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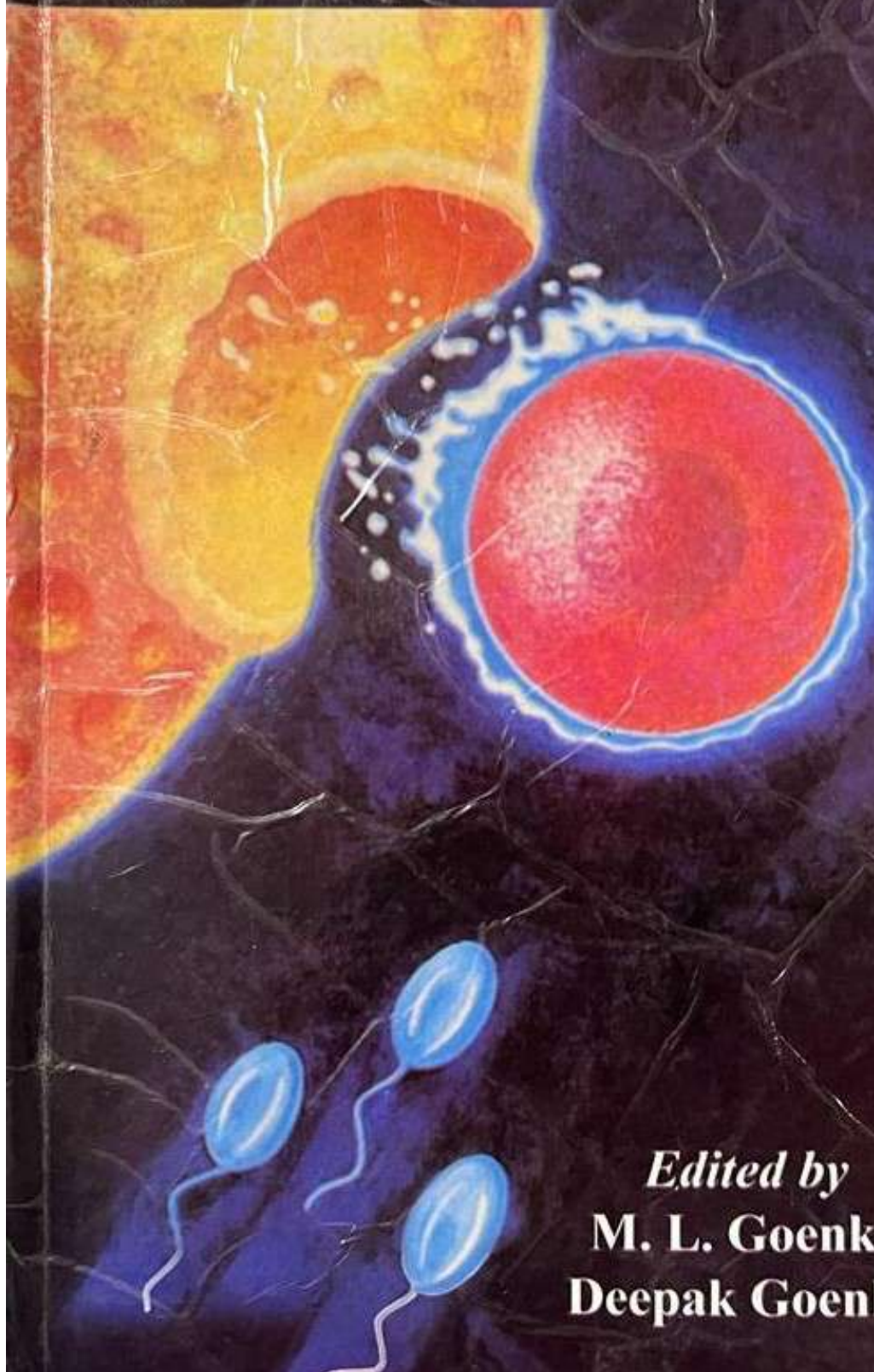
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22. Chapter (115) titled '**Genital tuberculosis**', for the "**Manual of Assisted Reproductive technologies and Laboratory Sciences (volume 1 Basic sciences and Clinical ART)**", edited by Dr. Gauri Devi, Prof (Col) Pankaj Talwar, Dr. Jayant Mehta (UK) and Dr Ashok Agarwal (USA) published in 3 volumes and released at the annual international conference at ESHRE at MILAN on 4th July 2022.
23. Chapter titled '**Pre-implantation Genetic testing PGT: Where and when to offer**', sent for publication for a book titled "Algorithms for Infertility & Reproductive Medicine" edited by Dr Kamini Rao. The book aims to serve as an indispensable reference guide to all clinicians and post graduate students providing a scientific, step by step approach to infertility management.
24. Chapter titled '**ART and PCOS**' sent for publication for a book titled 'PCOS', to be edited by Dr. Surveen Ghumman. They aim to bring it out as a standard reference book including the latest developments in the field. It will be useful in daily practice as a ready reckoner for practitioners and for the teaching commitments of academicians all over the world.

Coffee table book edited on Dr. Abha Majumdar 2019

Edited Autobiography of Dr. Abha Majumdar "The journey of a life saver", in 2022

RECENT ADVANCES IN INFERTILITY MANAGEMENT



Edited by
M. L. Goenka
Deepak Goenka

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Myoma and Infertility: Should we Remove Myoma in Infertile Women?

Abha Majumdar

Consultant incharge Unit of IVF & Reproductive Medicine

Department of obstetrics and Gynaecology

Sir Ganga Ram Hospital

New Delhi, India

E-Mail: abhamajumdar@hotmail.com

ABSTRACT

Uterine myomas are most common tumours found in women. Their occurrence increases with age; they occur in 20-50% of women over the age of 30 years. The role of uterine leiomyoma as a cause of infertility is still a matter of debate. A significant number of pregnant women with fibroids have history of infertility before pregnancy. Impaired gamete transport, distortion of endometrial cavity, impairment of blood supply to endometrium and atrophy and ulceration might be responsible for decreased implantation in patients carrying these tumours.

It has been observed that more than half of the women who have not previously given birth subsequently conceive following myomectomy for treatment of infertility. The long duration of infertility before surgery, absence of other infertility factors and the short time interval subsequent to surgery before conception occurs suggest that myomectomy is of benefit to infertile patients with leiomyomata. The only concern associated with myomectomy is the integrity of uterine wall and post operative adhesion formation. Each of these complications can jeopardise either reproductive performance or infertility management. Various approaches such as laparoscopic myomectomy or laparotomy and myomectomy for removal of myomata are still under debate. Criteria for selection of patients for each of these procedures is still undetermined in different hands and centres. One fact is universally accepted is that a submucous myoma is best-removed hysteroscopically and should be removed before infertility treatment.



