

Summer Training at



(April 16-June 9, 2012)

A Study on Usage of DHEA & Folic Acid in Poor Ovarian Reserve

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**Under the guidance of
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**Post Graduate Diploma in Pharmaceutical Management
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Certificate

This is to certify that Mr. Trilochan Dua from Institute of Health Management Research, Jaipur has undergone summer training in Sun Pharmaceuticals, Mumbai from 16 April to 9 June 2012.

The Candidate himself carried out the project. His approach to the study has been sincere, scientific and analytical. This summer training is partial fulfilment of the course requirement is recommended for the award Post Graduate Diploma in Pharmaceutical Management.

I wish him success in all his future endeavours.

Dr. P.R. Sodani

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ACKNOWLEDGEMENT

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For the successful completion of my work, I am thankful to my guides Mr.A.D.K. Rajesh (Marketing Manager) Inca Life sciences, Mr. Sanjay Sahai (General Manager-Strategic Marketing) who helped me throughout my assignment.

I would like to express my sincere gratitude towards Mr. Paresh Shah, Ms Anupama Dang for providing the best of working environment and ambience.

I would also like to thanks all the Sales Officers of “Sun Pharma (Inca Life sciences)” who helped me during field work and for sharing their Valuable time with me.

Once again, thanking all those who have helped me directly and indirectly in completing my project.

SCOPE OF PROJECT-

With the rising cases of Poor ovarian reserve due to lifestyle changes such as Smoking, Alcohol consumption, obesity, career oriented women, Caffeine intake, Excess of exercise which leads to Infertility.

Improvement of oocytes/embryo quality with DHEA supplementation potentially suggests a new concept of ovarian aging, where ovarian environments, but not oocytes themselves, age. DHEA may, thus, represent a first agent beneficially affecting aging ovarian environments.

Thus, Dehydroepiandrosterone (DHEA) has been reported to improve pregnancy chances with POR, and is now utilized by approximately one third of all I.V.F centres worldwide. (1)

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EXECUTIVE SUMMARY-

In vitro Fertility Doctor (I.V.F)-Sample Size -25

- 1) I.V.F. Doctor (**25**) treat **715** infertility patients in a month, which means each doctor, treat **29** patients in a month.
- 2) Out of total infertility patients treated by I.V.F+I.U.I+ GYNE. Doctors (**say 100%**), I.V.F Doctor treat **43%** of infertility patients in a month.
- 3) I.V.F Doctor (**25**) treats **195** patients of Poor ovarian reserve in a month, which means each I.V.F Doctor treats around 8 patients of Poor ovarian reserve (P.O.R) in a month.
- 4) In the treatment of Poor ovarian reserve I.V.F Doctor prefers to prescribe **DHEA** mostly, followed by **Hmg** and **Clomiphene**.
- 5) In the treatment of Poor ovarian reserve, least preferred molecules by I.V.F Dr are **L-arginine** and **GnRH**.
- 6) Out of **25** I.V.F Doctors surveyed, **20** I.V.F Doctor Prescribe DHEA in Poor ovarian reserve. It means **80%** of I.V.F Doctor Prescribe DHEA in Poor Ovarian reserve.
- 7) **20** I.V.F Doctor prescribe DHEA to 105 Poor ovarian reserve patients. It means, average frequency of prescribing DHEA by 1 doctor in a month is 5 patients.
- 8) I.V.F Doctors prescribe DHEA to 40% of Poor ovarian reserve Patients. It means I.V.F Doctor Prescribe DHEA to 40 patients of Poor ovarian reserve out of 100 (P.O.R) Patients.
- 9) I.V.F Doctors Prescribe DHEA Maximum at a Dose of 25mg BID, followed by 25mg TID in Poor ovarian reserve(P.O.R)
- 10) I.V.F Doctors are the maximum Prescribers of DHEA, Prescribe DHEA maximum times (17) for 3 Months in Poor Ovarian Reserve Patients.
- 11) **OVIGYN-D** is the Maximum Prescribed Brand by I.V.F, I.U.I and Gynecologist **OVISTERONE** is second preferred brand by I.V.F, I.U.I and Gynecologist.
- 12) I.V.F Doctors are the major prescribers of DHEA in Poor Ovarian Reserve. They Prescribe DHEA as Primary Drug of Treatment in 45% of Patients.
- 13) I.V.F Doctors gives equal preference to Antimullerian Hormone Testing and Antral Follicle Count to assess ovarian reserve.
- 14) I.V.F Doctors gives least preference to Day 3 FSH TEST to assess ovarian reserve.
- 15) **4 I.V.F Doctors** do not prefer to prescribe DHEA because of lack of awareness regarding role of DHEA in Poor ovarian reserve.

- 16) **2 Doctor** do not prescribe DHEA because no clinical evidence was available regarding role of DHEA in Poor ovarian reserve.

I.U.I-

- 1) I.U.I Doctors treats 25% of Infertility patients in a month.
- 2) I.U.I Doctors treat minimum number of Poor ovarian Reserve Patients in a month i.e., 21%.
- 3) I.U.I Doctors. gives equal preference to DHEA, Clomiphene and Hmg in Poor ovarian reserve.
- 4) I.U.I Doctors gives least preference to L-Arginine and GnRH in Poor ovarian reserve.
- 5) 52% of I.U.I doctors prescribe DHEA i.e., 15 out of 29 doctors.
- 6) I.U.I Doctors Prescribe DHEA to 25% of Poor ovarian reserve Patients.
- 7) I.U.I Doctors Prescribe DHEA Maximum at a Dose of 25mg BID, followed by 25mg TID in Poor ovarian reserve.
- 8) I.U.I Doctors Prescribe DHEA Maximum times for 3 Months, followed by 2 Months in poor ovarian reserve patients.
- 9) **OVIGYN-D** is the Maximum Prescribed Brand by I.U.I Doctors.
OVISTERONE is second preferred brand by I.U.I Doctors.
- 10) **I.U.I Doctors** Prescribe DHEA as primary drug of treatment in 20% of patients.
- 11) I.U.I Doctors gives equal preference to both AMH test and Antral follicle count test.
- 12) According to **I.U.I** Doctors, there were equal responses of **ovarian reserve improved** and **moderately improved** and in **2** cases there was no improvement in ovarian reserve.
- 13) In I.U.I doctors, non prescribers of DHEA are maximum, and only 1 Doctor was not aware about DHEA.
- 15) **I.U.I Doctor do not prescribe DHEA because of the following reasons-**
 - a) **No clinical Evidence-** 12 **I.U.I** Doctor do not prescribe DHEA because of no clinical evidence available.

b) No Human Trial Data- 7 I.U.I Doctor do not prescribe DHEA because of no human trial data available.

c) Lack of Awareness- 5 I.U.I Doctor do not prescribe DHEA due to lack of awareness of role of DHEA in Poor ovarian reserve.

Gynecologist-

- 1) Gynecologist treats 32% of Infertility Patients in a month.
- 2) Of the total number of Poor ovarian Reserve Patients in a Month gynecologist treats 35% of Poor ovarian Reserve Patients.
- 3) In Poor ovarian reserve, Gynecologist gives equal preference to prescribe Clomiphene and DHEA.
- 4) In Poor ovarian reserve, Gynecologist gives least preference to prescribe L-Arginine and GnRH.
- 5) 53% of Gynecologist prescribe DHEA i.e., 10 out of 19 doctors prescribe DHEA.
- 6) Gynecologist Prescribe DHEA to 35% of Poor ovarian reserve Patients.
- 7) **OVIGYN-D** is the Maximum Prescribed Brand by Gynecologist in Poor ovarian reserve.
OVISTERONE is second preferred brand by Gynecologist in Poor ovarian reserve.
- 8) Gynecologist Prescribe DHEA Maximum times at a Dose of 25mg BID in Poor ovarian reserve.
- 9) Gynecologist Prescribe DHEA Maximum times for 3 Months.
- 10) Gynecologist does not prescribe DHEA as primary drug of treatment in any patient of Poor ovarian reserve.
- 11) Gynecologist gives maximum preference to AMH test followed by Antral follicle count test.
- 12) Gynecologist gives least preference to Day 3 FSH test.
- 13) According to **Gynecologist**, in most of the cases ovarian reserve was moderately improved, and in 1 case there was no improvement in ovarian reserve.

14) All Gynecologists heard about DHEA, but they were not aware about its usage in Poor ovarian reserve.

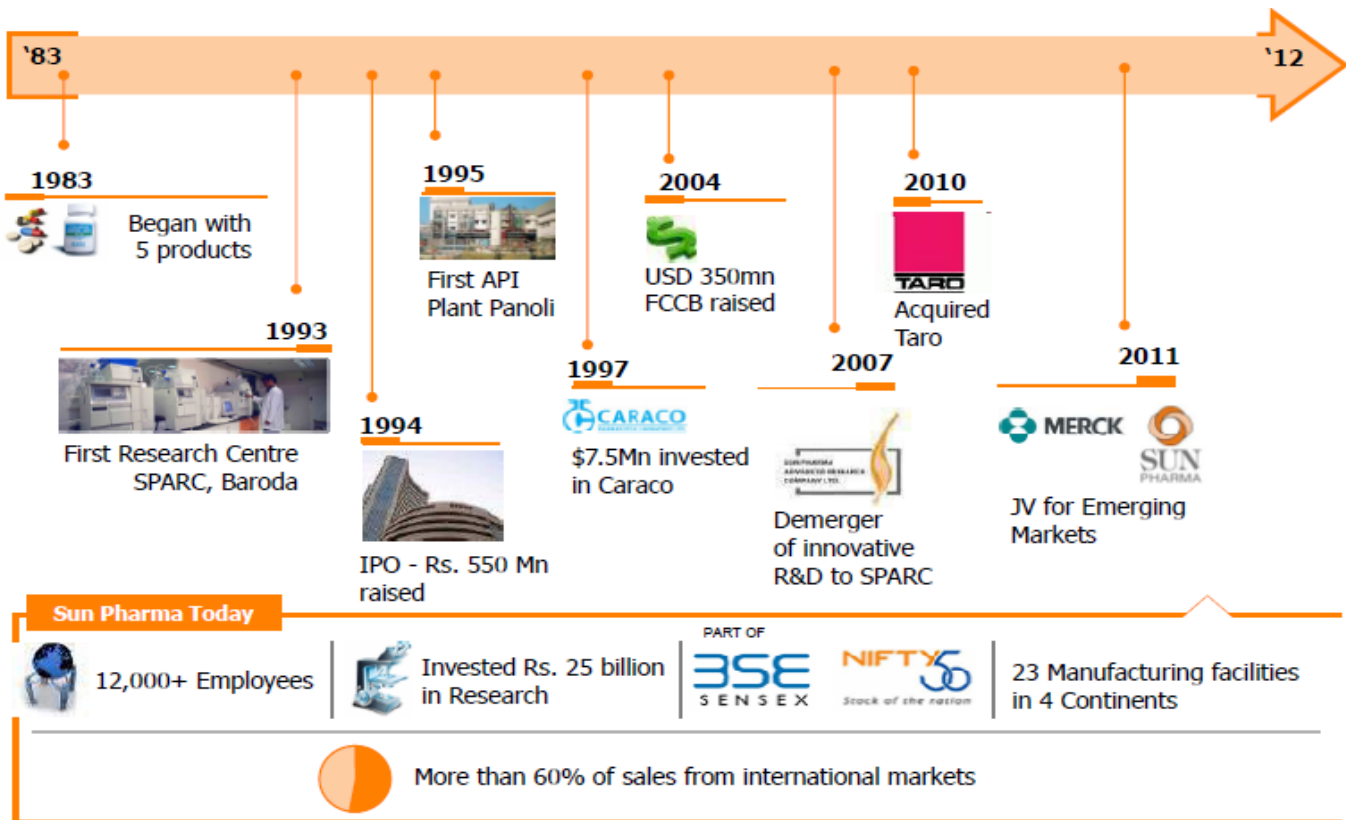
15) Gynecologist do not prefer to prescribe DHEA in Poor ovarian reserve because of following reasons-

- a) No clinical Evidence**
- b) No Human Trial Data**
- c) Long Duration of Therapy**
- d) Lack of Awareness**

COMPANY PROFILE-

- ▶ Sun Pharma pioneered specialty marketing in the Indian pharma industry when the company began in 1983. Today, company has reached leadership in each of the therapy areas that they operate in, and have built a reputation of trust and quality with their customers.

SUN PHARMA JOURNEY FROM 1983-2012



Strategy and Approach

Create sustainable revenue streams

- Focus: Chronic therapies
- Differentiation: Technically complex products
- Speed to market



Seek cost leadership

- Vertical integration : Development through Manufacturing (API and Finished Dosage) to Marketing
- Optimize operational costs

Balance profitability and investments for future

- Acquisitions yielding high ROI
- Development of complex generics

There are 17 divisions of SUN PHARMA delivering promotional message to specialty customers.

Therapy Focused Marketing



Delivering promotional message to specialty customers.

