. They arise from modification of an raising peptide, or by designing similar systems that mimic peptides (Milton *et al.*, 1992).

In silico (computational) methods are mostly applied to pharmacology hypothesis development and testing. The method comprises of database searching, QSAR, similarity searching, pharmacophore identification, computational modeling and docking. The discovery and optimization of novel molecules with affinity to a target and the classification of ADMET properties have been identified only by using the above in silico methods. (Ekins, 2007)
Protein data bank

Originally Brookhaven National Laboratory developed the protein data bank in 1971. It was maintained by world wide protein data bank ww PDB from 2003 onwards. The members this bank are RCSBPDB (USA), PDBE (UK), PDBJ (Japan) and BMRB (USA). Archive of information about the 3D structure of macromolecules and their complexes determined by x-ray crystallography, NMR spectroscopy and Cryo-electron microscopy are present in ww PDB. Simple and advanced searches can be performed by the users relating to sequences, structure and function of macromolecules. (Sussman et al., 1998)

Ligand method preparation

The phytocompounds save in .sdf were converted to .pdb format using openbabel 2.3.1. Ligand was prepared using MGL tools by adding hydrogen atom to check the valencies of the heavy atoms. Ligand was minimized by computing gasteiger charges and saved in PDBQT.

Aim

To identify the phytoconstituents that promote fertility and investigate their pharmacological action through insilico analysis.

Objective

- To survey the prevalence of infertility in the study area
- To assess the metabolic variations causing infertility
- To screen and identify the phytochemical constituents
- To determine the possible activity of the specific phytochemical constituent that promote fertility.
Scope

- Discovery of a promising drug to promote fertility
- As it is an indigenous herb easy availability, easy accessibility and economic benefits are strongly anticipated.