Practical Approach to Infertility Management

Editor
Kanthi Bansal

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Cervical Factor Infertility

Chapter 14

Abha Jundar

For successful conception to occur, gametes of both sexes have to meet in the ampulla of the fallopian tube, even though neither of them, i.e. the sperm nor the oocyte, is produced here. Therefore it appears mandatory to have a patent and functional genital tract tube for them to reach each other. The oocyte is picked by the tubal fimbria and passed further into the tube by tubal peristalsis. On the other hand the sperm, which are deposited in the vagina, traverse the cervical canal and uterine cavity and then reach the fallopian tube by their own motility. The cervix is unique because it is the only organ of the body, which connects the external environment to the peritoneal cavity by a central endocervical canal. The endocervical canal opens on one side into the vagina and to the external environment and on the other side into the uterus, fallopian tube and subsequently into the peritoneal cavity. Thus the cervix is an important organ which not only protects sperm and promotes natural conception, but also acts as a guard for the female genital tract and protects it and the peritoneal cavity from external insults.

ANATOMY

The cervix is a fibromuscular 4 to 5 cm long tubular organ which has a canal in its center called the endocervical canal. This opens into the vagina on one side and is called the external cervical os and into the uterine cavity on the other side and is called the internal cervical os. The external os usually points towards the posterior vaginal fornix.

The endocervical canal is lined by mucous membrane, which invaginates into cervical crypts and its branches thus, increases the storage space as well as the secreting capacity of the cervical canal



The Heart & Soul of ART

.....is in the Laboratory

the Inside Story

*A Practical Textbook
on Embryology,
Andrology
& Infertility Lab Work*

*A Tribute to Infertility
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CHAPTER

27

Assisted Hatching: Benefits and Limitations

*Abha Majumdar
Gaurav Majumdar*



INTRODUCTION

Over the last decade many attempts have been made to improve embryo implantation, after *in vitro* fertilization (IVF). A high incidence of chromosomal anomalies has been observed in embryo generated from IVF. However, genetic factors alone cannot explain low implantation rate of morphologically normal embryos, indicating that a number of other factors could be involved. One of these factors possibly is the inability of the embryo to hatch out successfully from within its outer covering, i.e. the zona pellucida (ZP). It has been reported that only 25 to 30 percent of embryo hatch in optimal culture conditions *in vitro* (Fehilly *et al*, 1985; Lindenberg *et al*, 1989; Dokras *et al*, 1991). If the rate of hatching is similar *in vivo*, it may explain the low implantation rates after IVF-ET. An embryo must hatch out completely before it can implant into the uterine endometrium (Figure 27.1).

The impaired hatching may be due to the extended time in culture, in an artificial environment, causing hardening or increased thickness of the zona pellucida. Hence, it has been proposed that either an artificial 'opening' or 'softening' of the zona pellucida might be able to promote the hatching process thereby improve the overall implantation and thus pregnancy rate after IVF-ET (Cohen *et al*, 1990a, Tucker *et al*, 1991). In addition, it was also noted that any method of artificially disrupting the zona pellucida changed the timing and rate of blastocysts hatching, when

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Principles and Techniques of In Vitro Fertilization

Dr. Abha Majumdar

OBJECTIVES

The reader will be able to

- List the indication of IVF
- Describe the technique of IVF
- Enumerate the complications
- Discuss the results

In assisted reproduction, conception occurs outside the body – in the laboratory i.e. in vitro, hence the term 'in vitro fertilization' (IVF). However, further development of the fetus occurs within the maternal womb after replacement of the embryo.

Babies conceived and delivered by this method of assisted reproduction are commonly referred to as *test tube babies*.

Historical Aspects

The treatment of infertility took a dramatic leap forward with the development of in-vitro fertilization (IVF). The first human IVF baby was Louise Brown, born on the 25th of July 1978, by the efforts of doctors Steptoe and Edward from England. They used laparoscopy to recover the oocyte from Louise's mother, who suffered from bilateral tubal block. Enormous research has greatly improved the procedure, and has added new techniques such as cryopreservation of embryos, intra-cytoplasmic sperm injection, pre-implantation genetic diagnosis, in vitro maturation, nuclear and cytoplasmic transfers and stem cell culture.

The process of normal conception is likely to be disturbed if-

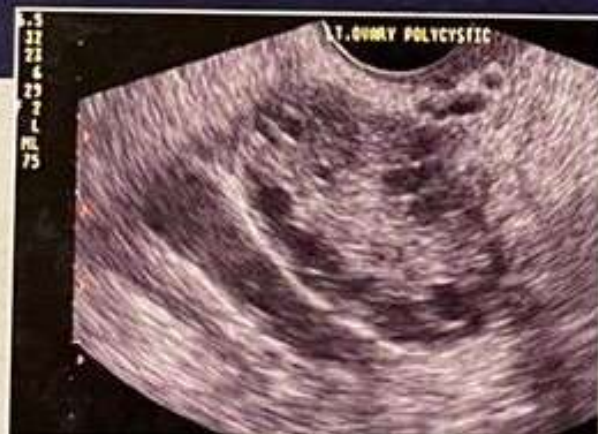
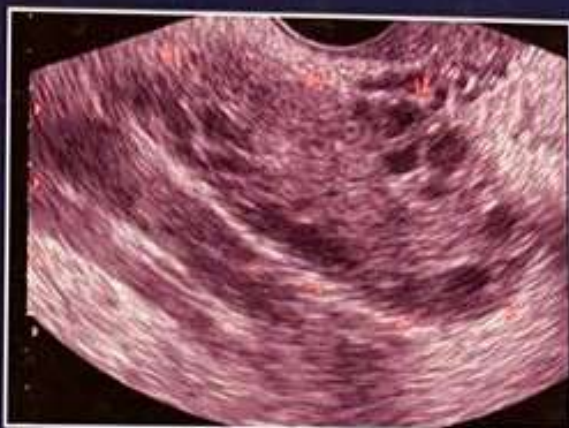
- Tubes are blocked or non functional
- Semen parameters like sperm count or motility are low or morphology is abnormal.

Indications for IVF

Infertile patients that need to be treated by IVF are usually those who have undergone certain simpler treatment regimens without success.

Polycystic Ovary Syndrome

An Update



Editors

Gita Ganguly Mukherjee • BN Chakravarty



Federation of Obstetric and Gynaecological Societies of India

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PCOS and Menstrual Irregularities

INTRODUCTION

Polycystic ovarian syndrome is a complex disorder characterized by chronic anovulation, hyperandrogenism manifested by various degrees of hirsutism, obesity, large cystic ovaries and insulin resistance. Menstrual irregularities may single handedly signal this condition in adolescents or it may coexist with other symptoms. The signs and symptoms of this syndrome stem from disruption of the normal ovulatory menstrual cycle.^{1,6}

INCIDENCE: PCOS AND MENSTRUAL IRREGULARITY

PCOS is present in 4-10% of females in the premenopausal age group⁷ and in 30% amongst women attending infertility clinics.⁸ Out of all women who show polycystic ovaries on ultrasound, 50-85% will have symptoms and signs of the syndrome such as menstrual irregularities and/or hirsutism.⁷ A cross section of anovulatory women at any point of time will reveal that approximately 75% will have polycystic ovaries.⁹

PATHOPHYSIOLOGY

PCOS

The etiology of polycystic ovarian syndrome is largely unknown. Most theories on its pathogenesis can be divided in two groups.^{10,11}

- Those postulating a primary central defect leading to increased secretion of luteinizing hormone followed by hyperstimulation of the ovaries and hyperandrogenism.¹⁰

PCOS is an abnormality of the hypothalamic-pituitary-ovarian system. An important characteristic of this syndrome is inappropriate gonadotropin secretion. LH is tonically elevated throughout the menstrual cycle, FSH is normal or low, the LH to FSH ratio is often greater than 3 and there is an exaggerated response of LH to pulsatile gonadotropin-releasing hormone (GnRH).¹² Although levels of circulating FSH in patients with PCOS are similar to those in normal individuals, induction of



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Foreword

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in patients with cervical stenosis and histories of difficult ET. Many groups have performed embryo transfer under hysteroscopic control, with excellent results.