Gastroenterology, Orthopedics



Cardiology, Diabetology



Psychiatry, Neurology



Ophthalmology



Rheumatology, Dermatology



Asthma, COPD



Oncology



Fertility, Gynecology, Urology



Gynecology



Preferred Choice of Doctors

Leadership in key therapeutic areas*

Specialist	Feb '07	Feb '12
Psychiatrists	1	1
Neurologists	1	1
Cardiologists	1	1
Orthopaedic	1	1
Ophthalmologists	1	1
Gastroenterologists	2	1
Diabetologists	1	2
Chest Physicians	5	4
Nephrologists	4	5
Oncologists	4	7
Consulting Physicians	5	8
Gynaecologists	10	7
Urologists	8	10
ENT Specialists	5	21

*Ranks based on prescription share

Top 10 Brands contribute 20% of India Sale

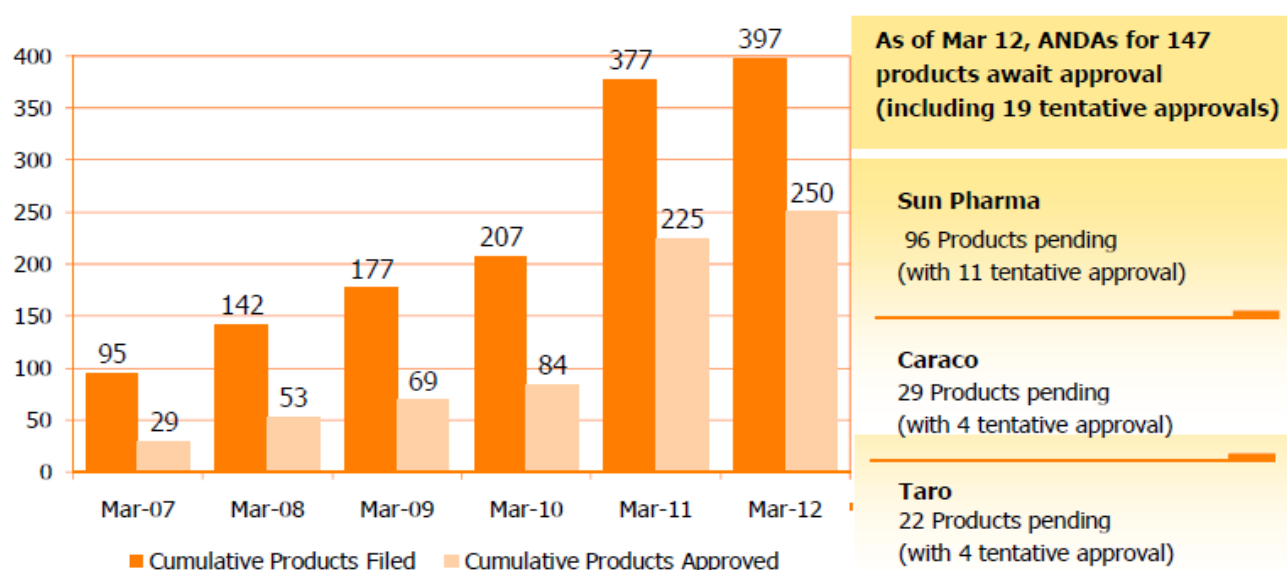
Brand Name	Therapy area
Pantocid	Proton pump inhibitor/ antiulcerant
Glucored Group	Oral antidiabetic
Aztor	CVS, cholesterol reducing agent
Susten	Women's healthcare
Pantocid-D	Proton pump inhibitor/ antiulcerant
Gemer	Oral antidiabetic
Levipil	CNS
Clopilet	CVS, anticlotting agent
Repace Group	CVS, Hypertension
Cardivas	CVS

Key Deals & Rationale

Year	Deals	Country	Rationale
2011	100% ownership of Caraco	US	Privatization
2011	Formation of Sun-MSD JV	Emerging Markets	Develop and commercialize technology based combinations products
2010	Acquired Taro Pharmaceutical Industries Ltd.	Israel	Dermatology & Topical Product Manufacturing Plant at Israel & Canada
2009	Caraco acquired some products of Forest's Inwood business	US	Increased generic product offerings
2008	Acquired Chattem Chemicals, Inc.	Tennessee, US	Import registration with DEA, API Plant approved by DEA in Tennessee, US
2005	Assets of Able labs	New Jersey, US	Dosage form plant (NJ, US) and IP
2005	Formulation plant in Bryan	Ohio, US	Dosage form plant (Ohio, US)
2005	Acquired ICN Hungary	Hungary	API and dosage form plant (Hungary)
1999	Merged Milmet Labs	India	Ophthalmology brands
1998	Brands from Natco	India	Respiratory brands
1997	Acquired Caraco	Detroit, US	Dosage form Plant
1997	Merged Tamilnadu Dadha Pharmaceuticals Ltd (TDPL)	Chennai, India	Gynecology and oncology brands; API and dosage form plant
1996	Acquired MJ Pharma	Halol, India	Dosage form plant (now USFDA approved)
1996	Bulk Drug plant from Knoll Pharma	Ahmednagar, India	API plant (now USFDA approved)

ANDA Pipeline : Significant ramp up

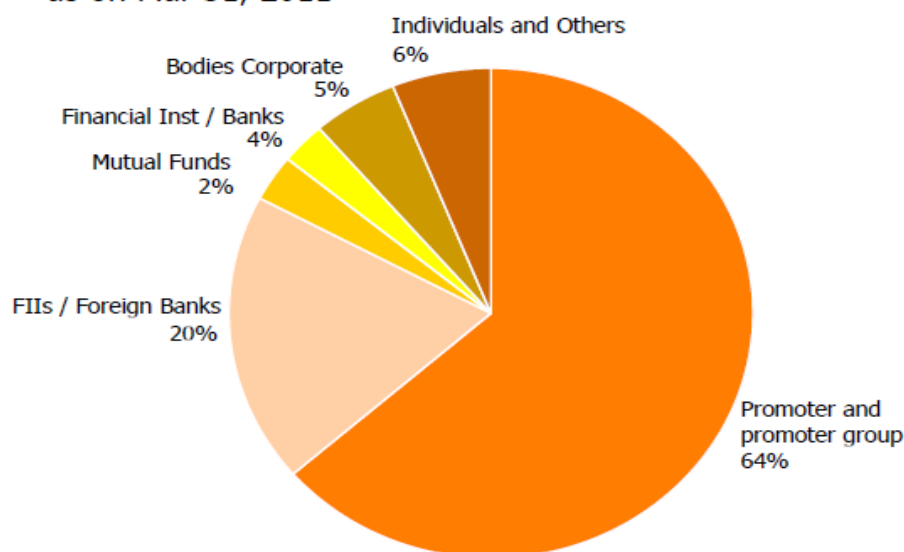
Products Filed and Approved Status



(Taro numbers added since Mar 2011)

Shareholding Pattern

as on Mar 31, 2011



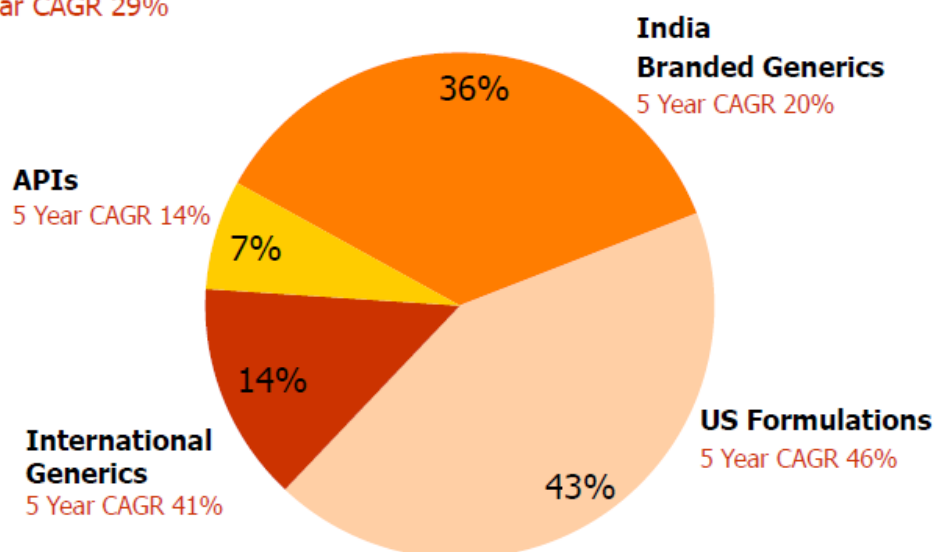
- Rs 1,000 Invested in the 1994 IPO is currently worth more than Rs. 270,000

- Total shares outstanding : 1,035 million
- Total free float (shares) : 375 million
- Average daily trading volume (12 months) : 1.0 million

Revenue Composition

2011-12 Annual Gross Sales : Rs 81173 million

5 Year CAGR 29%



Finished Dosage sales 92%
5 year CAGR 31%

International sales 62%
5 year CAGR 39%



From a modest start with products that are used in ICU settings such as Adenject and Cardiject, Inca's product basket now features products used for infertility management, gynecology and urology.(2)

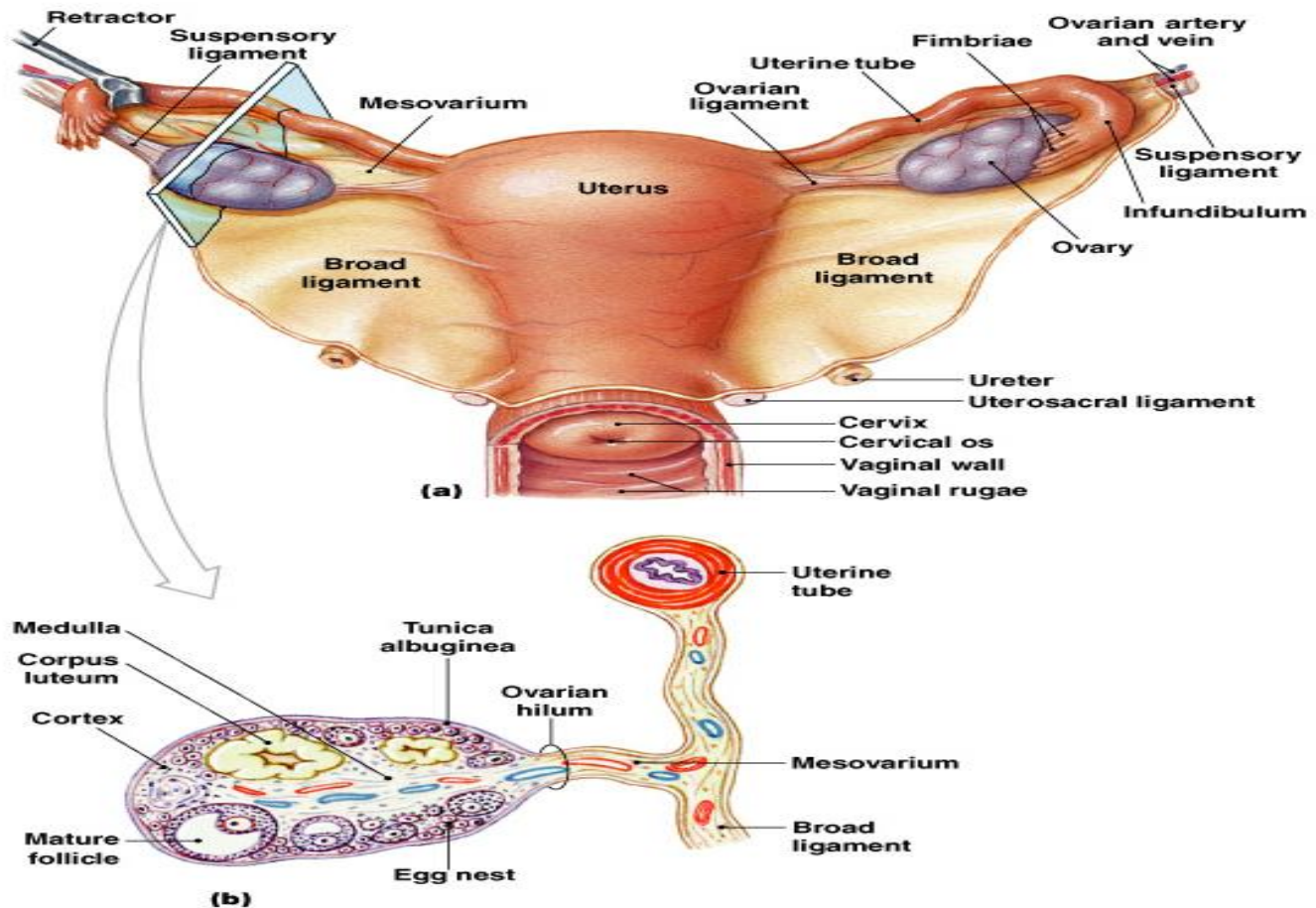
Therapy area coverage:

- ♦ Fertility
- ♦ Gynecology
- ♦ Urology

Top 5 brands:

- ♦ Lupride Group
- ♦ Fertigyn
- ♦ Caberlin
- ♦ Tropan
- ♦ GMH

Introduction to Female Reproductive System-



The female reproductive system consists of the external genitalia (vulva and vagina) and the pelvic or internal organs (uterus, fallopian tubes and ovaries). The four primary structure are:

1. **Vagina**
2. **Uterus and cervix**
3. **Fallopian tubes**
4. **Ovaries**

Vagina-

The vagina is a thin-walled hollow tube extending from the vulva outside, to the uterus inside. It is around 3 to 4 inches long. It serves several functions such as:

1. Receiving the penis during intercourse
2. Providing a passageway for sperm into the uterus
3. Releasing the menstrual flow
4. Serving as the passageway through which the infant is delivered

Uterus-

The uterus is a hollow, muscular female reproductive organ, which lies in the pelvic cavity (see figure 1). It holds and nourishes the fetus during the entire duration of pregnancy. It expels the fetus into the outside world during labor. It is composed of three layers:

- Endometrium (innermost layer of mucous glands and supporting tissues)
- Myometrium (thick middle layer composed of muscle fibers)
- Perimetrium (outermost layer)

The cervix is the specialized portion of the uterus that separates the uterus from the vagina. It is composed mainly of connective tissues (collagen and elastin and blood vessels. It is about 2.5 cm in length.)