CONCLUSION

Assessing the endometrial cavity is an integral part of the infertility evaluation. It appears that hysteroscopy is the most sensitive method amongst the tools to evaluate the cavity, recognizing the benefits of hysteroscopy from both a diagnostic and therapeutic viewpoint, the clinician must decide in which setting to perform the procedure.

Thus to conclude, "the hysteroscope which was literally looking for an indication a decade ago has become an indispensable tool today."

— Alan Decherney, 85.

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43.3 Hysteroscopic Guided Biopsy, Polypectomy and Myomectomy

Abha Majumdar, Tejshree Singh

INTRODUCTION

Hysteroscopy is a minimally invasive intervention that can be used to diagnose and treat many intrauterine and endocervical problems. Hysteroscopic polypectomy, myomectomy, and directed endometrial biopsy are just a few of the commonly performed procedures. Given their safety and efficacy, diagnostic and operative hysteroscopy have become standards in gynecologic practice.¹

SURGICAL ANATOMY

Endometrial Polyps

1. Endometrial polyps are localized overgrowths of the endometrium that project into the uterine cavity. They develop because of excessive multiplication of the endometrial cells, may be hormonally

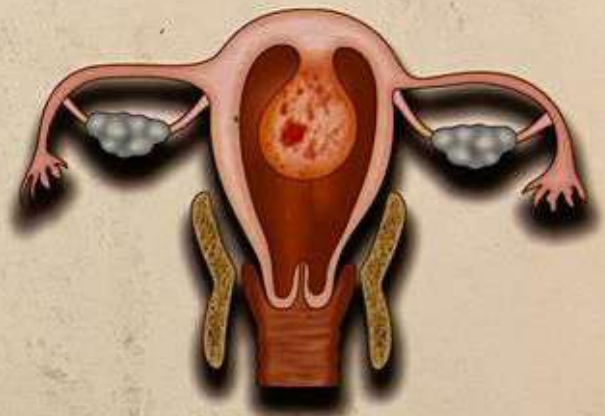
dependent and increase in size depending upon estrogen levels.

2. Polyps may be sessile or pedunculated and rarely include areas of neoplastic growth. Specifically, adenomatous hyperplasia and endometrial adenocarcinomas have been reported in only 0.6% of cases of endometrial polyps.
3. They can usually be detected on an ultrasound scan on second or third post-menstrual day or in mid-cycle, when estrogen levels are maximal, and the endometrium is echogenic.
4. The prevalence of polyps is estimated to be 10 to 24% in hysterectomy samples. Endometrial polyps are rare among women younger than 20 years of age.
5. The incidence of these polyps rises steadily with increasing age, peaks in the fifth decade and then declines after menopause.

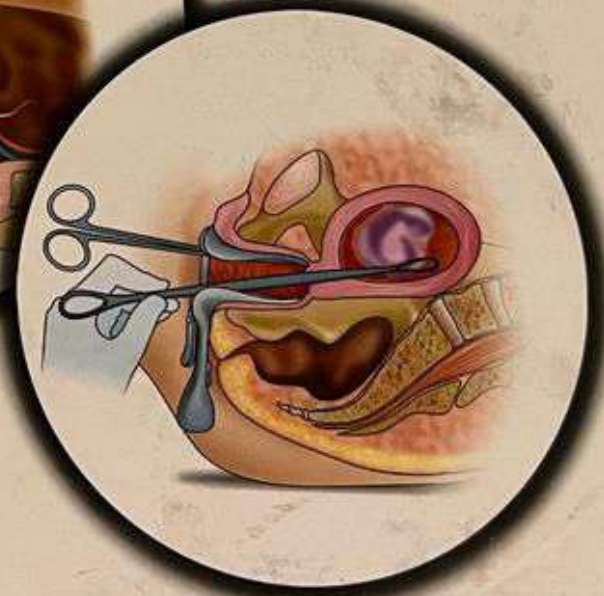
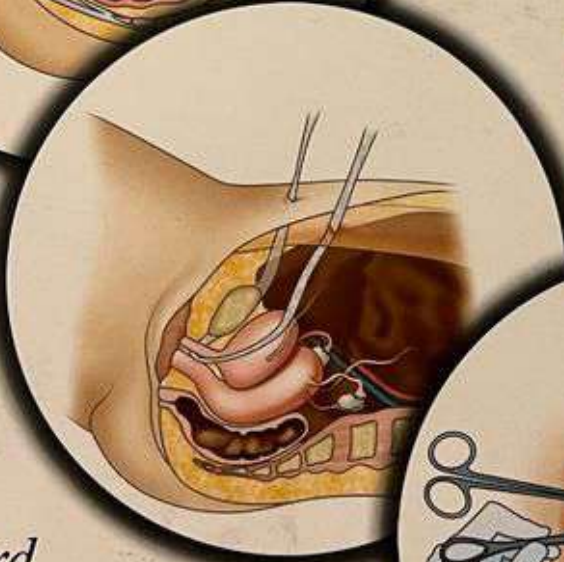
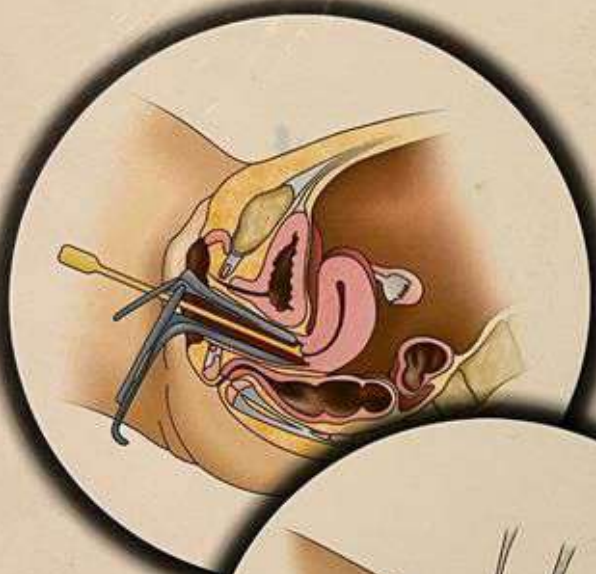


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TEXTBOOK OF GYNECOLOGY



Sudha Salhan



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Anusuya Dass

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Androgens are present in females in early fetal life when adrenal gland secretes significant quantities of dehydroepiandrosterone sulphate (DHEAS). In the middle of the first decade, at about 6 to 7 years of age, these begin to rise again. This phase is termed as "adrenarche" and is clinically manifested by the appearance of pubic and axillary hair. In normal girls, the androgen levels continue to rise throughout the second decade and are maintained at relatively steady levels until the menopause. These contribute in maintenance of body fat and weight, libido and normal functioning of the reproductive system in terms of ovulation. On the other hand, excess of androgens, either by overproduction or reduced clearance may hamper reproductive performance.