Fallopian Tubes-

The uterine tubes or fallopian tubes are a pair of 10 cm (4 inch) long structures that extend from the sides of the uterus. Their free ends are shaped like a trumpet and lie close to the ovaries. The free ends have finger-like projections called **fimbriae**.

The functions of the fallopian tubes are:

- A passageway for ova from the ovaries to the uterus
- A place for fertilization to occur

Ovaries-The two ovaries are the female gonads that contain ova or eggs. The ovaries contain about 2 million ova at the time of birth, but many of these degenerate and die automatically, and by puberty, only 300,000-400,000 eventually remain. Through the age of 13 to 45 years, only 400 eggs actually mature to fully matured ova, while the remaining ova degenerate and die.. The ovary is located in the lateral wall of the pelvis in a region called the **ovarian fossa (fossa lies beneath the external iliac artery and in front of the ureter and the internal iliac artery.)**

ORGAN	FUNCTIONS
Vagina	1) Passageway of Menstrual Flow 2) Female organ for Coitus 3) Passageway for fetus during birth.
Uterus	1) Nourishes fetus until sufficiently mature to function outside mother's body. 2) Uterine muscles propels fetus outside.
Fallopian Tubes	1) Provides passageway for ovum. 2) Site of Fertilization.
Ovaries	1) Endocrine gland that secrete estrogen and progesterone. 2) Contain ova within follicles for maturation during the woman's reproductive cycle.

Hormones which controls Female Reproductive System-

Gonadotropin Releasing Hormone (GnRH)-

GnRH is the main controlling hormone for the female reproductive hormone secretion. Cells in the hypothalamus form GnRH that is delivered to the anterior pituitary, which in turn forms LH and FSH. GnRH is a unique hormone because it simultaneously controls the secretion of 2 hormones – LH and FSH.

Pituitary gland-

The pituitary gland, like the hypothalamus is inside the brain and is a small pea-sized gland weighing 1-4 g. It is divided into two regions or lobes:

- Anterior pituitary
- Posterior pituitary

The anterior pituitary too forms several hormones, but the important hormones are LH (luteinizing hormone) and FSH (Follicle stimulating hormone).

The anterior pituitary hormones – LH and FSH – are also called as ‘gonadotropin’ Both FSH and LH hormones are responsible for the growth and maturation of a single ovum in the ovary each month.

Estrogen and Progesterone-

FSH and LH released from the pituitary act on target organs, which are the ovaries and uterus. Under the influence of FSH and LH, two hormones are formed by the ovaries – Estrogen and Progesterone.

Female ovarian sex hormones-

The two ovarian sex hormones are estrogen and progesterone.

Estrogen- is known as the female hormone because it plays an important role in shaping the female body and preparing it for the uniquely female function of shaping the female function of pregnancy. For instance, estrogen is vital for the development of breasts and hips. In addition, the vagina, uterus, and other female organs depend on estrogen in the body to mature. About 90% of the estrogen is made by the ovaries. Other organs like adrenal glands, liver and kidney also manufacture small amounts of estrogen.

Progesterone is the second most important female hormone. Like estrogen, progesterone is also made by the ovaries, with small amounts made by the adrenals. The function of progesterone is to stimulate the growth of a cushion-like lining in the uterus where the fertilized egg can grow and develop into a fetus. It also helps the breasts to make milk and is essential to maintain the pregnancy.

Different Estrogen Hormones-

Although 6 different natural estrogens have been isolated from human females, only three are present in significant quantities:

- Estradiol (most potent and major secretory product) – it is rapidly oxidized to estrone
- Estrone – hydration produces Estriol, which is much weaker

- Estrinol

Functions of Estrogen-

Estrogens have many functions. Among the important functions are:

- Development and maintenance of the female reproductive system and secondary sex characters.
- Promotion of growth and development of the vagina, uterus, fallopian tubes and breasts.
- Inhibiting the release of pituitary FSH and LH.

Progesterone-

Progesterone is formed by the corpus luteum. Progestin is the term used for progesterone and its derivatives.

Functions of Progesterone-

HORMONE	SOURCE	ACTION
GnRH	Hypothalamus	Stimulates Anterior pituitary to secrete Follicle Stimulating Hormone and Luteinizing Hormone
Follicle Stimulating Hormone	Anterior Pituitary	Stimulates ovaries to develop mature follicles(with ova);follicles produce increasingly high level of estrogen.
Luteinizing Hormone	Anterior Pituitary	Stimulates the release of ovum by the follicle; follicle then converted into corpus luteum that secretes progesterone.
Estrogen	Ovary(Follicle);Placenta	Stimulates thickening of and maintains endometrium.
Progesterone	Ovary(Corpus leuteum);placenta	Stimulate thickening of and maintains endometrium.
Human Chorionic Gonadotropin	Embryo(if pregnancy)	Stimulate production of progesterone

The most important effect of progesterone is on the uterus – it transforms the proliferative endometrium into secretory endometrium.

HORMONES AND FEMALE REPRODUCTIVE PROCESS

FEMALE INFERTILITY-

Infertility is the failure of a couple to become pregnant after one year of regular, unprotected intercourse. In both men and women the fertility process is complex.

About 10% of couples who wish to have a baby are still unable to after a year of unprotected sex. About half of these couples can achieve pregnancy within two years after appropriate treatment of the woman, the man, or both. Even under ideal circumstances, the probability that a woman will get pregnant during a single menstrual cycle is only about 30%. And. When conception does occur, only 50% to 60% of pregnancies advance beyond week twenty. (The inability of a woman to produce a live birth because of abnormalities that cause miscarriages is called infecundity.

Males and females each account for 40% of infertility. In the remaining 20%, either both partners are responsible or the cause is unclear. Although this report specifically addresses infertility in women, it is equally important for the male partner to be tested at the same time.

In order for a woman to become pregnant:-

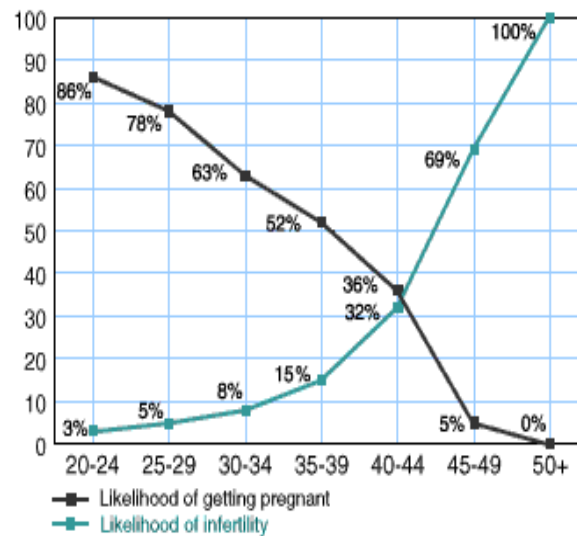
- 1) Egg must be released from one of her ovaries (ovulation)
- 2) Egg must go through the fallopian tube toward the uterus
- 3) Sperm must join with the egg in the fallopian tube (fertilization)
- 4) Fertilized egg must attach to the uterine wall (implantation)

Infertility can result from problems that interfere with any of these steps.

Factors which increases the chances of infertility in women are-

- 1) Age
- 2) Stress
- 3) Poor Diet
- 4) Smoking
- 5) Alcohol
- 6) STDs
- 7) Overweight
- 8) Underweight
- 9) Caffeine Intake
- 10) Excess Exercise

- 1) **AGE-** A woman's fertility naturally starts to decline in her late 20s. After age 35 a woman's fertility decreases rapidly. A woman is born with all the eggs she will have, and with time, the supply diminishes.(3)



2) **Weight Problems-**

Over/Under weight, body weight plays a vital role in fertility. Obesity has been associated with infertility and menstrual irregularities.

Women who are overweight but without Polycystic Ovarian Syndrome (PCOS) suffer the same problems with ovulation and menstrual anomalies as women with PCOS. (4)

3) **Smoking-**

Smokers(women) suffer a risk of menopause 1.5-3 years earlier than normal, decreased oestrogen with breakthrough bleeding and a shortened luteal phase of the menstrual cycle.

Also nicotine, a component of cigarette smoke has been shown to concentrate in cervical mucus and the metabolites have also been found in the follicular fluid. This is believed to be responsible for delayed follicular growth and maturation in smokers. (5).

4) **Alcohol-**

Alcohol has also been shown to alter estrogen and progesterone levels and also cause anovulation (menstruation without ovulation). During pregnancy, an average of 2 drinks per day or more can produce fetal alcohol syndrome birth defects. Consumption of more than 100gram of alcohol a week (1drink per day) is associated with 60% increase in ovulation difficulties.

Increased caffeine consumption affects the ability to become pregnant and carry the pregnancy. This is because caffeine clearance from the body is decreased during the luteal phase.

Menstrual disorders(eg-painful menstruation, heavy flow, premenstrual discomfort, and irregular or absent cycles)have been associated with chronic heavy drinking. These disorders can have adverse effects on fertility. Further, continued drinking may lead to early menopause. (6)

5) Career oriented women-

Women aged 19 to 26 are twice as likely to get pregnant during their monthly "fertile windows" as women aged between 35 and 39.

Women in the 21st century are often just as career-oriented as men, resulting in their lack of desire to give up the freedom and security of their career to carry a child for nine months. Once the baby is delivered, the mother is typically the parent who is given leave to stay home for the first weeks, even though more jobs have changed their policy to allow fathers to stay at home with pay under paternity leave.

Ovarian Reserve-

Ovarian reserve is an estimate supply of oocytes remaining in the ovary and is closely associated with reproductive potential.

The decline in fecundity with female age, long before menopause occurs, is a well known phenomenon. The concentration of primordial follicles in the ovarian cortex undergoes steady depletion with age, starting already before birth. An embryo at the age of 8 weeks has storage of 600,000 oocytes and, at the age of 5 months storage of 700,000 oocytes. At birth 1000,000 oocytes are present and by puberty only 25% of oocytes remain. At the age of about 37 years the loss of follicles accelerates with rapid loss of reproductive capacity, although menstrual periods might be irregular. This precedes the menopause, caused by dysfunctional ovaries, and is determined by the store of germ cells and the rate of depletion during life.

Physiology of Ovarian Reserve-

Unlike sperm, which men produce throughout their adult lives, women's are born with finite supply of oocytes. Women make all the oocytes they will ever have before they are born, this supply begins to be depleted even before birth and continue until Menopause with accelerated rate of loss at around age 37 years. On average, a female fetus at 20 weeks gestation contains approximately 7 million oocytes, reduced at birth to 1-2 million oocytes and only 25% are left at puberty, about 400,000 of recruitable oocytes. By the beginning of every menstrual cycle a relatively fixed proportions of all the remaining oocytes becomes recruited i.e, sensitized to gonadotropins from which one follicle or two will achieve dominance and progress to ovulation.(7).

Factors affecting ovarian reserve-

A decline of fertility is observed at the age of 34 years, while the last pregnancy is seen at an average of 41 years and in this way female age serve as an ovarian reserve test. Some women are not able to conceive in their thirties due to –

- 1) Alcohol Intake
- 2) Smoking
- 3) Obesity

Effect of Smoking on Ovarian Reserve-

Cigarette smoking in women appears to significantly reduce their ovarian reserve and lead to poor response to ovarian stimulation at an earlier age.

It is a detrimental association between cigarette smoking by women and their ovarian reserve as measured by follicular phase serum FSH concentrations and their response to ovarian stimulation for IVF treatment.

Their diminished ovarian response appears at an even younger age, but may be overcome by increasing the gonadotropin dosage, provided that the basal serum FSH is within normal limits.

Effect of obesity on Fertility-

Obesity was associated with reduced fertility for all subgroups of women and persisted for women with regular cycles. Studies suggest that weight loss could increase fecundity for overweight and obese women, regardless of menstrual cycle regularity, parity, smoking habits and age.

(. Women, family demands and health: the importance of employment status and socio-economic position. Soc Sci Med 2004;59(2):263-274.)

METHODS TO ASSESS OVARIAN RESERVE-

Ovarian reserve screening is one mechanism by which fertility specialist can partially predict the reproductive potential of a specific patient as well as the potential of her oocytes to result in a healthy pregnancy.

Methods for assessing ovarian reserve are-

- 1) **Cycle Day 3 FSH Concentration** – Cycle Day 3 FSH Concentration is an indirect estimate of ovarian reserve, being a measure of the amount of Inhibin B/ Estradiol that a cohort of follicles is producing, and the feedback effects at the level of Pituitary gland.

Patients with low basal FSH Concentrations (threshold values vary between 10.8-25 MIU/ml) responded better to ovulation induction, as demonstrated by the number of mature oocytes.

The validity of FSH Screening depends on the time in the cycle the sample is collected. Timing is considered optimal when circulating E2 Levels are at their nadir, which is typically around cycle 3.

- 2) **Cycle Day 3 Serum Estradiol Concentration-** The Follicular phase length changes from a mean of 16.9 days in a patients ages 18-20 years, to a mean of 10.4 days in regularly menstruating women aged 40-45 Years. A more well advanced recruitment by cycle Day 3 might be responsible for the condensed follicular phases in older

women. This early dominant follicle selection is expressed by relatively high serum Estradiol concentration.

- 3) **Serum Antimullerian Hormone Level-** Also known as Mullerian Inhibiting substance (MIS) is produced by the granulosa cells of preantral and small antral follicles. Since the number of ovarian follicles decline with age ;(AMH) can be used as a marker for ovarian reserve.
- 4) **Passive Ovarian Reserve Testing: Transvaginal Ultrasound, Part 1** Diminished ovarian reserve means that fewer follicles are available for stimulation and recruitment by fertility drugs. By allowing physicians to view the ovaries and assess the number of follicles, Transvaginal ultrasound aid in the assessment of ovarian volume.

Ultrasound ovarian volume has also been used to predict the risk for ovarian hyperstimulation syndrome. However, it has been theorized that ultrasound ovarian volume done at the beginning of the treatment cycle is more closely related to the number of follicles found during the pre-treatment period rather than the number of oocytes developed during treatment. It is uncertain that ovarian size or follicular number is a better indicator of ovarian reserve. The more follicles present, the larger the number of eggs retrieved during the treatment cycle

Passive Ovarian Reserve Testing: Transvaginal Ultrasound, Part 2 Among patients taking GnRH-a before a treatment cycle, abnormally high E2 levels are often associated with large ovarian cysts (identified by transvaginal ultrasound). Such E2 elevations may be improved by short-term continuation of GnRH-a. Using this approach, the cyst frequently resolves and the treatment cycle can continue. It is important to note that the additional GnRH-a exposure during this brief interval has not been associated with significantly reduced response to fertility drugs, nor has it adversely affected pregnancy rates.

- 5) **Clomiphene Citrate Challenge Test, Part, Clomiphene citrate challenge test** (CCCT) is a dynamic approach. Its purpose is to stimulate the ovary to initiate egg production in response to a fertility drug called clomiphene (Clomid or Serophene). In theory, the CCCT was designed to detect low ovarian reserve that would not be discovered by a single FSH and/or E2 measurements.

The CCCT is based on the assumption that adequate ovarian reserve is associated with a healthy group of developing follicles. This healthy group of follicles should be capable of producing enough inhibin and E2 to suppress FSH production and resist the effects of clomiphene.

Clomiphene works by shutting down the estrogen receptors on the hypothalamus and tricking the hypothalamus into thinking the patient doesn't have enough estrogen. In response, the hypothalamus works harder to induce the pituitary gland to produce more FSH and LH. This, in turn, initiates follicular growth.

Dynamic Ovarian Reserve Testing: Clomiphene Citrate Challenge Test, Part 2 when undergoing CCCT, the first step is to measure day 3 FSH and E2. Then 100mg of clomiphene is administered on cycle days 5 through 9, and FSH and E2

measurements are repeated on cycle day 10 . In general, a high day 10 FSH suggests poor ovarian reserve.

- 6) **Antral Follicle Count-** The antral follicle count (AFC) is defined as the number of follicles smaller than 10 mm in diameter. The AFC has been shown to be a predictor of the number of oocytes retrieved in controlled ovarian hyperstimulation protocols the cancellation rates in IVF , and for predicting pregnancy loss in IVF pregnancies. The AFC has also been shown to be a predictor of the number of immature oocytes retrieved for *in vitro* maturation (IVM) . There is no significant difference between right-sided and left-sided antral follicle counts within the same individual . The AFC was shown to be a superior, or at least an equivalent, prediction tool for poor IVF response or hyper IVF response when compared to ovarian volume measurement and complex endocrine challenge tests. Furthermore, the AFC has been established to be equally as useful as AMH in OR status determination and/or ovarian responsiveness.

ASSISTED REPRODUCTIVE TECHNIQUES-

Assisted reproductive technologies (ART) have been primarily developed to combat sterility and infertility in the medical sciences.

The birth of the first IVF baby Louise Brown in 1987 established by Steptoe and Edwards opened up a new horizon of hope in the lives of many infertile couples. After 1987 the progress and advancements made in the field of ART has grown by leaps and bounds and does not seem to be stopping. For e.g. male infertility was considered which initially involved only a small fraction of patients benefiting from IVF, with the development of ICSI techniques (intracytoplasmic sperm injection) now involves up to 35% of cycles.

The procedures listed below are some of the innovating advances made in the field of Reproduction

- 1) **IUI (Intrauterine insemination):** This involves removal, cleaning, increasing the density and putting the sperm directly into the uterus thereby bypassing the cervix.
- 2) **IVF (In vitro fertilization):** This involves induction of multiple follicles, removing them that is egg retrieval, fertilization with the sperm outside the body and finally transfer of the embryo in the uterus.
- 3) **GIFT (Gamete Intrafallopian transfer):** Involves putting of the sperm that is the gametes in the fallopian tube at the time of ovulation.
- 4) **ZIFT (Zygote intrafallopian transfer):** This involves transfer of the zygote that is the union of the sperm and the egg in the fallopian tube after IVF. It will develop into the embryo in the fallopian tube if the conditions are right.
- 5) **TET (Tubal embryo transfer)** This involves the transfer of the embryo in the fallopian tube after IVF.

- 6) **ICSI (Intra cytoplasmic sperm injection)** this involves injection of a single sperm in the ova in the laboratory. This is a specialized technique requiring a machine called the manipulator and has revolutionized treatment of male infertility.
- 7) **AH (Assisted hatching)** This involves cutting the Zona of the embryo with a laser or by chemicals and thereby assisting in its implantation in the uterus.

The success rate of the IVF cycles has increased to 30% with the help of use of fertility drugs to provide more oocytes.

MOLECULE USED TO TREAT POOR OVARIAN RESERVE –

- 1) **Dehydroepiandrosterone (DHEA)**
- 2) **Clomiphene Citrate**
- 3) **Human menopausal gonadotrophins (Hmg)**
- 4) **Follicle stimulating hormone (FSH)**
- 5) **Luteinizing hormone (LH)**
- 6) **L-Arginine**

Dehydroepiandrosterone(DHEA) + Folic Acid Combination -

DHEA-

Dehydroepiandrosterone is a product of dehydroepiandrosterone 3-sulfate and is a precursor of at least two hormones, testosterone and Estradiol. DHEAS is the most abundant circulating adrenal hormone in humans.

Dehydroepiandrosterone has been labeled as the “Youth Hormone” because its levels peak during adulthood. Dehydroepiandrosterone (DHEA) is a steroid hormone that's produced naturally by the adrenal glands. The body converts DHEA into male and female sex hormones, such as estrogen and testosterone. DHEA is also available in supplement form.

DHEA supplements are made from a substance called diosgenin, which is found in [Soy](#) and [Wild yams](#). Wild yam cream and supplements are often touted as natural sources of DHEA, but the body can't convert wild yam to DHEA on its own—it must be done in a laboratory.

Casson and associates were first to suggest therapeutic benefits from supplementation with dehydroepiandrosterone (DHEA) in women with Poor ovarian reserve (POR). They also suggested that, in micronized form, the androgen offers potential for postmenopausal steroid replacement, adjunctive to estrogen that its conversion may not be symmetrical, favouring androgens over estrogen, with testosterone increasing and Estradiol remaining low. DHEA has immunomodulatory effects now therapeutically explored in autoimmune diseases that vaginally administered DHEA, while delivering equivalent hormone substantially diminishes bioconversion comparatively to oral micronized products and that abnormally low adrenal

DHEA secretion is potentiated by ovarian hypertstimulation with gonadotropins. They also reported that DHEA is well tolerated and increases IGF-1 levels. A main focus of this group's work was, thus, the compensation of adrenal cortical changes in aging women with DHEA. Their initial therapeutic use of DHEA in patients with POR was motivated by observed increases in IGF-1 after DHEA supplementation. Since growth hormone had been suggested to improve oocytes yields via IGF-1, they hypothesized that DHEA may be able to achieve similar effects.

Comparison of Pre and Post DHEA cycles in 25 women with Poor ovarian reserve. (8)

	Pre-DHEA	Post-DHEA	p-value
Cycle cancellations (%)	32.0	4.3	0.02
Number oocytes	3.4 ± 0.5	4.4 ± 0.5	<0.05
Fertilized oocytes (n)	1.4 ± 0.3	3.0 ± 0.5	<0.001
(%)	39	67	<0.001
Day 3 blastomeres	3.4 ± 0.4	4.7 ± 0.5	0.01
embryo grade	2.9 ± 0.1	3.4 ± 0.1	0.02
Cumulative embryoscore/oocytes	8.4 ± 1.5	16.1 ± 1.6	0.001
Number of transferred embryos	1.4 ± 0.2	2.4 ± 0.3	0.005
Normal day 3 embryos	1.2 ± 0.2	2.7 ± 0.4	0.001

* 25 patients were evaluated in their respective IVF cycle outcomes pre- and post-DHEA. This study design potentially biases outcome against positive DHEA effects since patients who entered DHEA supplementation after a prior failed IVF cycle, quite obviously, reflected, in view of their prior IVF treatment failure, a negatively selected patient population. Pre- and post DHEA cycles occurred at ages 39 ± 0.8 and 40.4 ± 0.8 years, respectively, also mildly biasing the study against positive DHEA findings. Post-DHEA patients were on supplementation 17.6 ± 2.13 weeks by time of second IVF cycle. Data extracted from Barad and Gleicher [16].

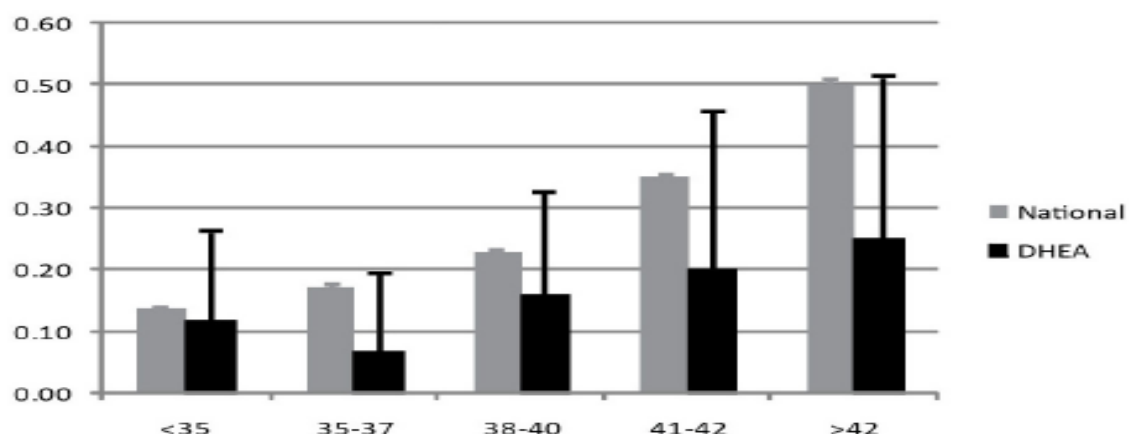
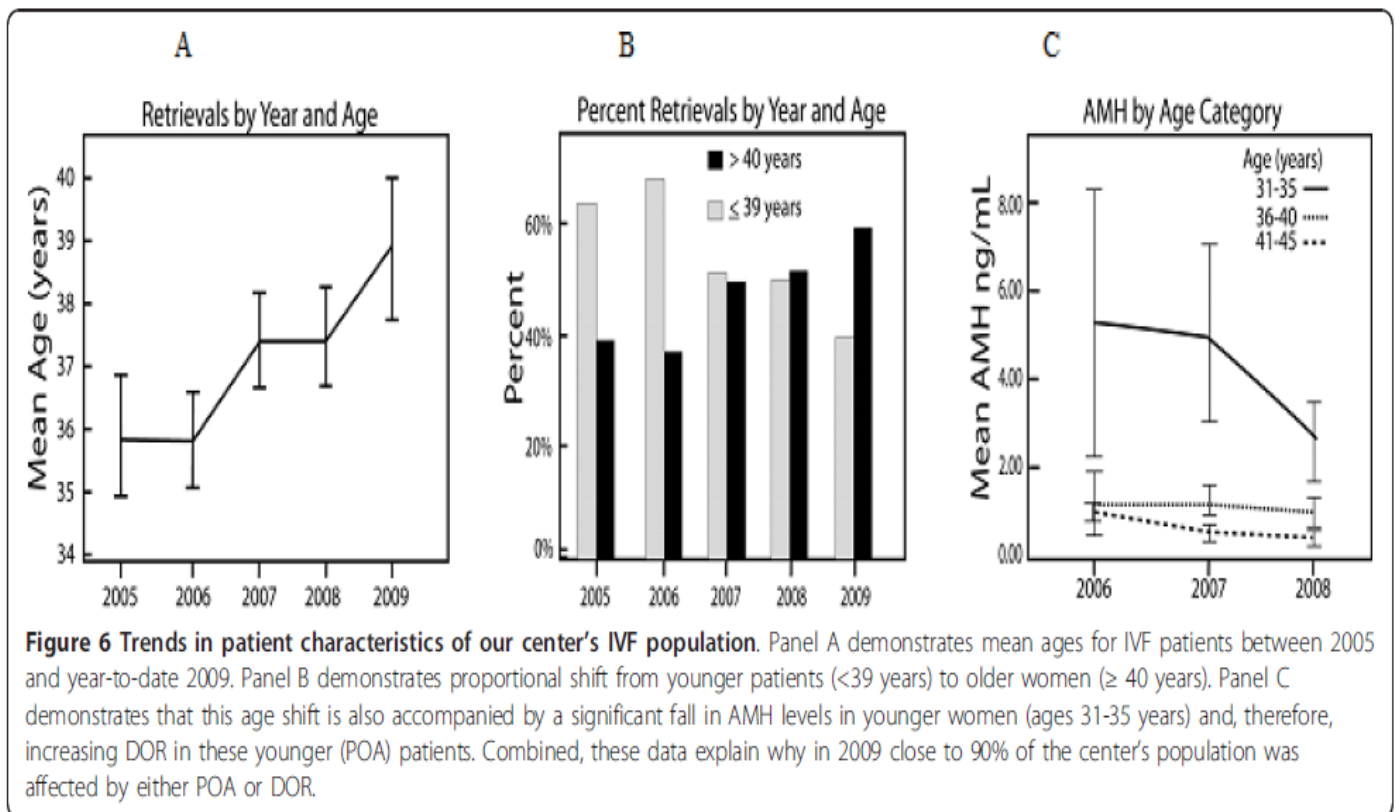