Androgens are Produced in Females in Three Compartments (Fig. 15.1)

1. Ovary—ovarian stroma and theca cells.
2. Adrenal—zona fasciculata and reticularis.
3. Periphery and liver—periphery includes skin, fat, pilosebaceous units and blood.

Type of Androgens Present in Females (Fig. 15.2)

1. Testosterone (T) produced 25% from ovary and 25% from adrenal and 50% by conversion of androstenedione (A) and dehydroepiandrosterone (DHEA) in extraglandular tissue (blood, skin, liver).
2. Androstenedione produced 50% from ovary and 50% from adrenal.

3. DHEA produced 10% from ovary and 90% from adrenal.
 4. DHEAS produced 100% from adrenal only.
 5. Dihydrotestosterone (DHT) is formed by peripheral conversion of T and A by the action of 5 α reductase.
- The principal circulating androgens are testosterone and its principal metabolite dihydrotestosterone (DHT). Androstenedione, dehydroepiandrosterone sulfate (DHEAS) are C19 steroids derived from the conversion of cholesterol in either the ovaries or the adrenal. DHT is the most biologically potent, followed by testosterone. Androstenedione, DHEA and DHEAS are comparatively weak androgens, with minimal effect on skin and hair growth under normal circumstances. DHT is derived exclusively from peripheral conversion of circulating testosterone and androstenedione in target tissues, in a reaction catalyzed by enzyme 5 α reductase.

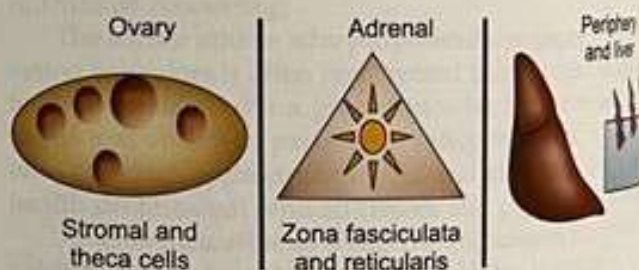
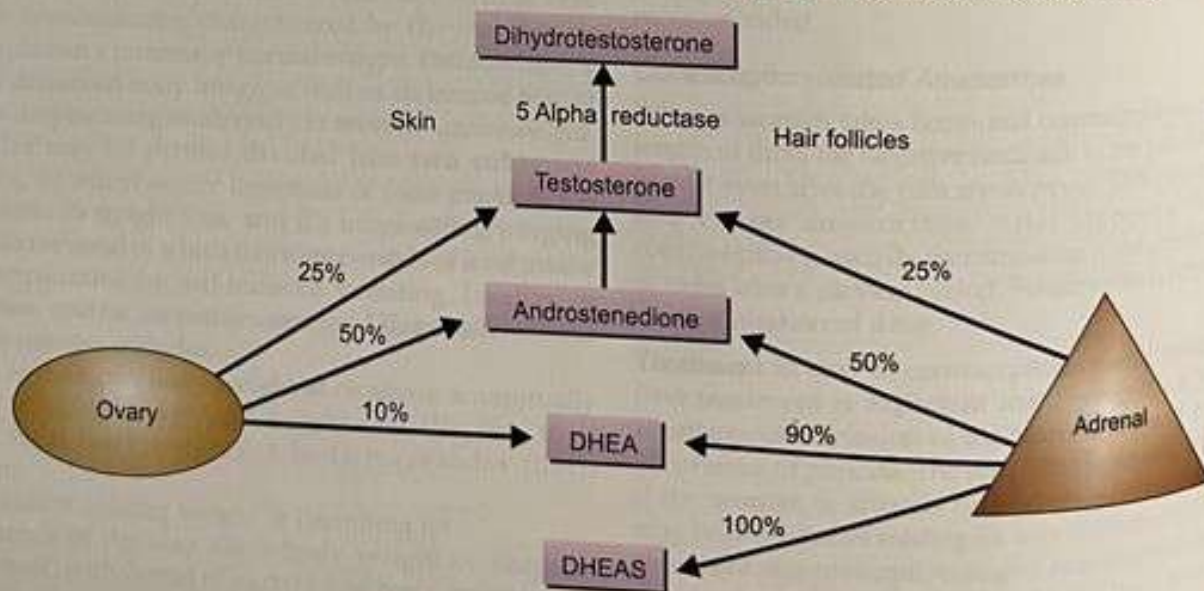


Fig. 15.1: Three compartments of androgen production



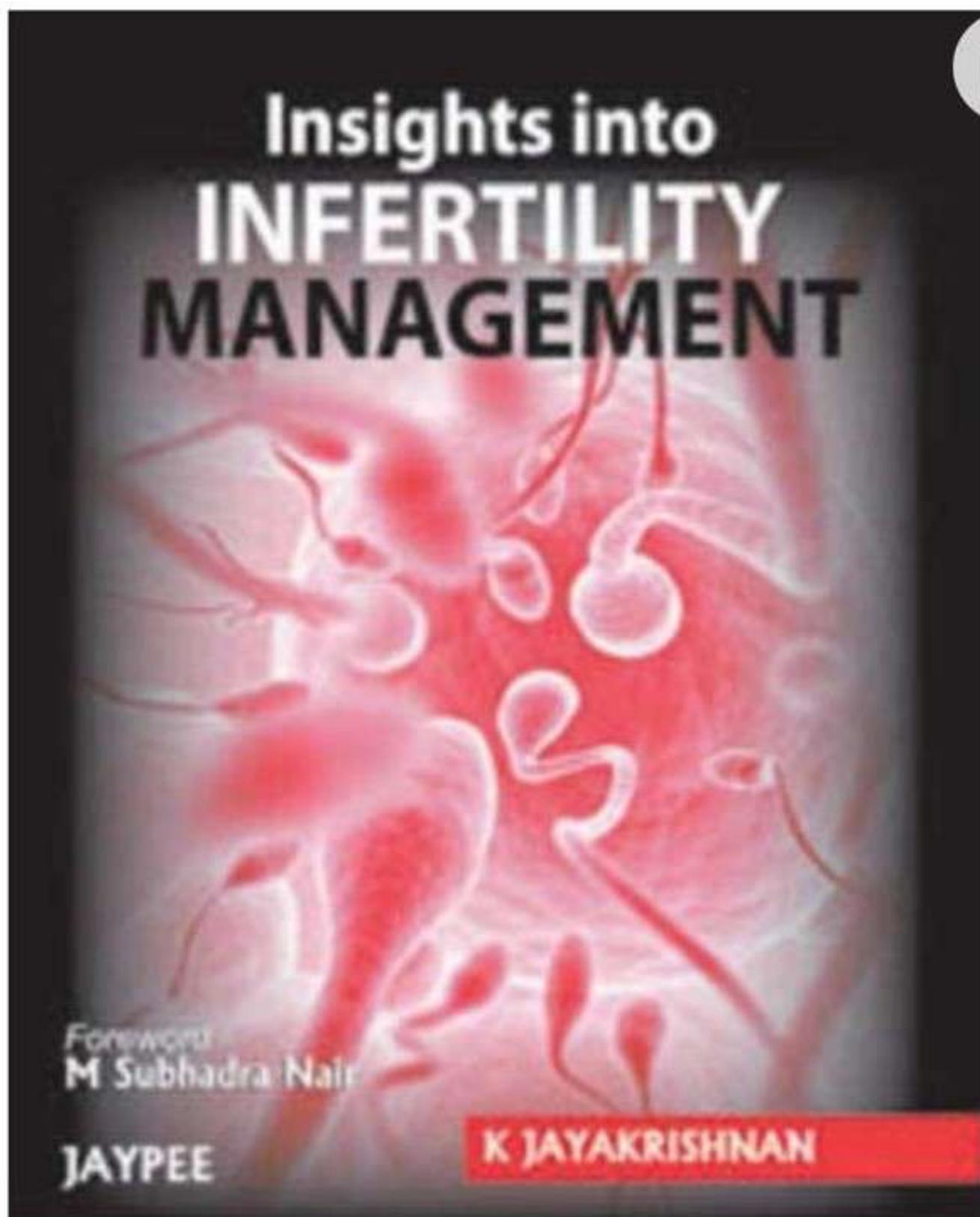
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Narendra Malhotra