Figure 3 Age-stratified miscarriage rates in DHEA supplemented DOR patient in comparison to national U.S. IVF pregnancies. DHEA pretreated patients demonstrated significantly lower miscarriage rates at all ages. The difference was, however, relatively small under age 35 years and progressively increased after that age. Modified with permission from Gleicher et al [28].

Significant fall in AMH Level in younger women (age 31-35 years)-



- 1) This data shows current best available evidence which suggests that DHEA improves ovarian function, increases pregnancy chances and, by reducing aneuploidy, lowers miscarriage rates.
- 2) DHEA over time also appears to objectively improve ovarian reserve. Recent animal data support androgens in promoting preantral follicle growth and reduction in follicle atresia.

Folic acid-

Folic acid is a form of the water-soluble **vitamin B9**. Water soluble means it dissolves in water. It is carried through the bloodstream and excreted in urine. The human body does not store folic acid, we have to consume it every day in order to make sure we have adequate amounts. Folic acid is a key factor in the making (synthesis) of nucleic acid - nucleic acid is one of a family of large molecules including DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). (9)

Vitamin B9 (folic acid and folate inclusive) is vital for several bodily functions, including:

- To synthesize DNA, RNA and to repair
- Aiding rapid cell division and growth

- To produce healthy red blood cells
- **It is important for pregnant women to have enough folic acid to prevent major birth defects of her baby's brain or spine (neural tube defects, including spina bifida and anencephaly)**
- Enhances brain health.

In 1992, the FDA (Food and Drug Administration) advised fortifying the country's food supply with folic acid. In 1998 folic acid started being added to breads and other grains.

Who should take Folic Acid-

All women of child-bearing age should take folic acid, not only those who are planning to get pregnant, in order to be effective in preventing birth defects, women should take folic acid before getting pregnant as well as during the first four weeks after conception.

According to the Teratology Society, all women who are capable of having babies should take 0.4mg folic acid, or make sure they consume enough fortified cereal grain products to reach 0.4mg of folic acid per day.

The online journal *PLOS Medicine* wrote in 2009 that females who take folic acid supplements for at least 12 months before becoming pregnant could cut their risk of having a premature baby by about half

Natural sources of folic acid-

Dark green vegetables are good sources of folic acid. The following foods are known to be rich in folic acid:

- Asparagus
- Baker's yeast
- Broccoli
- Brussel sprouts
- Cabbage
- Cauliflower
- Egg yolk
- Jacket potato (large)
- Kidney
- Lentils
- Lettuce
- Liver (pregnant women should not consume liver)
- Many fruits have moderate amounts, papaya and kiwi have more
- Milk
- Oranges
- Parsnips

- Peas
- Spinach
- Sunflower seeds
- Wholewheat bread (usually fortified)

Rationale of Dehydroepiandrosterone (DHEA) and Folic Acid-

Dhea is used to improve the fertility of a women by increasing the number of oocytes and also by improving the quality of oocytes (improvement in ovarian reserve) and Folic acid helps to prevent major birth defects of baby's brain or spine (neural tube defects, including spina bifida and anencephaly)

RESEARCH OBJECTIVE

- 1) To study Doctors perception regarding usage of DHEA/DHEA+ Folic acid combination in Poor ovarian reserve.
- 2) To identify major customers (Doctor) of DHEA/DHEA+ Folic Acid combination prescribed for poor ovarian reserve

RESEARCH METHODOLOGY

A structured questionnaire consisting of open ended questions was designed within the scope of the given objectives.

S. No.	PARAMETER	DESCRIPTION
1.	Research type	Exploratory Research
2.	Data collection	Primary & Secondary
3.	Measurement technique	Structured Questionnaire
4.	Sample selection	Area and speciality wise
5.	Sample size	73
6.	Sample unit	I.V.F Doctors-25, I.U.I Doctors-29, Gynaecologist-19
7.	Sampling Technique	Convenience sampling based on geography
8.	Analysis of Data	Using Microsoft Excel.

Primary Data: Field work done in different areas of Mumbai (zone wise)

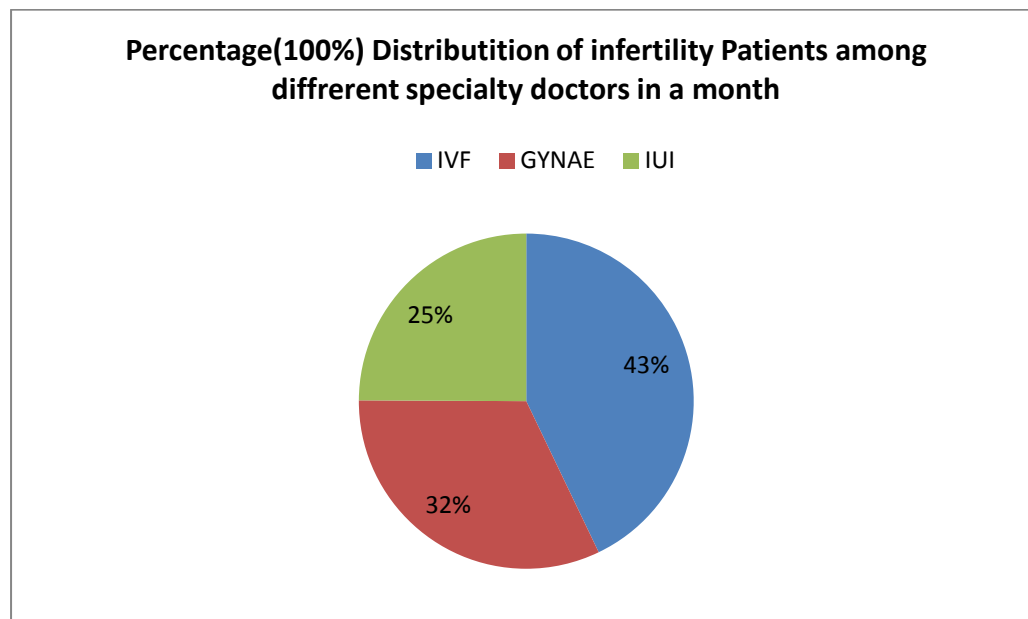
Zone	Areas
Western	Andheri, Jogeshwari, Goregaon, Kandivali, Borivali, Malad
Central	Dader, Thane , Bhiwandhi

ANALYSIS OF COLLECTED DATA FROM
I.V.F (25), I.U.I (29), GYNEC0LOGIST (19)
DOCTORS

Q1) Doctor, do you treat patients of Infertility?

All 73 doctors included in study treat patients of infertility.

Q2 Doctor how many patients of Infertility you treat in a month?

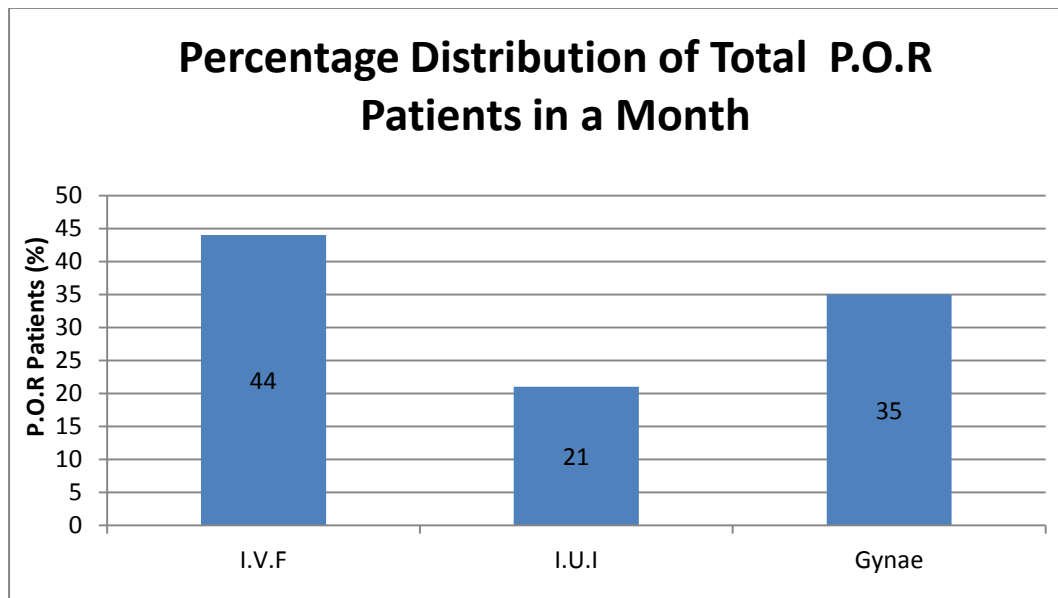


Specialty Dr.	Infertility Patients (1 Month)	Average Patient/Dr.	Percentage Distribution of Patient (%)
I.V.F (25)	715	29	43
I.U.I (29)	482	17	25
GYNAEC. (19)	408	22	32

INTERPRETATION-

- 1) Of the Total Infertility Patients (among I.V.F ,I.U.I & Gynec.) in a month I.V.F Doctors treat maximum percentage of Infertility Patients i.e., 43%
- 2) It is followed by Gynecologist who treats 32% of Infertility Patients in a month.
- 3) I.U.I Doctors treats 25% of Infertility patients in a month.

Q3 How many cases of Infertility are because of Poor ovarian reserve (P.O.R)?

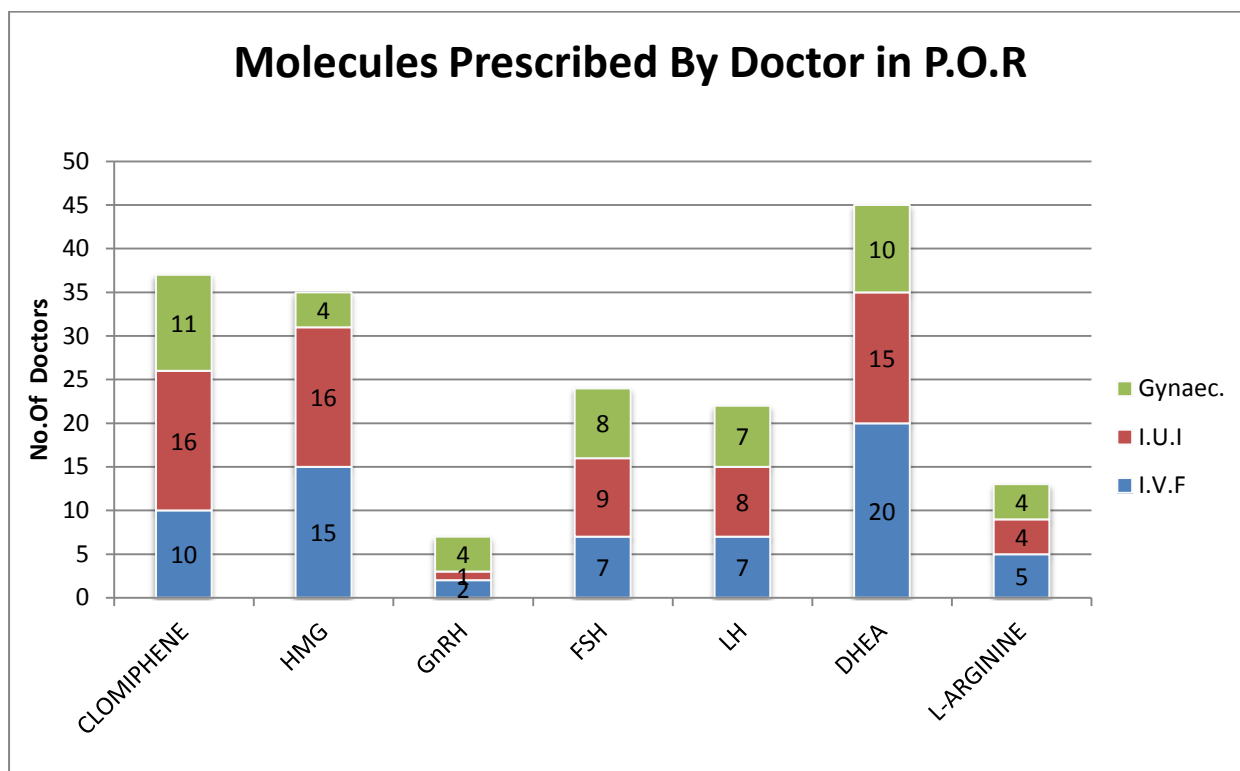


Specialty Dr.	P.O.R Patients	Average Patient/Dr.	Percentage Distribution of Patient (%)
I.V.F	195	7.8	44
I.U.I	108	3.7	21
GYNAEC.	122	6.4	35

INTERPRETATION-

- 1) Of the total number of Poor ovarian Reserve Patients in a Month I.V.F Doctors treat maximum number of patients i.e., 44%
- 2) It is followed by Gynecologist who treats 35% of Poor ovarian Reserve Patients in a month.
- 3) I.U.I Doctors treat minimum number of Poor ovarian Reserve Patients in a month i.e., 21%.

Q4 Which Molecule you prefer to prescribe in Poor ovarian reserve (P.O.R)?



SPECIALITY Dr.	CLOMIPHENE	HMG	GnRH	FSH	LH	DHEA	L -ARGININE
I.V.F	10	15	2	7	7	20	5
I.U.I	16	16	1	9	8	15	4
GYNAEC.	11	4	4	8	7	10	4

INTERPRETATION-

I.V.F –

- 1) In P.O.R, I.V.F Dr. prefers to prescribe DHEA, followed by Hmg and Clomiphene.
- 2) In P.O.R, least preferred molecules by I.V.F Dr are L-arginine and GnRH.

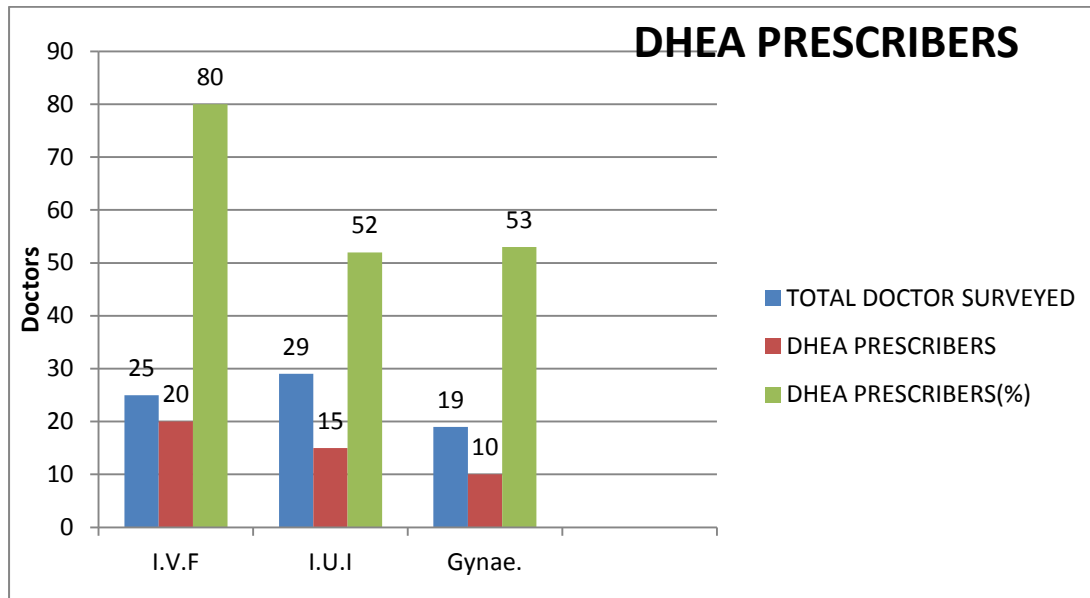
I.U.I-

- 1) In P.O.R, I.U.I Dr. gives equal preference to DHEA, Clomiphene and Hmg.
- 2) In P.O.R, I.U.I Dr. gives least preference to L-Arginine and GnRH.

GYNAECOLOGIST-

- 1) In P.O.R, Gynec. Dr. gives equal preference to prescribe Clomiphene and DHEA.
- 2) In P.O.R, Gynec. Dr. gives least preference to prescribe L-Arginine and GnRH.

Q5 Doctor do you prescribe DHEA/DHEA and Folic acid combination?

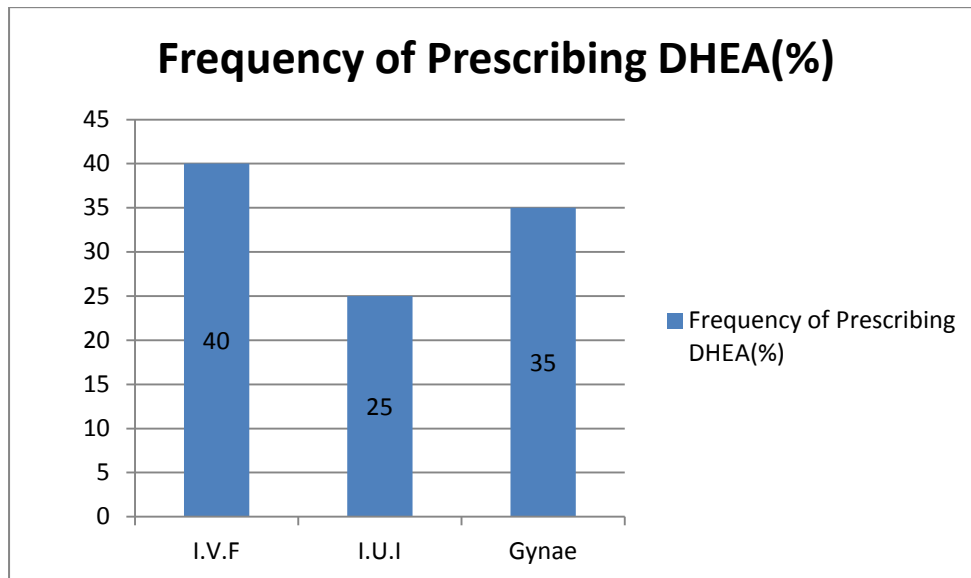


Specialty Dr.	Total Doctors Surveyed	DHEA Prescribers	DHEA Prescribers (%)
I.V.F	25	20	80
I.U.I	29	15	52
Gynaec.	19	10	53

INTERPRETATION-

- 1) Out of 25 I.V.F Doctors surveyed, 20 I.V.F Doctor Prescribe DHEA. It means 80% of I.V.F Doctor Prescribe DHEA in Poor Ovarian reserve.
- 2) 53% of Gynaec. Doctors prescribe DHEA i.e., 10 out of 19 doctors prescribe DHEA.
- 3) 52% of I.U.I doctors prescribe DHEA i.e., 15 out of 29 doctors.

Q6 (a) Doctor how often you prescribe DHEA in Poor ovarian reserve (P.O.R) Patients?

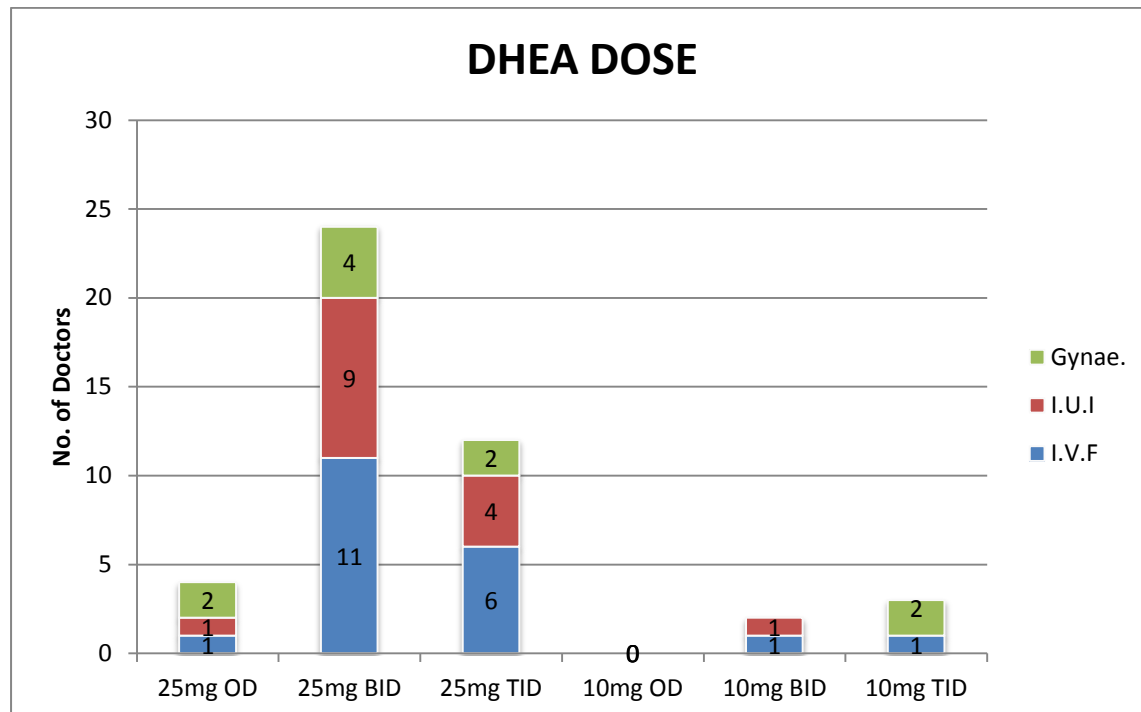


Specialty Dr.	Frequency of Prescribing DHEA	Average Frequency/Dr.	Percentage (%)
I.V.F (20)	105	5.25	40
I.U.I (15)	50	3.33	25
GYNAEC. (19)	45	4.5	35

INTERPRETATION-

- 1) I.V.F Doctors prescribe DHEA to 40% of Patients. It means I.V.F Doctor Prescribe DHEA to 40 patients of Poor ovarian reserve Patients out of 100 Patients.
- 2) Gynecologist Prescribe DHEA to 35% of Poor ovarian reserve Patients.
- 3) I.U.I Doctors Prescribe DHEA to 25% of Poor ovarian reserve Patients.

Q6 (b) Doctor, what is the Dose you prescribe for DHEA and Combination in Poor ovarian reserve (P.O.R)

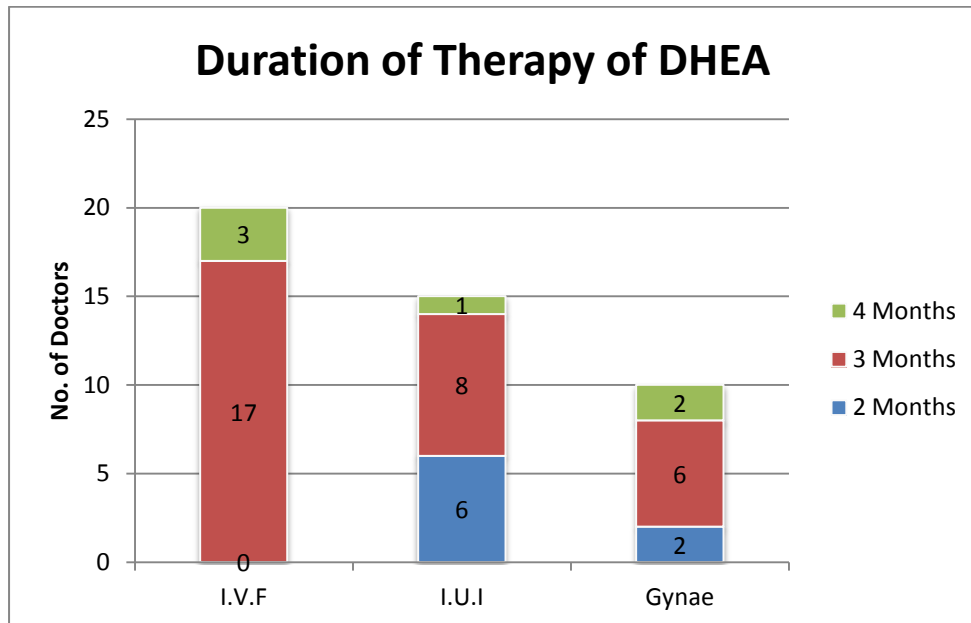


DOSE	I.V.F	I.U.I	GYNAEC.
25mg OD	1	2	2
25mg BID	11	9	4
25mg TID	6	4	2
10mg OD	0	0	0
10mg BID	1	1	0
10mg TID	1	0	2

INTERPRETATION-

- 1) I.V.F Prescribe DHEA Maximum times at a Dose of 25mg BID, followed by 25mg TID in Poor ovarian reserve(P.O.R)
- 2) I.U.I Prescribe DHEA Maximum times at a Dose of 25mg BID, followed by 25mg TID in P.O.R.
- 3) Gynaec .Doctors Prescribe DHEA Maximum times at a Dose of 25mg BID in P.O.R.