PK Shah

Hema Divakar



Editors
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Hyperandrogenism

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Androgens are present in females in early fetal life when adrenal gland secretes significant quantities of dehydroepiandrosterone sulfate (DHEAS). In the middle of the first decade at about 6–7 years of age these begin to rise again. This phase is termed as “adrenarche” and is clinically manifested by the appearance of pubic and axillary hair. In normal girls the androgen levels continue to rise throughout the second decade and are maintained at relatively steady levels until the menopause. These contribute in maintenance of body fat and weight, libido and normal functioning of the reproductive system in terms of ovulation. On the other hand excess of androgens, either by overproduction or reduced clearance may hamper reproductive performance.

ANDROGENS PRODUCTION IN FEMALES

Androgens are produced in females in three compartments (Fig. 1):

1. **Ovary:** Ovarian stroma and theca cells.
2. **Adrenal:** Zona fasciculata and reticularis.
3. **Periphery and liver:** Periphery includes skin, fat, pilosebaceous unit and blood.

Ovarian Androgen Secretion

The theca interna and the stromal cells of the ovary synthesize the androgens. The ovaries secrete mainly androstenedione and testosterone and small quantities of dehydroepiandrosterone (DHEA). The menopausal ovary, which is devoid of oocytes and follicles, still secretes androgens from the stromal cells and the hilum. Testosterone

is secreted mainly by the ovaries and is used as a marker of ovarian androgen secretion. Luteinizing hormone (LH) controls androgen synthesis in the ovaries.¹

Adrenal Androgen Secretion

The adrenals mainly secrete DHEA, DHEAS and androstenedione, (5 and 11 androstenedione). Small quantities of testosterone also are secreted directly by the adrenals. DHEAS and 11-androstenedione are not secreted by the ovaries and, therefore, are used as markers of adrenal androgen secretion. The control of their secretion clearly is under the control of adrenocorticotrophic hormone (ACTH). However, prolactin, estrogen, and a hypothetical pituitary hormone; cortical androgen-stimulating hormone (CASH) or adrenal androgen-stimulating hormone (AASH), have been proposed as separate regulators of adrenal androgen production.¹

Peripheral Androgens

The principal circulating androgens are testosterone and its metabolite dihydrotestosterone (DHT), androstenedione and DHEAS. All are C19 steroids derived from the conversion of cholesterol in either the ovaries or the adrenal. DHT is the most biologically potent, followed by testosterone. Androstenedione and, to some degree, DHEA are converted to testosterone in the skin. Twenty-five percent of circulating testosterone is secreted directly by the ovaries, 25% directly by the adrenals and the remaining 50% is derived from peripheral conversion of androstenedione to testosterone.¹ Androstenedione, DHEA and DHEAS are comparatively weak androgens with minimal effect on skin and hair growth under normal circumstances. DHT is derived exclusively from peripheral conversion of circulating testosterone

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CHAPTER 10

Amenorrhea

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INTRODUCTION

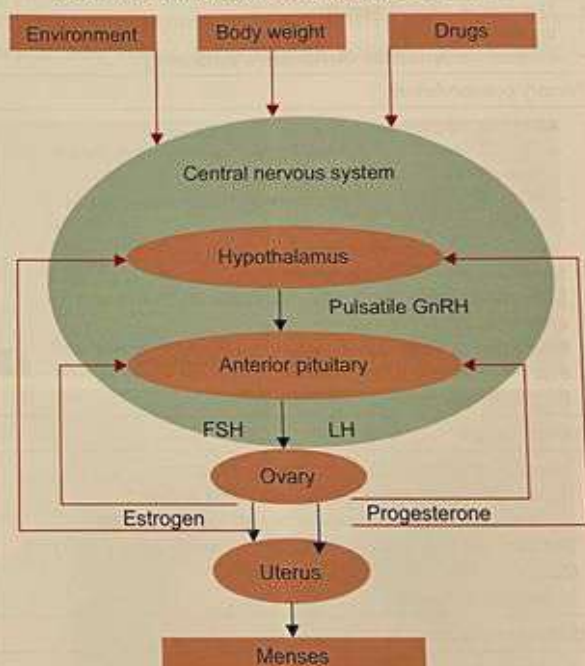
Amenorrhea is absence of menses in a young girl till a particular age or in a woman of reproductive age for a definite period. This is categorized into two types; primary and secondary amenorrhea. Primary amenorrhea is diagnosed if a girl fails to menstruate by the age of 15 years in the presence of secondary sexual characteristics or by the age of 13 years in absence of secondary sexual characteristics.¹ Secondary amenorrhea, on the other hand, is defined as cessation of menses in otherwise regularly menstruating women for a length of time equivalent to her three menstrual cycles or for 6 months.²

PHYSIOLOGY OF MENSTRUATION (FLOWCHART 1)

Normal menstrual flow requires a patent outflow tract between internal genital organs and perineum, i.e. patency and continuity of uterine cavity with the cervical canal and vaginal canal to the perineal area. To achieve menstruation the uterine cavity needs to be lined with endometrium which must develop under the influence of steroidal hormones secreted by the ovary. These steroidal hormones are estrogen and progesterone; estrogen causes proliferation of the endometrium and primes it to the effect of progesterone which in turn leads to secretory changes within this estrogen-primed endometrium. Withdrawal of progesterone secretion stops to support endometrial growth and brings about shedding of this carefully designed endometrium, thus resulting in menstruation.

The ovarian steroid production is orchestrated by the higher centers from the brain comprising of the pituitary gland and the hypothalamus. The principal pituitary hormones are follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from its anterior lobe,

Flowchart 1: Hypothalamo-pituitary-ovarian axis.



(GnRH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone)

which influence the cyclical ovarian steroid production. Hypothalamus regulates pituitary by secreting pulsatile gonadotropin-releasing hormone (GnRH) which reaches pituitary via the portal vessels of the pituitary stalk and thus a hypothalamic-pituitary-ovarian (HPO) axis is established. Environmental factors like stress, excessive weight loss or gain, and certain drugs can influence the menstrual pattern through the hypothalamus and central nervous system. The ovarian hormones estrogen and progesterone also provide feedback signals to anterior pituitary and hypothalamus to control their secretions.

Surveen Ghumman

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Surveen Ghumman
Editor

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Obstetrics & Gynecology

A Case-based Approach



Indrani Ganguli
Harsha Khullar

Forewords
John Studd & S K Bhandari



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Hyperprolactinemia

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Abha Majumdar¹ and Neeti Tiwari²

¹Director and ²Associate Consultant
Center of IVF and Human Reproduction,
Sir Ganga Ram Hospital and Research Centre,
New Delhi

CASE VIGNETTE

A 28-year-old married woman presented at the outpatient department of reproductive medicine with the complaint of amenorrhea for last 6 months.

Present history: Over the last 2 years, her cycle intervals were getting longer ranging from 45 to 60 days with normal flow lasting only for 1–2 days.

Past and personal history: She was married for 4 years but has not conceived despite regular intercourse. Her past medical and surgical history was not significant.

On examination, milky discharge was expressed from nipples of both breasts.

Her investigations revealed elevated serum prolactin levels of 235 ng/ml and normal thyroid profile. Her ultrasound pelvis was essentially normal with endometrial thickness 3 mm. Magnetic resonance imaging (MRI) of the head revealed a pituitary micro-adenoma of 6 mm size.



Individualized Controlled Ovarian Stimulation

**G.A. Rama Raju
Baidyanath Chakraborty**

ELSEVIER

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Review of the Standard Protocols for Controlled Ovarian Stimulation, Alternative Controlled Ovarian Stimulation Protocols and Individualized Treatments in Assisted Reproductive Techniques

Abha Majumdar

Director and Head, Centre of IVF and Human Reproduction,
Institute of Obstetrics and Gynaecology, Sir Ganga Ram Hospital,
New Delhi

Roshi Satija

Consultant Genesis Clinic, F-431 New Rajinder Nagar,
New Delhi

INTRODUCTION

For more than 3 decades gonadotropin releasing hormone agonist (GnRHa) has been incorporated in gonadotropin stimulation protocols for women undergoing IVF. This was done to avoid premature rise or surges of luteinizing hormone (LH) to reduce cancellation of cycles. Apart from this the advantages of adding agonist to these gonadotropin stimulated cycles was efficient patient scheduling and development of synchronized larger cohort of follicles leading to significant numbers of pre-ovulatory follicles, mature oocytes and embryos. All this eventually facilitated improved IVF outcome and pregnancy rates.¹

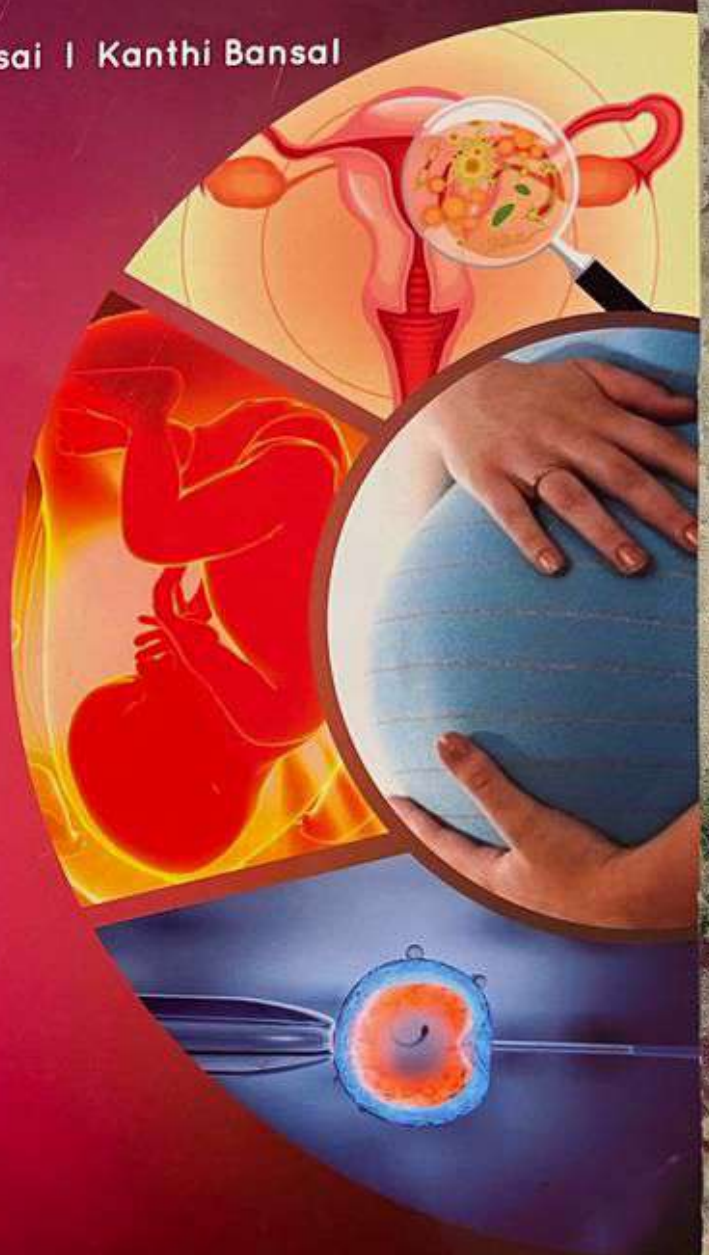
The incorporation of GnRHa to gonadotropin stimulation protocols made it so convenient in terms of time management that this soon became the first-line stimulation protocol for women undergoing IVF. Gonadotropin releasing hormone antagonist is a long-acting agonist and usually started in the mid-



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Choosing the right gonadotropin in stimulation for ART

Abha Majumdar, Roshi Satija

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Choosing the right gonadotropin for stimulation for assisted reproductive techniques/in vitro fertilization (ART/IVF)

Definition: The correct individualization of treatment protocols in IVF should be based on the correct prediction of ovarian response, namely poor, normal and hyper responder. The aim is then to choose the ideal treatment protocol with the right gonadotropin according to this prediction. This should not only enable us to diminish the risk of cycle cancellation due to inadequate response but also prevent development of ovarian hyper-stimulation syndrome (OHSS) also.