Q6 (c) Doctor in Poor ovarian reserve (P.O.R) patients what is the Duration of therapy you prescribe for DHEA & combination.

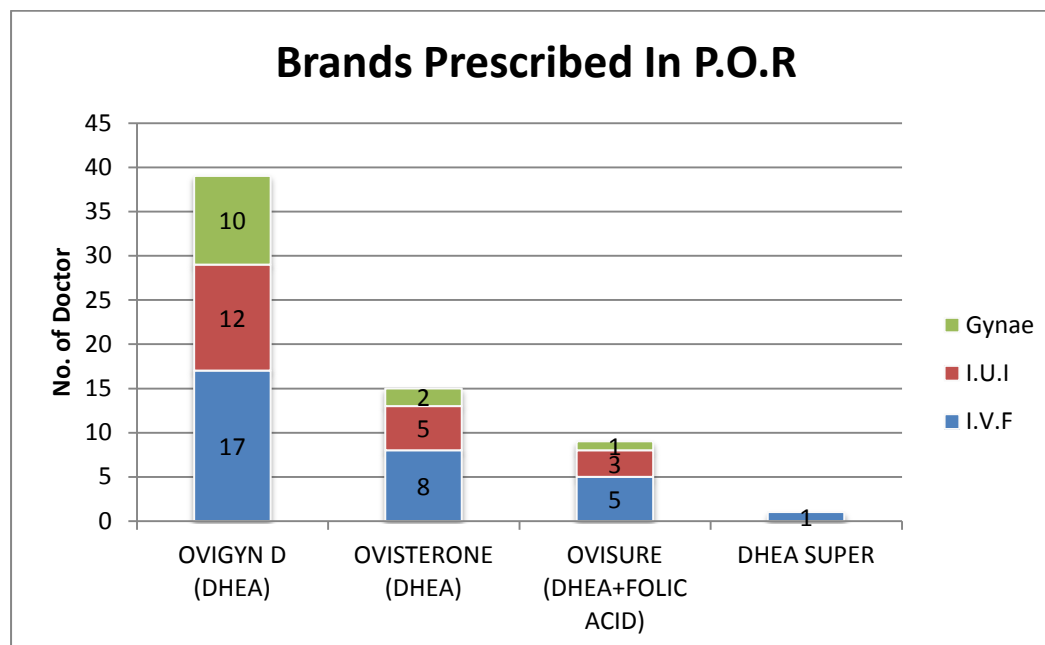


Duration of Therapy	I.V.F	I.U.I	Gynaec.
2 Months	-	6	2
3 Months	17	8	6
4 Months	3	1	2

INTERPRETATION-

- 1) Maximum Dose of DHEA Prescribed by I.V.F, I.U.I and Gynecologist is 4 Months.
- 2) Minimum Dose of DHEA Prescribed by I.V.F, I.U.I And Gynecologist is 2 Months.
- 3) I.V.F Doctors Maximum Prescribers of DHEA, Prescribe DHEA maximum times (17) for 3 Months in Poor Ovarian Reserve Patients.
- 4) I.U.I Doctors Prescribe DHEA Maximum times for 3 Months, followed by 2 Months in poor ovarian reserve patients.
- 5) Gynecologist Prescribe DHEA Maximum times for 3 Months.

Q7 Doctor, which brands of DHEA/DHEA& Folic Acid you prescribe to Poor ovarian reserve (P.O.R) patients?



	OVIGYN-D(ALKEM)	OVISTERONE(JV'S)	OVISURE	DHEA SUPER
I.V.F	17	8	5	1
I.U.I	12	5	3	0
GYNAEC.	10	2	1	0

INTERPRETATION-

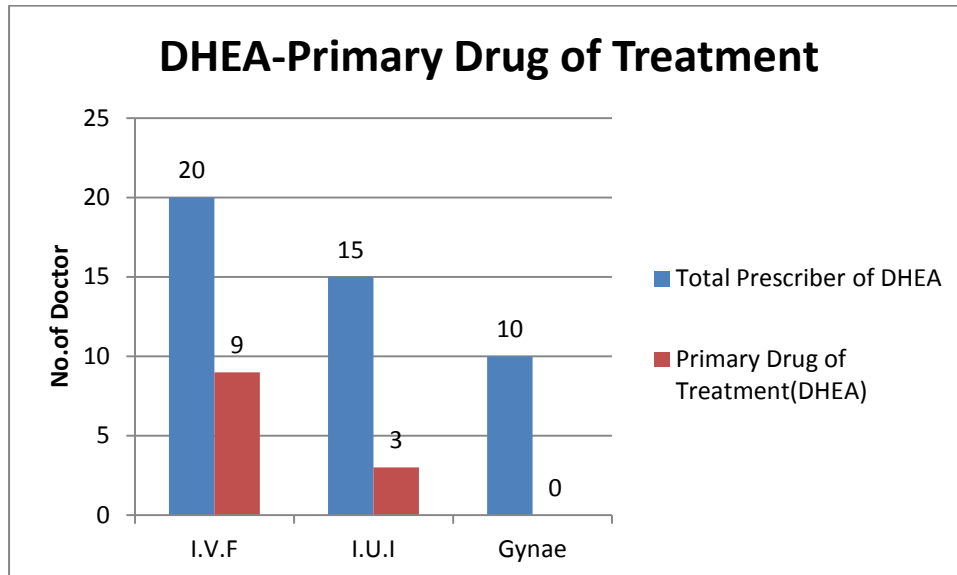
OVIGYN-D is the Maximum Prescribed Brand by I.V.F, I.U.I and Gynecologist

OVISTERONE is second preferred brand by I.V.F, I.U.I and Gynecologist.

OVISURE Is very less Preferred by I.V.F, I.U.I and Gynecologist.

OVIGYN-D is the Market Leader, followed by **OVISTERONE**

Q8 Doctor you prescribe DHEA as primary drug of treatment/secondary drug of treatment?

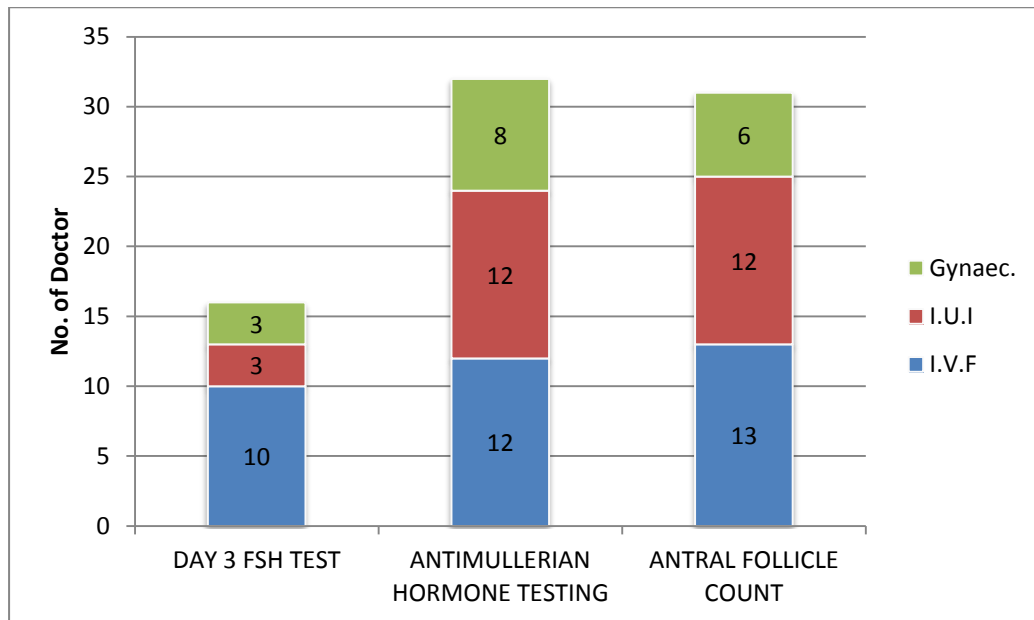


Specialty Dr.	Total prescribers of DHEA	DHEA-Primary drug of Treatment
I.V.F	20	9
I.U.I	15	3
Gynec.	10	0

INTERPRETATION-

- 1) I.V.F Doctors, major prescribers of DHEA in Poor Ovarian Reserve Prescribe DHEA as Primary Drug of Treatment in 45% of Patients.
- 2) I.U.I Doctors Prescribe DHEA as primary drug of treatment in 20% of patients.
- 3) Gynecologist does not prescribe DHEA as primary drug of treatment in any patient.

Q 9 Doctor how do you monitor the improvement in ovarian reserve in patients treated with DHEA?



Specialty Dr.	Day 3 FSH TEST	AMH	Antral Follicle Count
I.V.F	10	12	13
I.U.I	3	12	12
Gynaec.	3	8	6

INTERPRETATION-

I.V.F-

- 1) I.V.F Dr. gives equal preference to AMH Testing and Antral Follicle Count to assess ovarian reserve.
- 2) I.V.F Dr. gives least preference to Day 3 FSH TEST to assess ovarian reserve.

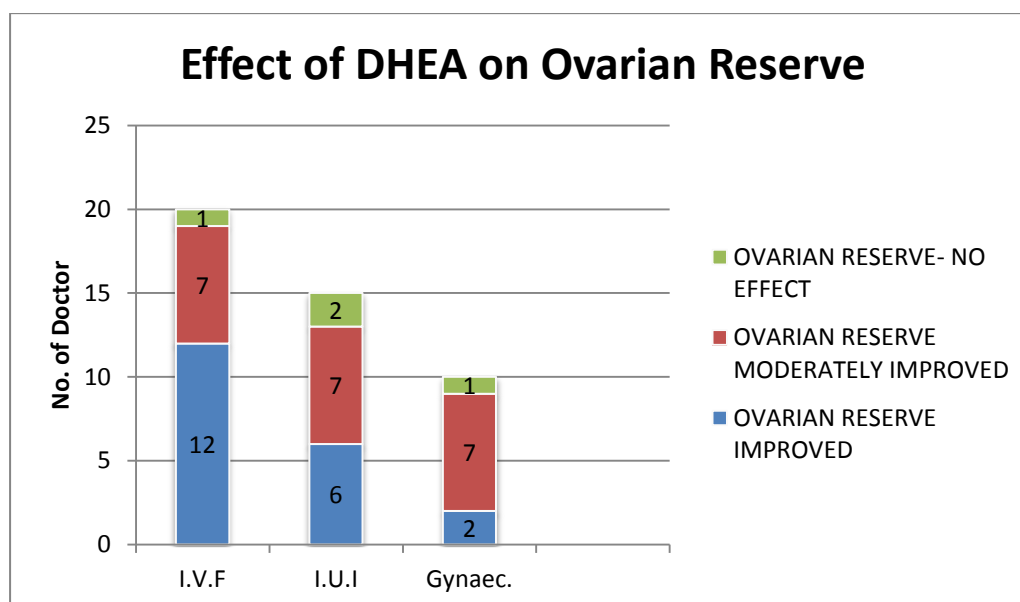
I.U.I-

- 1) I.U.I Dr. gives equal preference to both AMH test and Antral follicle count test.

Gynecology-

- 1) Gynecologist gives maximum preference to AMH test followed by Antral follicle count test.
- 2) Gynecologist gives least preference to Day 3 FSH test.

Q 10 Doctor in your day to day practice, how was the response of DHEA in patients of poor ovarian reserve. (P.O.R)?