With regards to refusal of IVF treatment for women who have been predicted as poor responders, it is commonly agreed not to exclude anyone from their first IVF attempt only on the basis of the ovarian reserve test, as the accuracy of these tests can be poor for the prediction of pregnancy^{1 2 3}. Antral follicle count (AFC) and anti mullerian hormone (AMH) appear to be amongst the best predictive markers of ovarian reserve, but neither are completely reliable, with a false positive rate of 10–20%⁴.

Patient Profile: Prediction of ovarian response can be done by taking into account various clinical as well as investigative parameters of a woman. The following table tends to profile patients so as to identify them regarding their expected normal, hyper and poor response.

HYPER RESPONDER	NORMAL RESPONDER	POORRESPONDER
Underlying PCOS	Regular cycles	Regular or short cycles
Thin built	Normal built	Obese
Age < 30	Age < 37	Age >37
FSH <8miu/ml	FSH <12miu/ml	FSH > 12miu/ml
AMH >25pmol/l	AMH 10-25pmo/l	AMH <3 to 9 pmol/l
(>3.5ng/ml)	(1.5-3.4 ng/ml)	(0.5 to 1.4 ng/ml)
AFC >12 each ovary	AFC 7 to 11	AFC <7
Previous hyper response to stimulation	Previous normal response to stimulation	Previous poor response to stimulation

Therapy

The success of ART is the ability to have a single healthy child per initiated cycle while minimizing the associated risks. This translates into offering every single woman the best treatment tailored to her own unique characteristics, thus maximizing success, eliminating iatrogenic risks and minimizing the risk of cycle cancellation which would lead to reduced costs and possibly a lower number of couples dropping out of ART programmes.

Pre-requisites to optimise individualized controlled ovarian stimulation (iCOS) with the right protocol and right gonadotropin for women undergoing IVF

Complicated Cases in **Assisted Reproductive Techniques**



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Co-editors
Rohan Palshetkar
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A Cohort of Clomiphene Resistant Anovulatory Women with Polycystic Ovary Syndrome and Altered Response to FSH Stimulation

INTRODUCTION

The outcome of ovulation induction in anovulatory polycystic ovarian syndrome (PCOS) may depend, in part, not only on the pharmacologic compounds used, but also on individual patient characteristics, such as age, body mass index (BMI), hyper-androgenism, luteinizing hormone (LH) hyper-secretion, anti Mullerian hormone (AMH) levels, and possibly antral follicle count (AFC) with ovarian volume of these women. There exists a subset of clomiphene citrate (CC) resistant PCOS women who require stimulation of ovulation with high doses of human menopausal gonadotropin (hMG), after not having responded to chronic low dose step up regimes of recombinant follicle stimulating hormone (rFSH).

CASE REPORT

The study consisted of a cohort of 18 anovulatory CC resistant PCOS women who responded to high doses of hMG, after not having responded to normal incremental doses of rFSH. Ovulation induction was started with rFSH 50/75 IU which was increased by 25 units every 5 to 7 days according to low-dose step up protocol. Follicular response was monitored by serum estradiol (E2) levels and ultrasound (USG) follicle monitoring (FM). On further follow up, this cohort of women

Abha Majumdar¹
Poonam Mishra²

¹Director and Head, Center of IVF and Human Reproduction, Sir Ganga Ram Hospital, New Delhi, India

²Fellow for Fellowship in Reproductive Medicine by the National Board of Examinations, Center of IVF and Human Reproduction, Sir Ganga Ram Hospital, New Delhi, India

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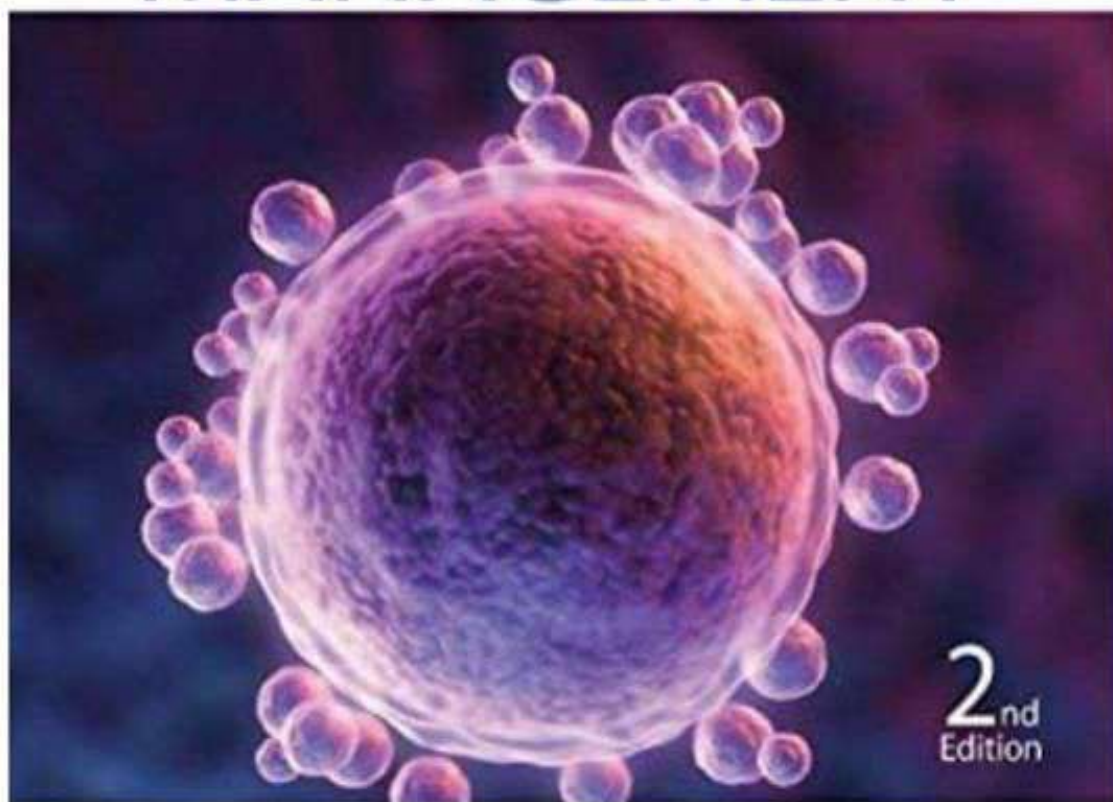
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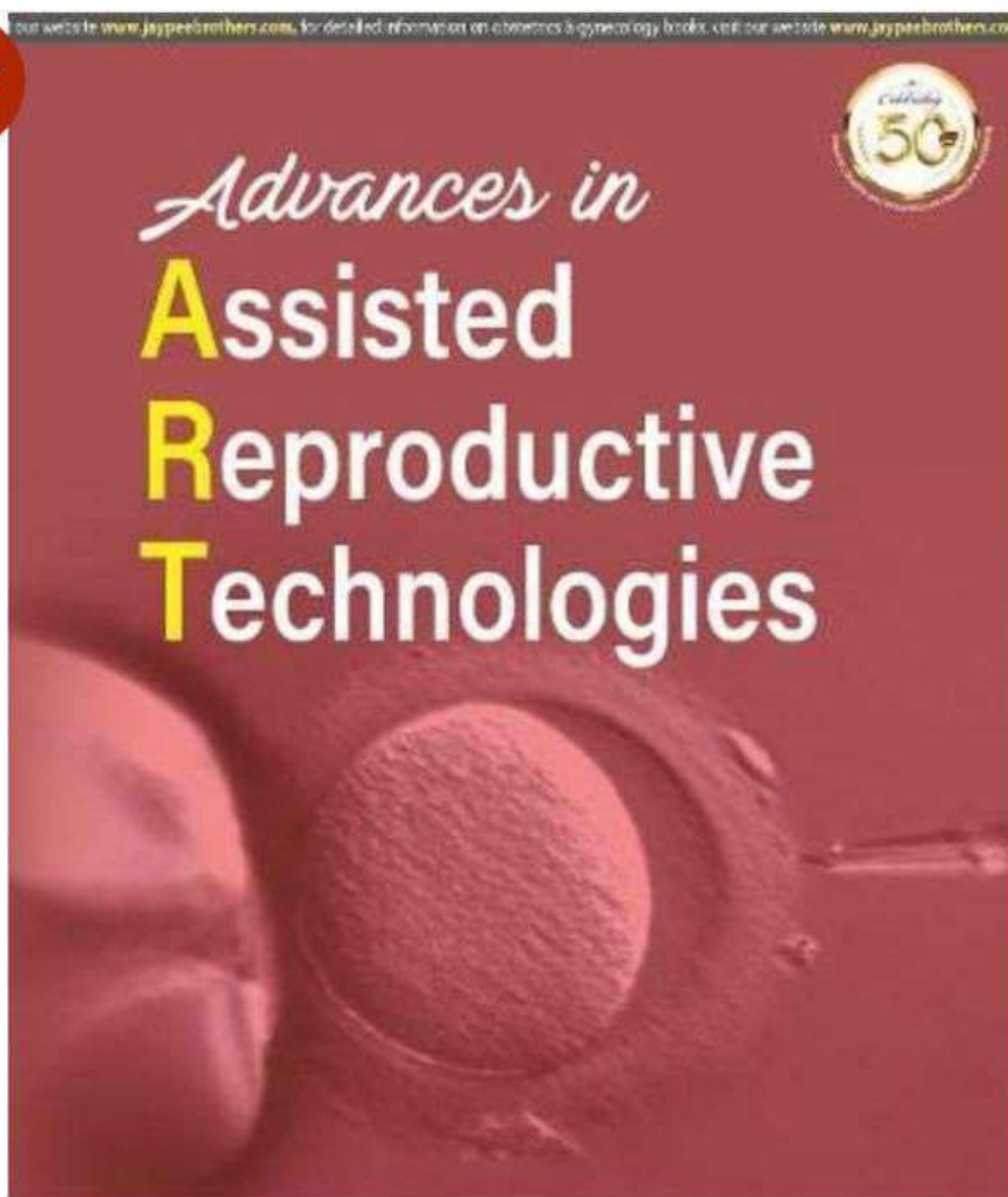
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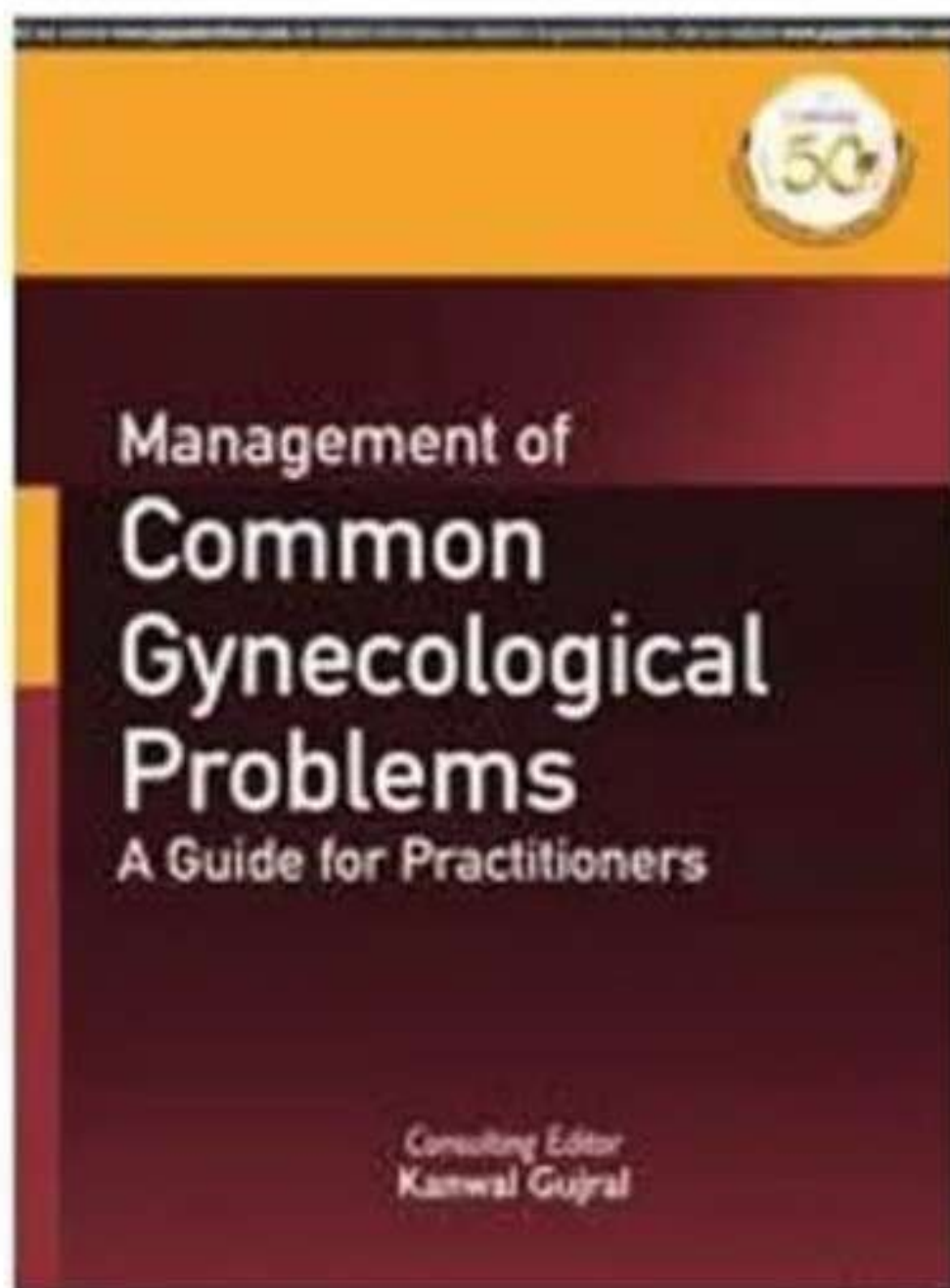
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