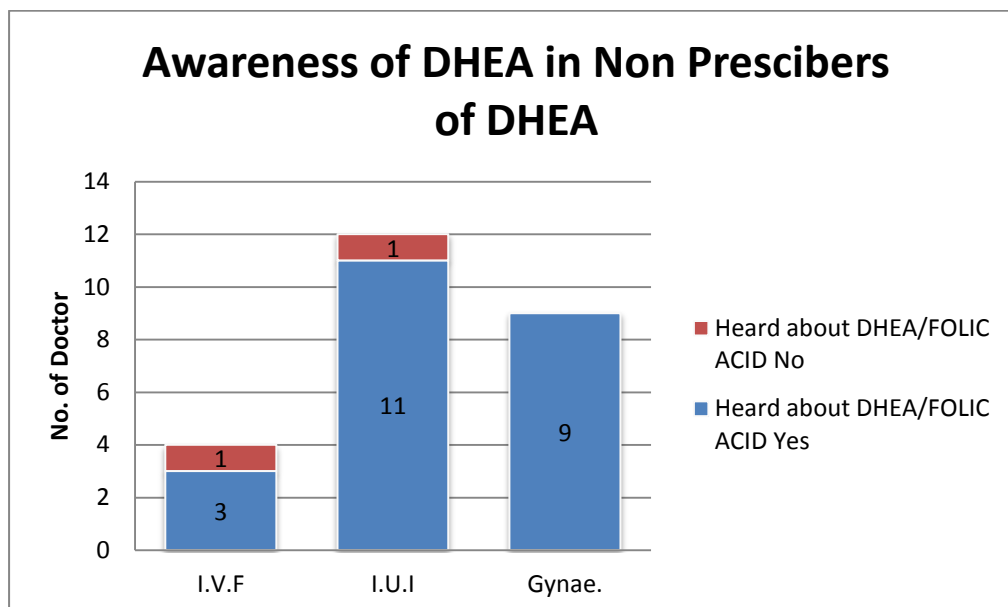


Specialty Dr.	O.R –Improved	O.R-Moderately Improved	O.R-No Effect
I.V.F	12	7	1
I.U.I	6	7	2
Gynaec.	2	7	1

INTERPRETATION-

- 1) According to **I.V.F** Doctors, in most patients ovarian reserve was improved, in some cases it was moderately improved and in only **1** case there was no improvement in ovarian reserve.
- 2) According to **I.U.I** Doctors, there were equal responses of ovarian reserve improved and moderately improved and in **2** cases there was no improvement in ovarian reserve.
- 3) According to **Gynecologist**, in most of the cases ovarian reserve was moderately improved, and in **1** case there was no improvement in ovarian reserve.

Q 11 If answer to Q 5 is No, then Dr. have you heard about Dhea+ Folic acid combination?

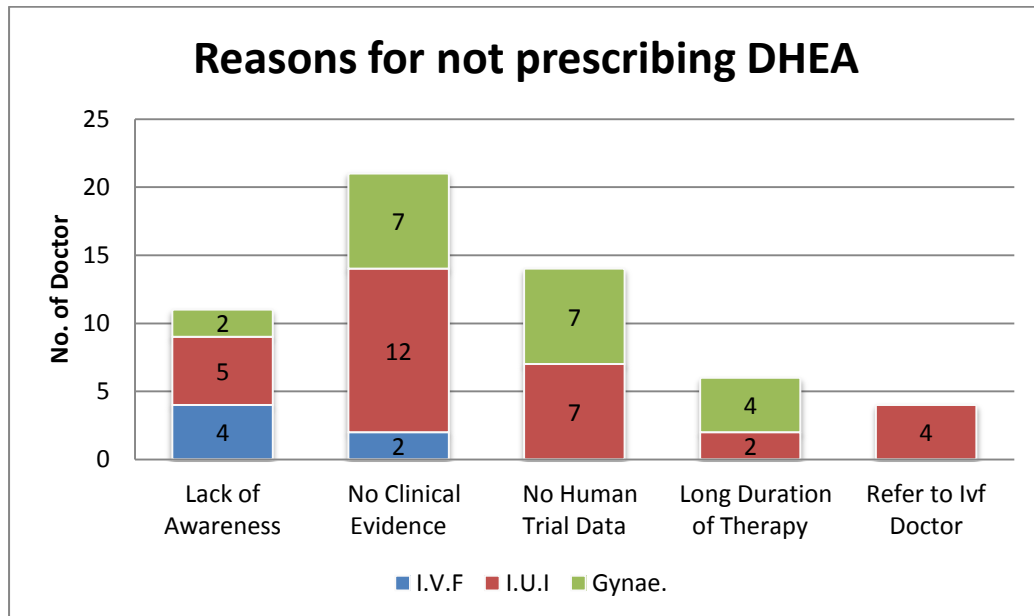


Specialty Dr.	Heard about DHEA/FOLIC ACID	
	YES	NO
I.V.F	3	1
I.U.I	11	1
Gynaec.	9	0

INTERPRETATION-

- 1) Out of non prescribers of DHEA, 1 I.V.F Dr. did not heard about use of DHEA in Poor ovarian reserve.
- 2) In I.U.I doctors, non prescribers of DHEA are maximum, and only 1 Dr. was not aware about this molecule.
- 3) All Gynecologists heard about DHEA, but they were not aware about its usage in Poor ovarian reserve.

Q 12 Doctor is there any specific reason for not prescribing DHEA+FOLIC ACID combination?



Specialty Dr.	Lack of Awareness	No clinical Evidence	No Human Trial Data	Long Duration of Therapy	Refer to I.V.F Doctor
I.V.F	2	4	2	0	0
I.U.I	5	12	7	2	4
Gynaec.	2	7	7	4	0

INTERPRETATION-

I.V.F-

- 1) **4 I.V.F Doctors** do not prefer to prescribe DHEA because of lack of awareness of role of DHEA in Poor ovarian reserve.
- 2) **2 Doctor** do not prescribe DHEA because no clinical evidence was available regarding role of DHEA in Poor ovarian reserve.

I.U.I-

1) I.U.I Doctor do not prescribe DHEA because of the following reasons-

a) No clinical Evidence- 12 I.U.I Doctor do not prescribe DHEA because of no clinical evidence available.

b) No Human Trial Data- 7 I.U.I Doctor do not prescribe DHEA because of no human trial data available.

c) Lack of Awareness- 5 I.U.I Doctor do not prescribe DHEA due to lack of awareness of role of DHEA in Poor ovarian reserve.

d) Long Duration of Therapy- 2 I.U.I Doctor do not prescribe DHEA due to long duration of therapy. Patient does not want to wait for 3-4 months for conceiving.

e) Refer to I.V.F Doctor- 4 I.U.I Doctor refer their Poor ovarian reserve patients to I.V.F Doctors.

Gynecologist-

1) Gynecologist do not prefer to prescribe DHEA because of following reasons-

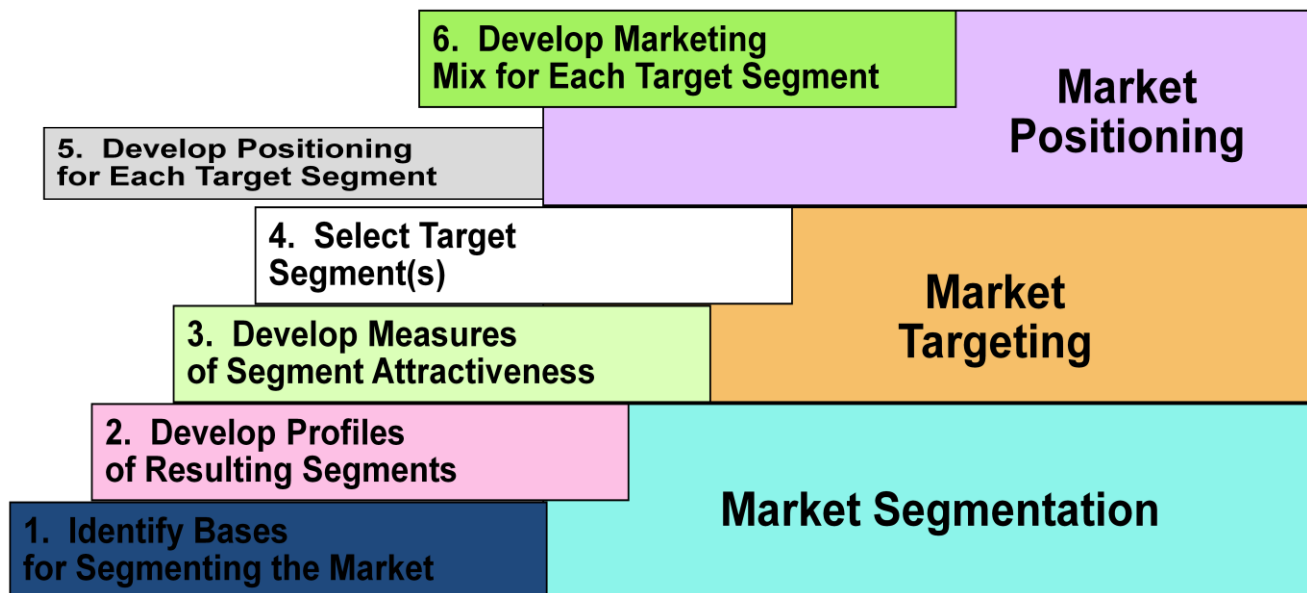
a) No clinical Evidence- 7 Doctors do not prefer to prescribe DHEA in poor ovarian reserve due to non availability of clinical evidence regarding role of DHEA in poor ovarian reserve.

b) No Human Trial Data-Due to lack of availability of human trial data on DHEA in poor ovarian reserve, 7 Doctors do not prefer to prescribe DHEA.

c) Long Duration of Therapy- 4 Doctors do not prescribe DHEA due to long duration of therapy of DHEA in Poor ovarian reserve.

d) Lack of Awareness- 2 Doctors do not prescribe DHEA due to lack of awareness regarding role of DHEA in Poor ovarian reserve.

Recommendation-



Market Segmentation-

1) Identify Bases for segmenting the Market-

DHEA+FOLIC ACID should be promoted only to those doctors who treat patients of Poor ovarian reserve leading to Infertility.

2) Profiles of Resulting Segment-

- a) I.V.F Doctors
- b) I.U.I Doctors
- c) Gynecologist

Market Targeting-

1) Measures of Segment Attractiveness-

- a) I.V.F Doctors treat maximum number of Poor ovarian reserve patients in a month.
- b) DHEA is mostly prescribed by I.V.F doctors in Poor ovarian reserve patients as both Primary and secondary drug of treatment. Followed by I.U.I Doctors and Gynecologist.

Target Segment-

1) I.V.F Doctors

2) **I.U.I Doctors**- Those doctors who treat Poor ovarian reserve patients.

3) **Gynecologist**-Those doctors who treat Poor ovarian reserve patients.

Market Mix for each target segment-

I.V.F-

Product-Dehydroepiandrosterone (DHEA)+Folic acid combination

Price-

Price of Products available in market-

BRAND NAME	COMPOSITION	COMPANY NAME	M.R.P (in Rs.)
Ovigyn D	DHEA	Alembic	50
Ovisterone	DHEA	JV'S Laboratory	124.80
Ovisure	DHEA	Alkem	
Stimugest	DHEA+FOLIC ACID	Besin Healthcare	167

Place- DHEA+Folic Acid should be promoted in Metro cities and Class A towns.

Promotion-

I.V.F-

- 1) According to findings, most of the doctors (I.V.F) were aware about DHEA+Folic Acid, but some doctor was not convinced about its usage in Poor ovarian reserve. To overcome this problem **Research articles** containing clinical trial data of DHEA in Poor ovarian reserve should be given to non prescribers of DHEA.
- 2) To increase the frequency of prescribing DHEA + Folic Acid doctors should be told that **clomiphene** and **hmg** they are prescribed in cases of infertility caused by **polycystic ovarian syndrome** while **DHEA** is prescribed for Poor ovarian reserve leading to Infertility.

I.U.I-

- 1) In I.U.I Doctors aggressive promotion needs to be done because non awareness of DHEA in POR is very high.
- 2) Research Article should be distributed to all I.U.I doctors to convince them about the need of DHEA+FOLIC Acid in Poor ovarian reserve.

Gynecologist-

- 1) Opportunity for DHEA with gynecologist is very high as all the doctors were aware about this molecule.
- 2) Research articles including human trial data needs to be distributed among gynecologist to convince them about the use of DHEA in Poor ovarian reserve.

Market Positioning-

- 1) To increase the frequency of prescribing DHEA + Folic Acid doctors should be told that **clomiphene and Hmg** they are prescribed in cases of infertility caused by **polycystic ovarian syndrome** while DHEA is specific for infertility due to poor ovarian reserve.

Questionnaire

Name-

Date-

Address-

Speciality-

1) Doctor do you treat patients of Infertility.

a) Yes

b) No

2) How many patients of Infertility you treat in a month__.

3) How many cases of Infertility are because of poor ovarian reserve__.

4) Which molecule you prefer to prescribe in poor ovarian reserve-

Molecule	Dose	Duration of Therapy

5) Doctor do you prescribe DHEA /DHEA and Folic acid combination. (Yes-Refer to Q6, No-Refer to Q11)

a) Yes

b) No

In which Indication-_____

6) If yes, then-

	In POR patients how often you Rx (out of 10 patients)	Dose	Duration of Therapy	Which Brands you Rx
DHEA & Combination				a) b)

(If in few patients of POR, Dr does not prefer DHEA then refer to Q 7)

7) In the remaining cases of POR, what do you Rx and why.

8) Doctor you prescribe DHEA as-

Primary Drug of Treatment	Supplement with other Drug
	1)
	2)

9) Doctor how do you monitor the improvement in ovarian reserve in patients treated with DHEA.

- a) Day 3 FSH Test
- b) Antimullerian Hormone Testing
- c) Antral Follicle Count.(Vaginal Ultrasound)

10) Doctor in your day to day practice, how was the response of DHEA in patients of poor ovarian reserve.

- a) Ovarian reserve improved.
- b) Ovarian reserve moderately improved.
- c) Ovarian reserve-No effect

(If answer to Q5 is No, then refer to Q11)

11) If no, then have you heard about Dhea+Folic Acid combination.

- a) Yes
- b) No

12) If yes, is there any specific reason for not prescribing DHEA+FOLIC ACID combination.

- a)
- b)

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